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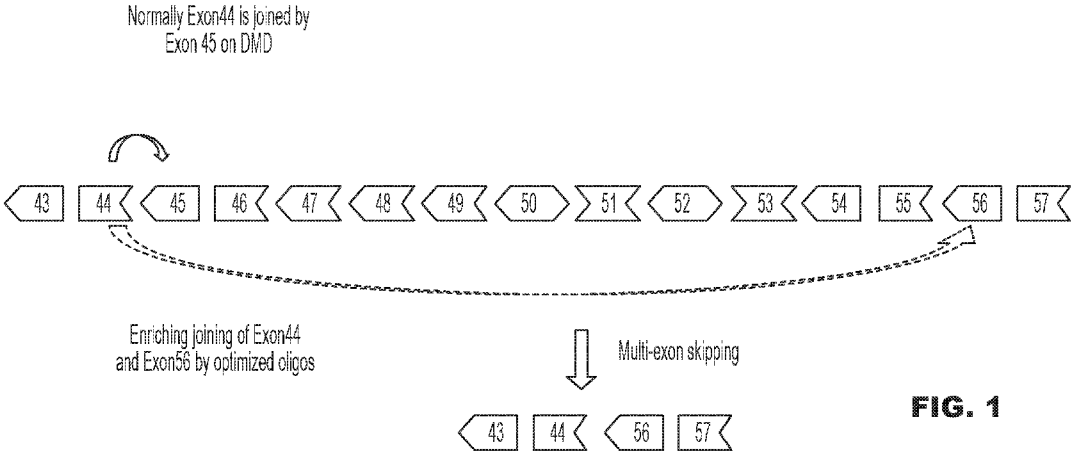

FIG. 1

(57) Abstract: Among other things, the present disclosure provides designed oligonucleotides, compositions, and methods of use thereof. In some embodiments, the present disclosure provides technologies useful for reducing levels of transcripts. In some embodiments, the present disclosure provides technologies useful for modulating transcript splicing. In some embodiments, provided technologies can alter splicing of a dystrophin (DMD) transcript. In some embodiments, the present disclosure provides methods for treating diseases, such as Duchenne muscular dystrophy, Becker's muscular dystrophy, etc.

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OLIGONUCLEOTIDE COMPOSITIONS AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to United States Provisional Application Nos. 62/656,949, filed April 12, 2018, 62/670,709, filed May 11, 2018, 62/715,684, filed August 07, 2018, 62/723,375, filed August 27, 2018, and 62/776,432, filed December 06, 2018, the entirety of each of which is incorporated herein by reference.

BACKGROUND

[0002] Oligonucleotides are useful in therapeutic, diagnostic, research and nanomaterials applications. The use of naturally occurring nucleic acids (*e.g.*, unmodified DNA or RNA) for therapeutics can be limited, for example, because of their instability against extra- and intracellular nucleases and/or their poor cell penetration and distribution. There is a need for new and improved oligonucleotides and oligonucleotide compositions, such as, *e.g.*, new oligonucleotides and oligonucleotide compositions capable of modulating exon skipping of Dystrophin for treatment of muscular dystrophy.

SUMMARY

[0003] Among other things, the present disclosure encompasses the recognition that structural elements of oligonucleotides, such as base sequence, chemical modifications (*e.g.*, modifications of sugar, base, and/or internucleotidic linkages, and patterns thereof), and/or stereochemistry (*e.g.*, stereochemistry of backbone chiral centers (chiral internucleotidic linkages), and/or patterns thereof), can have significant impact on oligonucleotide properties, *e.g.*, activities, toxicities, *e.g.*, as may be mediated by protein binding characteristics, stability, splicing-altering capabilities, *etc.* In some embodiments, the present disclosure demonstrates that oligonucleotide compositions comprising oligonucleotides with controlled structural elements, *e.g.*, controlled chemical modification and/or controlled backbone stereochemistry patterns, provide unexpected properties, including but not limited to certain activities, toxicities, *etc.* In some embodiments, the present disclosure demonstrates that oligonucleotide properties, *e.g.*, activities, toxicities, *etc.*, can be modulated by chemical modifications (*e.g.*, modifications of sugars, bases, internucleotidic linkages, *etc.*), chiral structures (*e.g.*, stereochemistry of chiral internucleotidic linkages and patterns thereof, *etc.*), and/or combinations thereof.

[0004] In some embodiments, the present disclosure provides an oligonucleotide or an oligonucleotide composition. In some embodiments, an oligonucleotide or an oligonucleotide

composition is a DMD oligonucleotide or a DMD oligonucleotide composition. In some embodiments, a DMD oligonucleotide or a DMD oligonucleotide composition is an oligonucleotide or an oligonucleotide composition capable of modulating skipping of one or more exons of the target gene Dystrophin (DMD). In some embodiments, a DMD oligonucleotide or a DMD oligonucleotide composition is useful for treatment of muscular dystrophy. In some embodiments, an oligonucleotide or oligonucleotide composition is an oligonucleotide or oligonucleotide composition which comprises a non-negatively charged internucleotidic linkage. In some embodiments, an oligonucleotide or oligonucleotide composition which comprises a non-negatively charged internucleotidic linkage is capable of modulating the expression, level and/or activity of a gene target or a gene product thereof, including but not limited to, increasing or decreasing the expression, level and/or activity of a gene target or gene product thereof via any mechanism, including but not limited to: an RNase H-dependent mechanism, steric hindrance, RNA interference, modulation of skipping of one or more exon, etc. In some embodiments, the present disclosure pertains to an oligonucleotide or oligonucleotide composition which comprises a non-negatively charged internucleotidic linkage, in combination with any other structure or chemical moiety described herein. In some embodiments, the present disclosure pertains to a DMD oligonucleotide or DMD oligonucleotide composition which comprises a non-negatively charged internucleotidic linkage.

[0005] In some embodiments, the present disclosure provides technologies related to an oligonucleotide or an oligonucleotide composition for reducing levels of a transcript and/or a protein encoded thereby. In some embodiments, as demonstrated by example data described herein, provided technologies are particularly useful for reducing levels of mRNA and/or proteins encoded thereby.

[0006] In some embodiments, the present disclosure provides technologies, e.g., oligonucleotides, compositions and methods, etc., for altering gene expression, levels and/or splicing of transcripts. In some embodiments, a transcript is Dystrophin (DMD). Splicing of a transcript, such as pre-mRNA, is an essential step for the transcript to perform its biological functions in many higher eukaryotes. In some embodiments, the present disclosure recognizes that targeting splicing, especially through compositions comprising oligonucleotides having base sequences and/or chemical modifications and/or stereochemistry patterns (and/or patterns thereof) described in this disclosure, can effectively correct disease-associated mutations and/or aberrant splicing, and/or introduce and/or enhance beneficial splicing that lead to desired products, *e.g.*, mRNA, proteins, *etc.* which can repair, restore, or add new desired biological functions. e.g., one or more functions of Dystrophin.

[0007] In some embodiments, the present disclosure provides compositions and methods for altering splicing of DMD transcripts, wherein altered splicing deletes or compensates for an exon(s) comprising a disease-associated mutation.

[0008] For example, in some embodiments, a Dystrophin gene can comprise an exon comprising

one or more mutations associated with a disease, e.g., muscular dystrophy (including but not limited to Duchenne (Duchenne's) muscular dystrophy (DMD) and Becker (Becker's) muscular dystrophy (BMD)). In some embodiments, a disease-associated exon comprises a mutation (e.g., a missense mutation, a frameshift mutation, a nonsense mutation, a premature stop codon, etc.) in an exon. In some embodiments, the present disclosure provides compositions and methods for effectively skipping a disease-associated Dystrophin exon(s) and/or a different or an adjacent exon(s), while maintaining or restoring the reading frame so that a shorter (e.g., internally truncated) but partially functional dystrophin can be produced. A person having ordinary skill in the art appreciates that provided technologies (oligonucleotides, compositions, methods, *etc.*) can also be utilized for skipping of other exons, for example, those described in WO 2017/062862 and incorporated herein by reference, in accordance with the present disclosure to treat a disease and/or condition.

[0009] Among other things, the present disclosure demonstrates that chemical modifications and/or stereochemistry can be used to modulate transcript splicing by oligonucleotide compositions. In some embodiments, the present disclosure provides combinations of chemical modifications and stereochemistry to improve properties of oligonucleotides, *e.g.*, their capabilities to alter splicing of transcripts. In some embodiments, the present disclosure provides chirally controlled oligonucleotide compositions that, when compared to a reference condition (*e.g.*, absence of the composition, presence of a reference composition (*e.g.*, a stereorandom composition of oligonucleotides having the same constitution (as understood by those skilled in the art, unless otherwise indicated constitution generally refers to the description of the identity and connectivity (and corresponding bond multiplicities) of the atoms in a molecular entity but omitting any distinction arising from their spatial arrangement), a different chirally controlled oligonucleotide composition, etc.), combinations thereof, etc.), provide altered splicing that can deliver one or more desired biological effects, for example, increase production of desired proteins, knockdown of a gene by producing mRNA with frameshift mutations and/or premature termination codons, knockdown of a gene expressing a mRNA with a frameshift mutation and/or premature termination codon, *etc*. In some embodiments, compared to a reference condition, provided chirally controlled oligonucleotide compositions are surprisingly effective. In some embodiments, desired biological effects (*e.g.*, as measured by increased levels of desired mRNA, proteins, *etc.*, decreased levels of undesired mRNA, proteins, *etc.*) can be enhanced by more than 5, 10, 15, 20, 25, 30, 40, 50, or 100 fold.

[0010] The present disclosure recognizes challenges of providing low toxicity oligonucleotide compositions and methods of use thereof. In some embodiments, the present disclosure provides oligonucleotide compositions and methods with reduced toxicity. In some embodiments, the present disclosure provides oligonucleotide compositions and methods with reduced immune responses. In some

embodiments, the present disclosure recognizes that various toxicities induced by oligonucleotides are related to cytokine and/or complement activation. In some embodiments, the present disclosure provides oligonucleotide compositions and methods with reduced cytokine and/or complement activation. In some embodiments, the present disclosure provides oligonucleotide compositions and methods with reduced complement activation via the alternative pathway. In some embodiments, the present disclosure provides oligonucleotide compositions and methods with reduced complement activation via the classical pathway. In some embodiments, the present disclosure provides oligonucleotide compositions and methods with reduced drug-induced vascular injury. In some embodiments, the present disclosure provides oligonucleotide compositions and methods with reduced injection site inflammation. In some embodiments, reduced toxicity can be evaluated through one or more assays widely known to and practiced by a person having ordinary skill in the art, *e.g.*, evaluation of levels of complete activation product, protein binding, *etc*.

[0011] In some embodiments, the present disclosure provides oligonucleotides with enhanced antagonism of hTLR9 activity. In some embodiments, certain diseases, *e.g.*, DMD, are associated with inflammation in, *e.g.*, muscle tissues. In some embodiments, provided technologies (*e.g.*, oligonucleotides, compositions, methods, *etc.*) provides both enhanced activities (*e.g.*, exon-skipping activities) and hTLR9 antagonist activities which can be beneficial to one or more conditions and/or diseases associated with inflammation. In some embodiments, provided oligonucleotides and/or compositions thereof provides both exon-skipping capabilities and decreased levels of toxicity and/or inflammation. In some embodiments, the present disclosure provides an oligonucleotide which comprises one or more non-negatively charged internucleotidic linkages, wherein the oligonucleotide agonizes TLR9 activity less than another oligonucleotide which does not comprise a non-negatively charged internucleotidic linkage or which comprises fewer non-negatively charged internucleotidic linkages and which is otherwise identical. In some embodiments, the present disclosure provides an oligonucleotide which comprises one or more non-negatively charged internucleotidic linkages, wherein the oligonucleotide agonizes TLR9 activity less than an otherwise identical oligonucleotide which does not comprise a non-negatively charged internucleotidic linkage or which comprises fewer non-negatively charged internucleotidic linkages. In some embodiments, the present disclosure pertains to an oligonucleotide comprising at least one non-negatively charged internucleotidic linkage. In some embodiments, the non-negatively charged internucleotidic is selected from: n001, n002, n003, n004, n005, n006, n007, n008, n009, or n010, or a chirally controlled stereoisomer of n001, n002, n003, n004, n005, n006, n007, n008, n009, or n010. In some embodiments, the present disclosure pertains to an oligonucleotide which comprises at least two non-negatively charged internucleotidic linkages, wherein the linkages are different from each other. In some embodiments, the present disclosure pertains to an

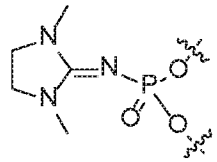
oligonucleotide comprising a CpG motif, wherein at least one internucleotidic linkage in the CpG (e.g., the p in CpG) or immediately upstream of the CpG (toward the 5' end of the oligonucleotide) or immediately downstream of the CpG (toward the 3' end of the oligonucleotide) is a non-negatively charged internucleotidic linkage. In some embodiments, TLR9 is a human TLR9. In some embodiments, TLR9 is a mouse TLR9.

[0012] In some embodiments, the present disclosure demonstrates that oligonucleotide properties, *e.g.*, activities, toxicities, *etc.*, can be modulated through chemical modifications. In some embodiments, the present disclosure provides an oligonucleotide composition comprising a plurality of oligonucleotides which have a common base sequence, and comprise one or more modified internucleotidic linkages (or "non-natural internucleotidic linkages", linkages that are not but can be utilized in place of a natural phosphate internucleotidic linkage (−OP(O)(OH)O−, which may exist as a salt form (−OP(O)(O^-)O−) at a physiological pH) found in natural DNA and RNA), one or more modified sugar moieties, and/or one or more natural phosphate linkages. In some embodiments, provided oligonucleotides may comprise two or more types of modified internucleotidic linkages. In some embodiments, a provided oligonucleotide comprises a non-negatively charged internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a neutral internucleotidic linkage comprises a triazole, alkyne, or guanidine (*e.g.*, cyclic guanidine) moiety. Such moieties are optionally substituted. In some embodiments, a provided oligonucleotide comprises a neutral internucleotidic linkage and another internucleotidic linkage which is not a neutral backbone. In some embodiments, a provided oligonucleotide comprises a neutral internucleotidic linkage and a phosphorothioate internucleotidic linkage. In some embodiments, provided oligonucleotide compositions comprising a plurality of oligonucleotides are chirally controlled and level of the plurality of oligonucleotides in the composition is controlled or pre-determined, and oligonucleotides of the plurality share a common stereochemistry configuration at one or more chiral internucleotidic linkages. For example, in some embodiments, oligonucleotides of a plurality share a common stereochemistry configuration at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50 or more chiral internucleotidic linkages, each of which is independently *Rp* or *Sp*; in some embodiments, oligonucleotides of a plurality share a common stereochemistry configuration at each chiral internucleotidic linkages. In some embodiments, a chiral internucleotidic linkage where a controlled level of oligonucleotides of a composition share a common stereochemistry configuration (independently in the *Rp* or *Sp* configuration) is referred to as a chirally controlled internucleotidic linkage.

[0013] In some embodiments, a modified internucleotidic linkage is a non-negatively charged (neutral or cationic) internucleotidic linkage in that at a pH, (e.g., human physiological pH (~ 7.4), pH of

a delivery site (e.g., an organelle, cell, tissue, organ, organism, etc.), etc.), it largely (*e.g.*, at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, etc.; in some embodiments, at least 30%; in some embodiments, at least 40%; in some embodiments, at least 50%; in some embodiments, at least 60%; in some embodiments, at least 70%; in some embodiments, at least 80%; in some embodiments, at least 90%; in some embodiments, at least 99%; etc.;) exists as a neutral or cationic form (as compared to an anionic form (e.g., $-O-P(O)(O^-)-O-$ (the anionic form of natural phosphate linkage), $-O-P(O)(S^-)-O-$ (the anionic form of phosphorothioate linkage), etc.)), respectively. In some embodiments, a modified internucleotidic linkage is a neutral internucleotidic linkage in that at a pH, it largely exists as a neutral form. In some embodiments, a modified internucleotidic linkage is a cationic internucleotidic linkage in that at a pH, it largely exists as a cationic form. In some embodiments, a pH is human physiological pH (~ 7.4). In some embodiments, a modified internucleotidic linkage is a neutral internucleotidic linkage in that at pH 7.4 in a water solution, at least 90% of the internucleotidic linkage exists as its neutral form. In some embodiments, a modified internucleotidic linkage is a neutral internucleotidic linkage in that in a water solution of the oligonucleotide, at least 50%, 60%, 70%, 80%, 90%, 95%, or 99% of the internucleotidic linkage exists in its neutral form. In some embodiments, the percentage is at least 90%. In some embodiments, the percentage is at least 95%. In some embodiments, the percentage is at least 99%. In some embodiments, a non-negatively charged internucleotidic linkage, e.g., a neutral internucleotidic linkage, when in its neutral form has no moiety with a pKa that is less than 8, 9, 10, 11. 12, 13, or 14. In some embodiments, pKa of an internucleotidic linkage in the present disclosure can be represented by pKa of CH_3–the internucleotidic linkage–CH_3 (i.e., replacing the two nucleoside units connected by the internucleotidic linkage with two $-CH_3$ groups). Without wishing to be bound by any particular theory, in at least some cases, a neutral internucleotidic linkage in an oligonucleotide can provide improved properties and/or activities, e.g., improved delivery, improved resistance to exonucleases and endonucleases, improved cellular uptake, improved endosomal escape and/or improved nuclear uptake, etc., compared to a comparable nucleic acid which does not comprises a neutral internucleotidic linkage.

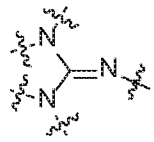
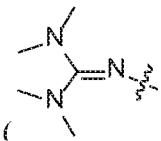
[0014] In some embodiments, a non-negatively charged internucleotidic linkage has the structure of e.g., of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc. In some embodiments, a non-negatively charged internucleotidic linkage comprises a triazole or alkyne moiety. In some embodiments, a non-negatively charged internucleotidic linkage comprises a guanidine moiety. In some embodiments, a non-negatively charged internucleotidic linkage comprises a cyclic guanidine moiety. In some embodiments, a modified internucleotidic linkage comprising a cyclic

guanidine moiety has the structure of:  . In some embodiments, a neutral internucleotidic linkage comprising a cyclic guanidine moiety is chirally controlled. In some embodiments, the present disclosure pertains to a composition comprising an oligonucleotide comprising at least one neutral internucleotidic linkage and at least one phosphorothioate internucleotidic linkage.

[0015] In some embodiments, a non-negatively charged internucleotidic linkage is n001, n002, n003, n004, n005, n006, n007, or n008. In some embodiments, a non-negatively charged internucleotidic linkage is chirally controlled, *e.g.*, n001R, n002R, n003R, n004R, n005R, n006R, n007R, n008R, n009R, n001S, n002S, n003S, n004S, n005S, n006S, n007S, n008S, n009S, *etc.*

[0016] In some embodiments, the present disclosure pertains to a composition comprising an oligonucleotide comprising at least one neutral internucleotidic linkage and at least one phosphorothioate internucleotidic linkage, wherein the phosphorothioate internucleotidic linkage is a chirally controlled internucleotidic linkage in the Sp configuration.

[0017] In some embodiments, the present disclosure pertains to a composition comprising an oligonucleotide comprising at least one neutral internucleotidic linkage and at least one phosphorothioate internucleotidic linkage, wherein the phosphorothioate internucleotidic linkage is a chirally controlled internucleotidic linkage in the Rp configuration.

[0018] In some embodiments, the present disclosure pertains to a composition comprising an oligonucleotide comprising at least one neutral internucleotidic linkage selected from a neutral internucleotidic linkage comprising an optionally substituted triazolyl group, a neutral internucleotidic linkage comprising an optionally substituted alkynyl group, and a neutral internucleotidic linkage comprising a moiety  , and at least one phosphorothioate internucleotidic linkage. In some embodiments, the present disclosure pertains to a composition comprising an oligonucleotide comprising at least one neutral internucleotidic linkage selected from a neutral internucleotidic linkage comprising an optionally substituted triazolyl group, a neutral internucleotidic linkage comprising an optionally substituted alkynyl group, and a neutral internucleotidic linkage comprising a Tmg group (), and at least one phosphorothioate internucleotidic linkage. In some embodiments, an oligonucleotide comprises at least one non-negatively charged internucleotidic linkage and at least one phosphorothioate

internucleotidic linkage. In some embodiments, the non-negatively charged internucleotidic linkage is n001. In some embodiments, the non-negatively charged internucleotidic linkage and the phosphorothioate internucleotidic linkage are independently chirally controlled. In some embodiments, each of the non-negatively charged internucleotidic linkage and the phosphorothioate internucleotidic linkages are independently chirally controlled.

[0019] In some embodiments, the present disclosure pertains to a composition comprising an oligonucleotide comprising at least one neutral internucleotidic linkage selected from a neutral internucleotidic linkage comprising an optionally substituted triazolyl group, a neutral internucleotidic linkage comprising an optionally substituted alkynyl group, and a neutral internucleotidic linkage comprising a Tmg group, and at least one phosphorothioate, wherein the phosphorothioate is a chirally controlled internucleotidic linkage in the Sp configuration.

[0020] In some embodiments, the present disclosure pertains to a composition comprising an oligonucleotide comprising at least one neutral internucleotidic linkage selected from a neutral internucleotidic linkage comprising an optionally substituted triazolyl group, a neutral internucleotidic linkage comprising an optionally substituted alkynyl group, and a neutral internucleotidic linkage comprising a Tmg group, and at least one phosphorothioate, wherein the phosphorothioate is a chirally controlled internucleotidic linkage in the Rp configuration.

[0021] Various types of internucleotidic linkages differ in properties. Without wishing to be bound by any theory, the present disclosure notes that a natural phosphate linkage (phosphodiester internucleotidic linkage) is anionic and may be unstable when used by itself without other chemical modifications in vivo; a phosphorothioate internucleotidic linkage is anionic, generally more stable in vivo than a natural phosphate linkage, and generally more hydrophobic; a neutral internucleotidic linkage such as one exemplified in the present disclosure comprising a cyclic guanidine moiety is neutral at physiological pH, can be more stable in vivo than a natural phosphate linkage, and more hydrophobic.

[0022] In some embodiments, an internucleotidic linkage (e.g., a non-negatively charged internucleotidic linkage, a chirally controlled non-negatively charged internucleotidic linkage, etc.) is neutral at physiological pH, chirally controlled, stable in vivo, hydrophobic, and may increase endosomal escape.

[0023] In some embodiments, an oligonucleotide or oligonucleotide composition is: a DMD oligonucleotide or oligonucleotide composition; an oligonucleotide or oligonucleotide composition comprising a non-negatively charged internucleotidic linkage; or a DMD oligonucleotide comprising a non-negatively charged internucleotidic linkage.

[0024] In some embodiments, an oligonucleotide has, as non-limiting examples, a wing-core-wing, wing-core, core-wing, wing-wing-core-wing-wing, wing-wing-core-wing, or wing-core-wing-wing

structure (in some embodiments, a wing-wing comprises or consists of a first wing and a second wing, wherein the first wing is different than the second wing, and the first and second wings are different than the core). A wing or core can be defined by any structural elements and/or patterns and/or combinations thereof. In some embodiments, a wing and core is defined by nucleoside modifications, sugar modifications, and/or internucleotidic linkages, wherein a wing comprises a nucleoside modification, sugar modification and/or internucleotidic linkage and/or pattern and/or combination thereof, that the core region does not have, or vice versa. In some embodiments, oligonucleotides of the present disclosure comprise or consist of a 5'-end region, a middle region, and a 3'-end region. In some embodiments, a 5'-end region is a 5'-wing region. In some embodiments, a 5'-wing region is a 5'-end region. In some embodiments, a 3'-end region is a 3'-wing region. In some embodiments, a 3'-wing region is a 3'-end region. In some embodiments, a core region is a middle region.

[0025] In some embodiments, each wing region (or each of the 5'-end and 3'-end regions) independently comprises one or more modified phosphate linkages and no natural phosphate linkages, and the core region (the middle region) comprises one or more modified internucleotidic linkages and one or more natural phosphate linkages. In some embodiments, each wing region (or each of the 5'-end and 3'-end regions) independently comprises one or more natural phosphate linkages and optionally one or more modified internucleotidic linkages, and the core (or the middle region) comprises one or more modified internucleotidic linkages and optionally one or more natural phosphate linkages. In some embodiments, a wing (or a 5'-end or 3'-end region) comprises modified sugar moieties. In some embodiments, a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage.

[0026] Among other things, the present disclosure encompasses the recognition that stereorandom oligonucleotide preparations contain a plurality of distinct chemical entities that differ from one another, *e.g.*, in the stereochemical structure of individual backbone chiral centers within the oligonucleotide chain. Without control of stereochemistry of backbone chiral centers, stereorandom oligonucleotide preparations provide uncontrolled (or stereorandom) compositions comprising undetermined levels of oligonucleotide stereoisomers. Even though these stereoisomers may have the same base sequence and/or chemical modifications, they are different chemical entities at least due to their different backbone stereochemistry, and they can have, as demonstrated herein, different properties, *e.g.*, activities, toxicities, distribution *etc*. Among other things, the present disclosure provides chirally controlled compositions that are or contain particular stereoisomers of oligonucleotides of interest; in contrast to chirally uncontrolled compositions, chirally controlled compositions comprise controlled levels of particular stereoisomers of oligonucleotides. In some embodiments, a particular stereoisomer may be defined, for example, by its base sequence, its pattern of backbone linkages, its pattern of backbone chiral centers, and pattern of backbone phosphorus modifications, etc. As is understood in the

art, in some embodiments, base sequence may refer solely to the sequence of bases and/or to the identity and/or modification status of nucleoside residues (*e.g.*, of sugar and/or base components, relative to standard naturally occurring nucleotides such as adenine, cytosine, guanosine, thymine, and uracil) in an oligonucleotide and/or to the hybridization character (*i.e.*, the ability to hybridize with particular complementary residues) of such residues. In some embodiments, the present disclosure demonstrates that property improvements (*e.g.*, improved activities, lower toxicities, *etc.*) achieved through inclusion and/or location of particular chiral structures within an oligonucleotide can be comparable to, or even better than those achieved through use of chemical modifications, *e.g.*, particular backbone linkages, residue modifications, *etc.* (*e.g.*, through use of certain types of modified phosphates [*e.g.*, phosphorothioate, substituted phosphorothioate, *etc.*], sugar modifications [*e.g.*, 2'- modifications, *etc.*], and/or base modifications [*e.g.*, methylation, *etc.*]). In some embodiments, the present disclosure demonstrates that chirally controlled oligonucleotide compositions of oligonucleotides comprising certain chemical modifications (*e.g.*, 2'-F, 2'-OMe, phosphorothioate internucleotidic linkages, lipid conjugation, *etc.*) demonstrate unexpectedly high exon-skipping efficiency.

[0027] In some embodiments, provided oligonucleotides are blockmers. In some embodiments, a blockmer is an oligonucleotide comprising one or more blocks.

[0028] In some embodiments, a block is a portion of an oligonucleotide. In some embodiments, a block is a wing or a core. In some embodiments, a blockmer comprises one or more blocks. In some embodiments, a 5'-block is a 5'-end region or 5'-wing. In some embodiments, a 3'-block is a 3'-end region or 3'-wing.

[0029] In some embodiments, provided oligonucleotide are altmers. In some embodiments, provided oligonucleotides are altmers comprising alternating blocks. In some embodiments, a blockmer or an altmer can be defined by chemical modifications (including presence or absence), *e.g.*, base modifications, sugar modification, internucleotidic linkage modifications, stereochemistry, *etc.*

[0030] In some embodiments, provided oligonucleotides comprise blocks comprising different internucleotidic linkages. In some embodiments, provided oligonucleotides comprise blocks comprising modified internucleotidic linkages and/or natural phosphate linkages.

[0031] In some embodiments, provided oligonucleotides comprise blocks comprising sugar modifications. In some embodiments, provided oligonucleotides comprise one or more blocks comprising one or more 2'-F modifications (2'-F blocks). In some embodiments, provided oligonucleotides comprise blocks comprising consecutive 2'-F modifications. In some embodiments, a block comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more consecutive 2'-F modifications.

[0032] In some embodiments, provided oligonucleotides comprises one or more blocks

comprising one or more 2'-OR^1 modifications (2'-OR^1 blocks), wherein R^1 is independently as defined and described herein and below. In some embodiments, provided oligonucleotides comprise both 2'-F and 2'-OR^1 blocks. In some embodiments, provided oligonucleotides comprise alternating 2'-F and 2'-OR^1 blocks. In some embodiments, provided oligonucleotides comprise a first 2'-F block at the 5'-end, and a second 2'-F block at the 3'-end, each of which independently comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more consecutive 2'-F modifications.

[0033] In some embodiments, provided oligonucleotides comprise a 5'-block wherein each sugar moiety of the 5'-block comprises a 2'-F modification. In some embodiments, provided oligonucleotides comprise a 3'-block wherein each sugar moiety of the 3'-block comprises a 2'-F modification. In some embodiments, such provided oligonucleotides comprise one or more 2'-OR^1 blocks, and optionally one or more 2'-F blocks, between the 5' and 3' 2'-F blocks. In some embodiments, such provided oligonucleotides comprise one or more 2'-OR^1 blocks, and one or more 2'-F blocks, between the 5' and 3' 2'-F blocks (*e.g.*, WV-3047, WV-3048, *etc.*).

[0034] In some embodiments, a block is a stereochemistry block. In some embodiments, a block is an *R*p block in that each internucleotidic linkage of the block is *R*p. In some embodiments, a 5'-block is an *R*p block. In some embodiments, a 3'-block is an *R*p block. In some embodiments, a block is an *S*p block in that each internucleotidic linkage of the block is *S*p. In some embodiments, a 5'-block is an *S*p block. In some embodiments, a 3'-block is an *S*p block. In some embodiments, provided oligonucleotides comprise both *R*p and *S*p blocks. In some embodiments, provided oligonucleotides comprise one or more *R*p but no *S*p blocks. In some embodiments, provided oligonucleotides comprise one or more *S*p but no *R*p blocks.

[0035] In some embodiments, provided oligonucleotides comprise one or more PO blocks wherein each internucleotidic linkage in a natural phosphate linkage.

[0036] In some embodiments, a 5'-block is an *S*p block wherein each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block is an *S*p block wherein each internucleotidic linkage is a modified internucleotidic linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block is an *S*p block wherein each internucleotidic linkage is a phosphorothioate linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block comprises 4 or more nucleoside units.

[0037] In some embodiments, a 3'-block is an *S*p block wherein each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block is an *S*p block wherein each internucleotidic linkage is a modified internucleotidic linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block is an *S*p block wherein each internucleotidic linkage is a phosphorothioate linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block

comprises 4 or more nucleoside units.

[0038] In some embodiments, provided oligonucleotides comprise alternating blocks comprising different modified sugar moieties and/or unmodified sugar moieties. In some embodiments, provided oligonucleotides comprise alternating blocks comprising different modified sugar moieties and unmodified sugar moieties. In some embodiments, provided oligonucleotides comprise alternating blocks comprising different modified sugar moieties. In some embodiments, provided oligonucleotides comprise alternating blocks comprising different modified sugar moieties, wherein the modified sugar moieties comprise different 2'-modifications. For example, in some embodiments, provided oligonucleotide comprises alternating blocks comprising 2'-OMe and 2'-F, respectively.

[0039] In some embodiments, the present disclosure provides an oligonucleotide composition comprising a plurality of oligonucleotides which:

1) have a common base sequence complementary to a target sequence in a transcript; and

2) comprise one or more modified sugar moieties and modified internucleotidic linkages.

[0040] In some embodiments, a provided oligonucleotide composition is characterized in that, when it is contacted with the transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[0041] In some embodiments, a reference condition is absence of the composition. In some embodiments, a reference condition is presence of a reference composition. Example reference compositions comprising a reference plurality of oligonucleotides are extensively described in this disclosure. In some embodiments, oligonucleotides of the reference plurality have a different structural elements (chemical modifications, stereochemistry, *etc.*) compared with oligonucleotides of the plurality in a provided composition. In some embodiments, a reference composition is a stereorandom preparation of oligonucleotides having the same chemical modifications. In some embodiments, a reference composition is a mixture of stereoisomers while a provided composition is a chirally controlled oligonucleotide composition of one stereoisomer. In some embodiments, oligonucleotides of the reference plurality have the same base sequence, same sugar modifications, same base modifications, same internucleotidic linkage modifications, and/or same stereochemistry as oligonucleotide of the plurality in a provided composition but different chemical modifications, e.g., base modification, sugar modification, internucleotidic linkage modifications, etc.

[0042] Example splicing systems are widely known in the art. In some embodiments, a splicing system is an *in vivo* or *in vitro* system including components sufficient to achieve splicing of a relevant target transcript. In some embodiments, a splicing system is or comprises a spliceosome (*e.g.*, protein and/or RNA components thereof). In some embodiments, a splicing system is or comprises an organellar

membrane (*e.g.*, a nuclear membrane) and/or an organelle (*e.g.*, a nucleus). In some embodiments, a splicing system is or comprises a cell or population thereof. In some embodiments, a splicing system is or comprises a tissue. In some embodiments, a splicing system is or comprises an organism, *e.g.*, an animal, *e.g.*, a mammal such as a mouse, rat, monkey, dog, human, *etc.*

[0043] In some embodiments, the present disclosure provides an oligonucleotide composition comprising a plurality of oligonucleotides which:

1) have a common base sequence complementary to a target sequence in a transcript; and

2) comprise one or more modified sugar moieties and modified internucleotidic linkages,

the oligonucleotide composition being characterized in that, when it is contacted with the transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under reference conditions selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[0044] In some embodiments, the present disclosure provides an oligonucleotide composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications.

[0045] In some embodiments, the present disclosure provides an oligonucleotide composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

which composition is chirally controlled and it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same base sequence, for oligonucleotides of the particular oligonucleotide type,

the oligonucleotide composition being characterized in that, when it is contacted with the transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under reference conditions selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[0046] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising oligonucleotides of a particular oligonucleotide type characterized by:

1) base sequence;

2) pattern of backbone linkages;

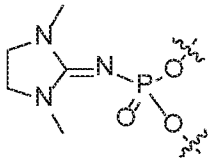
3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

which composition is a substantially pure preparation of a single oligonucleotide in that at least about 10% of the oligonucleotides in the composition have the common base sequence and length, the common pattern of backbone linkages, and the common pattern of backbone chiral centers.

[0047] In some embodiments, each region (e.g., a block, wing, core, 5'-end, 3'-end, or middle region, etc.) of an oligonucleotide independently comprises 3, 4, 5, 6, 7, 8, 9, 10 or more bases. In some embodiments, each region independently comprises 3 or more bases. In some embodiments, each region independently comprises 4 or more bases. In some embodiments, each region independently comprises 5 or more bases. In some embodiments, each region independently comprises 6 or more bases. In some embodiments, each sugar moiety in a region is modified. In some embodiments, a modification is a 2'-modification. In some embodiments, each modification is a 2'-modification. In some embodiments, a modification is 2'-F. In some embodiments, each modification is 2'-F. In some embodiments, a modification is 2'-OR^1. In some embodiments, each modification is 2'-OR^1. In some embodiments, a modification is 2'-OR^1. In some embodiments, each modification is 2'-OMe. In some embodiments, each modification is 2'-OMe. In some embodiments, each modification is 2'-MOE. In some embodiments, each modification is 2'-MOE. In some embodiments, a modification is an LNA sugar modification. In some embodiments, each modification is an LNA sugar modification. In some embodiments, each internucleotidic linkage in a region is a chiral internucleotidic linkage. In some embodiments, each internucleotidic linkage in a wing, or 5'-end or 3'-end region, is an *Sp* chiral internucleotidic linkage. In some embodiments, a chiral internucleotidic linkage is a phosphorothioate linkage. In some embodiments, a core or middle region comprises one or more natural phosphate linkages and one or more modified internucleotidic linkages. In some embodiments, a core or middle region comprises one or more natural phosphate linkages and one or more chiral internucleotidic linkages. In some embodiments, a core region comprises one or more natural phosphate linkages and one or more *Sp* chiral internucleotidic linkages. In some embodiments, a core or middle region comprises one or more natural phosphate linkages and one or more *Sp* phosphorothioate linkages.

[0048] In some embodiments, a region (e.g., a block, wing, core, 5'-end, 3'-end, middle region, etc.) of an oligonucleotide comprises a non-negatively charged internucleotidic linkage, e.g., of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc. In some embodiments, a region comprises a neutral internucleotidic linkage. In some embodiments, a region comprises an internucleotidic linkage which comprises a triazole or alkyne moiety. In some embodiments,

a region comprises an internucleotidic linkage which comprises a cyclic guanidine guanidine. In some embodiments, a region comprises an internucleotidic linkage which comprises a cyclic guanidine moiety. In some embodiments, a region comprises an internucleotidic linkage having the structure of  . In some embodiments, such internucleotidic linkages are chirally controlled.

[0049] In some embodiments, the base sequence of an oligonucleotide, e.g., the base sequence of a plurality of oligonucleotides of a particular oligonucleotide type, is or comprises a base sequence disclosed herein (e.g., a base sequence of an example oligonucleotide (e.g., those listed in the tables, examples, etc.), a target sequence, etc.) (or a portion thereof which is at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 bases long). In some embodiments, a provided oligonucleotide has a base sequence comprising the base sequence of any example oligonucleotides or another base sequence disclosed herein, and a length of up to 30 bases. In some embodiments, a provided oligonucleotide has a base sequence comprising the base sequence of any example oligonucleotides or another base sequence disclosed herein, and a length of up to 40 bases. In some embodiments, a provided oligonucleotide has a base sequence comprising the base sequence of any example oligonucleotides or another base sequence disclosed herein, and a length of up to 50 bases. In some embodiments, a provided oligonucleotide has a base sequence comprising at least 15 contiguous bases of the base sequence of an oligonucleotide example or another sequence disclosed herein, and a length of up to 30 bases. In some embodiments, a provided oligonucleotide has a base sequence comprising at least 15 contiguous bases of the base sequence of an oligonucleotide example or another sequence disclosed herein, and a length of up to 40 bases. In some embodiments, a provided oligonucleotide has a base sequence comprising at least 15 contiguous bases of the base sequence of an oligonucleotide example or another sequence disclosed herein, and a length of up to 50 bases. In some embodiments, a provided oligonucleotide has a base sequence comprising a sequence having no more than 5 mismatches from the base sequence of an example oligonucleotide or another sequence disclosed herein, and a length of up to 30 bases. In some embodiments, a provided oligonucleotide has a base sequence comprising a sequence having no more than 5 mismatches from the base sequence of an example oligonucleotide or another sequence disclosed herein, and a length of up to 40 bases. In some embodiments, a provided oligonucleotide has a base sequence comprising a sequence having no more than 5 mismatches from the base sequence of an example oligonucleotide or another sequence disclosed herein, and a length of up to 50 bases.

[0050] In some embodiments, the base sequence of a provided oligonucleotide is the base sequence of an example oligonucleotide or another sequence disclosed herein, and a pattern of backbone

chiral centers comprises at least one chirally controlled center which is a *Sp* linkage phosphorus of a phosphorothioate linkage. In some embodiments, the base sequence of a provided oligonucleotide is the base sequence of an example oligonucleotide or another sequence disclosed herein, the oligonucleotide has a length of up to 30 bases, and a pattern of backbone chiral centers comprises at least one chirally controlled center which is a *Sp* linkage phosphorus of a phosphorothioate linkage. In some embodiments, the base sequence of a provided oligonucleotide is the base sequence of an example oligonucleotide or another sequence disclosed herein, the oligonucleotide has a length of up to 40 bases, and a pattern of backbone chiral centers comprises at least one chirally controlled center which is a *Sp* linkage phosphorus of a phosphorothioate linkage. In some embodiments, the base sequence of a provided oligonucleotide comprises at least 15 contiguous bases of any example oligonucleotides or another sequence disclosed herein, the oligonucleotide has a length of up to 30, 40, or 50 bases, and a pattern of backbone chiral centers comprises at least one chirally controlled center which is a *Sp* linkage phosphorus of a phosphorothioate linkage.

[0051] In some embodiments, a mismatch is a difference between the base sequence or length when two sequences are maximally aligned and compared. As a non-limiting example, a mismatch is counted if a difference exists between the base at a particular location in one sequence and the base at the corresponding position in another sequence. Thus, a mismatch is counted, for example, if a position in one sequence has a particular base (*e.g.*, A), and the corresponding position on the other sequence has a different base (*e.g.*, G, C or U). A mismatch is also counted, *e.g.*, if a position in one sequence has a base (*e.g.*, A), and the corresponding position on the other sequence has no base (*e.g.*, that position is an abasic nucleotide which comprises a phosphate-sugar backbone but no base) or that position is skipped. A single-stranded nick in either sequence (or in the sense or antisense strand) may not be counted as mismatch, for example, no mismatch would be counted if one sequence comprises the sequence 5'-AG-3', but the other sequence comprises the sequence 5'-AG-3' with a single-stranded nick between the A and the G. A base modification is generally not considered a mismatch, for example, if one sequence comprises a C, and the other sequence comprises a modified C (*e.g.*, with a 2'-modification) at the same position, no mismatch may be counted.

[0052] In some embodiments, oligonucleotides of a particular type are chemically identical in that they have the same base sequence (including length), the same pattern of chemical modifications to sugar and base moieties, the same pattern of backbone linkages (*e.g.*, pattern of natural phosphate linkages, phosphorothioate linkages, phosphorothioate triester linkages, non-negatively charged linkages, and combinations thereof), the same pattern of backbone chiral centers (*e.g.*, pattern of stereochemistry (*Rp*/*Sp*) of chiral internucleotidic linkages), and the same pattern of backbone phosphorus modifications (*e.g.*, pattern of modifications on the internucleotidic phosphorus atom, such as $-S^-$, and $-L-R^1$ of

formula I).

[0053] In some embodiments, the present disclosure provides chirally controlled oligonucleotide compositions of oligonucleotides comprising multiple (*e.g.*, more than 5, 6, 7, 8, 9, or 10) internucleotidic linkages, and particularly for oligonucleotides comprising multiple (*e.g.*, more than 5, 6, 7, 8, 9, or 10) chiral internucleotidic linkages, wherein the oligonucleotides comprise at least one, and in some embodiments, more than 5, 6, 7, 8, 9, or 10 chirally controlled internucleotidic linkages. In some embodiments, in a chirally controlled composition of oligonucleotides each chiral internucleotidic linkage of the oligonucleotides is independently a chirally controlled internucleotidic linkage. In some embodiments, in a stereorandom or racemic composition of oligonucleotides, each chiral internucleotidic linkage is formed with less than 90:10, 95:5, 96:4, 97:3, or 98:2 diastereoselectivity. In some embodiments, in a stereoselective or chirally controlled composition of oligonucleotides, each chirally controlled internucleotidic linkage of the oligonucleotides independently has a diastereopurity of at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% at its chiral linkage phosphorus (either *R*p or *S*p). Among other things, the present disclosure provides technologies to prepare oligonucleotides of high diastereopurity. In some embodiments, diastereopurity of a chiral internucleotidic linkage in an oligonucleotide may be measured through a model reaction, *e.g.* formation of a dimer under essentially the same or comparable conditions wherein the dimer has the same internucleotidic linkage as the chiral internucleotidic linkage, the 5'-nucleoside of the dimer is the same as the nucleoside to the 5'-end of the chiral internucleotidic linkage, and the 3'-nucleoside of the dimer is the same as the nucleoside to the 3'-end of the chiral internucleotidic linkage.

[0054] As described herein, provided compositions and methods are capable of altering splicing of transcripts. In some embodiments, provided compositions and methods provide improved splicing patterns of transcripts compared to reference conditions selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof. An improvement can be an improvement of any desired biological functions. In some embodiments, for example, in DMD, an improvement is production of an mRNA from which a dystrophin protein with improved biological activities is produced.

[0055] In some embodiments, the present disclosure provides a method for altering splicing of a target transcript, comprising administering a provided composition, wherein the splicing of the target transcript is altered relative to reference conditions selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[0056] In some embodiments, the present disclosure provides a method of generating a set of spliced products from a target transcript, the method comprising steps of:

contacting a splicing system containing the target transcript with an oligonucleotide composition

comprising a plurality of oligonucleotides (e.g., a provided chirally controlled oligonucleotide composition), in an amount, for a time, and under conditions sufficient for a set of spliced products to be generated that is different from a set generated under reference conditions selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[0057] In some embodiments, the present disclosure provides a method for treating or preventing a disease, comprising administering to a subject an oligonucleotide composition described herein.

[0058] In some embodiments, the present disclosure provides a method for treating or preventing a disease, comprising administering to a subject an oligonucleotide composition comprising a plurality of oligonucleotides, which:

1) have a common base sequence complementary to a target sequence in a transcript; and

2) comprise one or more modified sugar moieties and modified internucleotidic linkages,

the oligonucleotide composition being characterized in that, when it is contacted with the transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under reference conditions selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[0059] In some embodiments, the present disclosure provides a method for treating or preventing a disease, comprising administering to a subject a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

which composition is chirally controlled and it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same base sequence, for oligonucleotides of the particular oligonucleotide type, wherein:

the oligonucleotide composition being characterized in that, when it is contacted with the transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under reference conditions selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[0060] In some embodiments, a disease is one in which, after administering a provided composition, one or more spliced transcripts repair, restore or introduce a new beneficial function. For example, in DMD, after skipping one or more exons, functions of dystrophin can be restored, or partially restored, through a truncated but (at least partially) active version. In some embodiments, a disease is one in which, after administering a provided composition, one or more spliced transcripts repair, a gene is

effectively knockdown by altering splicing of the gene transcript.

[0061] In some embodiments, a disease is muscular dystrophy, including but not limited to Duchenne (Duchenne's) muscular dystrophy (DMD) and Becker (Becker's) muscular dystrophy (BMD).

[0062] In some embodiments, a transcript is of Dystrophin gene or a variant thereof.

[0063] In some embodiments, the present disclosure provides a method of treating a disease by administering a composition comprising a plurality of oligonucleotides sharing a common base sequence comprising a nucleotide sequence, which nucleotide sequence is complementary to a target sequence in the target transcript,

the improvement that comprises using as the oligonucleotide composition a chirally controlled oligonucleotide composition characterized in that, when it is contacted with the transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under reference conditions selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[0064] In some embodiments, a common sequence comprises a sequence (or at least 15 base long portion thereof) of any oligonucleotide in Table A1.

[0065] In some embodiments, the present disclosure provides a method of administering an oligonucleotide composition comprising a plurality of oligonucleotides having a common nucleotide sequence, the improvement that comprises:

administering an oligonucleotide composition comprising the plurality of oligonucleotides each of which independently comprises one or more negatively charged internucleotidic linkages and one or more non-negatively charged internucleotidic linkages, wherein the oligonucleotide composition is optionally chirally controlled.

[0066] In some embodiments, the present disclosure provides a method of administering an oligonucleotide composition comprising a plurality of oligonucleotides having a common nucleotide sequence, the improvement that comprises:

administering an oligonucleotide composition comprising the plurality of oligonucleotides that is chirally controlled and that is characterized by reduced toxicity relative to a reference oligonucleotide composition of the same common nucleotide sequence.

[0067] In some embodiments, the present disclosure provides a method of administering an oligonucleotide composition comprising a plurality of oligonucleotides having a common nucleotide sequence, the improvement that comprises:

administering an oligonucleotide composition in which each oligonucleotide in the plurality includes one or more natural phosphate linkages and one or more modified phosphate linkages;

wherein the oligonucleotide composition is characterized by reduced toxicity when tested in at

least one assay that is observed with an otherwise comparable reference composition whose oligonucleotides do not comprise natural phosphate linkages.

[0068] In some embodiments, oligonucleotides can elicit proinflammatory responses. In some embodiments, the present disclosure provides compositions and methods for reducing inflammation. In some embodiments, the present disclosure provides compositions and methods for reducing proinflammatory responses. In some embodiments, the present disclosure provides methods for reducing injection site inflammation using provided compositions. In some embodiments, the present disclosure provides methods for reducing drug-induced vascular injury using provided compositions.

[0069] In some embodiments, the present disclosure provides a method, comprising administering a composition comprising a plurality of oligonucleotides of a common base sequence, which composition displays reduced injection site inflammation as compared with a reference composition comprising a plurality of oligonucleotides, each of which also has the common base sequence , but which differs structurally from the oligonucleotides of the plurality in that:

individual oligonucleotides within the reference plurality differ from one another in stereochemical structure; and/or

at least some oligonucleotides within the reference plurality have a structure different from a structure represented by the plurality of oligonucleotides of the composition; and/or

at least some oligonucleotides within the reference plurality do not comprise a wing region and a core region.

[0070] In some embodiments, the present disclosure provides a method, comprising administering a composition comprising a plurality of oligonucleotides of a common base sequence, which composition displays altered protein binding as compared with a reference composition comprising a plurality of oligonucleotides, each of which also has the common base sequence but which differs structurally from the oligonucleotides of the plurality in that:

individual oligonucleotides within the reference plurality differ from one another in stereochemical structure; and/or

at least some oligonucleotides within the reference plurality have a structure different from a structure represented by the plurality of oligonucleotides of the composition; and/or

at least some oligonucleotides within the reference plurality do not comprise a wing region and a core region.

[0071] In some embodiments, the present disclosure provides a method of administering an oligonucleotide composition comprising a plurality of oligonucleotides having a common nucleotide sequence, the improvement that comprises:

administering an oligonucleotide composition comprising a plurality of oligonucleotides that is

characterized by altered protein binding relative to a reference oligonucleotide composition of the same common nucleotide sequence.

[0072] In some embodiments, the present disclosure provides a method comprising administering a composition comprising a plurality of oligonucleotides of a common base sequence, which composition displays improved delivery as compared with a reference composition comprising a reference plurality of oligonucleotides, each of which also has the common base sequence but which differs structurally from the oligonucleotides of the plurality in that:

individual oligonucleotides within the reference plurality differ from one another in stereochemical structure; and/or

at least some oligonucleotides within the reference plurality have a structure different from a structure represented by the plurality of oligonucleotides of the composition; and/or

at least some oligonucleotides within the reference plurality do not comprise a wing region and a core region.

[0073] In some embodiments, the present disclosure provides a method of administering an oligonucleotide composition comprising a plurality of oligonucleotides having a common nucleotide sequence, the improvement that comprises:

administering an oligonucleotide comprising a plurality of oligonucleotides that is characterized by improved delivery relative to a reference oligonucleotide composition of the same common nucleotide sequence.

[0074] In some embodiments, the present disclosure provides a composition comprising any oligonucleotide disclosed herein. In some embodiments, the present disclosure provides a composition comprising any chirally controlled oligonucleotide disclosed herein.

[0075] In some embodiments, the present disclosure provides a composition comprising an oligonucleotide disclosed herein which is capable of mediating skipping of Dystrophin exon 45. In some embodiments, the present disclosure provides a composition comprising an oligonucleotide disclosed herein which is capable of mediating skipping of Dystrophin exon 51. In some embodiments, the present disclosure provides a composition comprising an oligonucleotide disclosed herein which is capable of mediating skipping of Dystrophin exon 53. In some embodiments, the present disclosure provides a composition comprising an oligonucleotide(s) disclosed herein which is capable of mediating skipping of multiple Dystrophin exons. In some embodiments, such a composition is a chirally controlled oligonucleotide composition.

[0076] In some embodiments, the present disclosure pertains to an oligonucleotide or an oligonucleotide composition capable of mediating skipping of a DMD exon or multiple DMD exons. In

some embodiments, a DMD exon is exon 51. In some embodiments, a DMD exon is exon 53. In some embodiments, a DMD exon is exon 45. In some embodiments, the present disclosure pertains to an oligonucleotide composition capable of mediating skipping of a DMD exon 53, wherein the oligonucleotide composition comprises at least one chirally controlled internucleotidic linkage.

[0077] In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of DMD exon 45. In some embodiments, the present disclosure pertains to an oligonucleotide composition capable of mediating skipping of DMD exon 45, wherein the oligonucleotide composition comprises at least one chirally controlled internucleotidic linkage and comprises at least one non-negatively charged internucleotidic linkage. In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of DMD exon 45 and comprises at least one non-negatively charged internucleotidic linkage.

[0078] In some embodiments, the present disclosure pertains to an oligonucleotide composition capable of mediating skipping of DMD exon 45, wherein the oligonucleotide composition comprises at least one non-negatively charged internucleotidic linkage. In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of DMD exon 45 and comprises at least one non-negatively charged internucleotidic linkage.

[0079] In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of DMD exon 51. In some embodiments, the present disclosure pertains to an oligonucleotide composition capable of mediating skipping of DMD exon 51, wherein the oligonucleotide composition comprises at least one chirally controlled internucleotidic linkage and comprises at least one non-negatively charged internucleotidic linkage. In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of DMD exon 51 and comprises at least one non-negatively charged internucleotidic linkage.

[0080] In some embodiments, the present disclosure pertains to an oligonucleotide composition capable of mediating skipping of DMD exon 51, wherein the oligonucleotide composition comprises at least one non-negatively charged internucleotidic linkage. In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of DMD exon 51 and comprises at least one non-negatively charged internucleotidic linkage.

[0081] In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of DMD exon 53. In some embodiments, the present disclosure pertains to an oligonucleotide composition capable of mediating skipping of DMD exon 53, wherein the oligonucleotide composition comprises at least one chirally controlled internucleotidic linkage and comprises at least one non-negatively charged internucleotidic linkage. In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of DMD exon 53 and comprises at least one non-negatively charged internucleotidic linkage.

[0082] In some embodiments, the present disclosure pertains to an oligonucleotide composition capable of mediating skipping of DMD exon 53, wherein the oligonucleotide composition comprises at least one non-negatively charged internucleotidic linkage. In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of DMD exon 53 and comprises at least one non-negatively charged internucleotidic linkage.

[0083] In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of multiple DMD exons. In some embodiments, the present disclosure pertains to an oligonucleotide composition capable of mediating skipping of multiple DMD exons, wherein the oligonucleotide composition comprises at least one chirally controlled internucleotidic linkage and comprises at least one non-negatively charged internucleotidic linkage. In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of multiple DMD exons and comprises at least one non-negatively charged internucleotidic linkage.

[0084] In some embodiments, the present disclosure pertains to an oligonucleotide composition capable of mediating skipping of a DMD exon, wherein the oligonucleotide composition comprises at least one non-negatively charged internucleotidic linkage. In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of a DMD exon and comprises at least one non-negatively charged internucleotidic linkage. In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of multiple DMD exons. In some embodiments, the present disclosure pertains to an oligonucleotide composition capable of mediating skipping of multiple DMD exons, wherein the oligonucleotide composition comprises at least one chirally controlled internucleotidic linkage and comprises at least one non-negatively charged

internucleotidic linkage. In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of multiple DMD exons and comprises at least one non-negatively charged internucleotidic linkage. In some embodiments, a DMD exon is any DMD exon disclosed herein, including but not limited to exon 45, exon 51, exon 52, exon 53, exon 55, exon 56, and exon 57.

[0085] In some embodiments, the present disclosure pertains to an oligonucleotide composition capable of mediating skipping of multiple DMD exons, wherein the oligonucleotide composition comprises at least one non-negatively charged internucleotidic linkage. In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition, wherein the oligonucleotide is capable of mediating skipping of multiple DMD exons and comprises at least one non-negatively charged internucleotidic linkage.

[0086] In some embodiments, the present disclosure provides a chirally controlled composition of an oligonucleotide capable of mediating skipping of Dystrophin exon 51. In some embodiments, the present disclosure provides a chirally controlled composition of an oligonucleotide capable of mediating skipping of Dystrophin exon 51 and disclosed herein.

[0087] In some embodiments, the present disclosure provides a composition of an oligonucleotide having a base sequence which is, comprises, or comprises a 15-base portion of the base sequence of UCAAGGAAGAUGGCAUUUCU, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally controlled. In some embodiments, the present disclosure provides a composition of an oligonucleotide having a base sequence which is UCAAGGAAGAUGGCAUUUCU, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally controlled. In some embodiments, the present disclosure provides a composition of an oligonucleotide having a base sequence which comprises UCAAGGAAGAUGGCAUUUCU, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally controlled. In some embodiments, the present disclosure provides a composition of an oligonucleotide having a base sequence which comprises a 15-base portion of the base sequence of UCAAGGAAGAUGGCAUUUCU, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally controlled. In some embodiments, the present disclosure provides a composition of an oligonucleotide having a base sequence which is, comprises, or comprises a 15-base portion of any of: UCAAGGAAGAUGGCAUUUCU, UCAAGGAAGAUGGCAUUUC, UCAAGGAAGAUGGCAUUU, UCAAGGAAGAUGGCAUU, UCAAGGAAGAUGGCAU, UCAAGGAAGAUGGCA, CAAGGAAGAUGGCAUUUCU, AAGGAAGAUGGCAUUUCU, AGGAAGAUGGCAUUUCU,

GGAAGAUGGCAUUUCU, GAAGAUGGCAUUUCU, CAAGGAAGAUGGCAUUUC, CAAGGAAGAUGGCAUUU, AAGGAAGAUGGCAUUUC, AAGGAAGAUGGCAUUU, AGGAAGAUGGCAUUU, or AAGGAAGAUGGCAUU, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally controlled.

[0088] In some embodiments, the present disclosure provides a chirally controlled composition of an oligonucleotide capable of mediating skipping of Dystrophin exon 53. In some embodiments, the present disclosure provides a chirally controlled composition of an oligonucleotide capable of mediating skipping of Dystrophin exon 53 and disclosed herein.

[0089] In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9517. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9519. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9521. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9524. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9714. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9715. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9747. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9748. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9749. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9897. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9898. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9899. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9900. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9906. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-9912. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-10670. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-10671. In some embodiments, the present disclosure provides a chirally controlled composition of oligonucleotide WV-10672.

[0090] In some embodiments, the present disclosure provides a composition of an oligonucleotide having a base sequence which is, comprises, or comprises a 15-base portion of the base sequence of CUCCGGUUCUGAAGGUGUUC, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally controlled. In some embodiments, the

present disclosure provides a composition of an oligonucleotide having a base sequence which is CUCCGGUUCUGAAGGUGUUC, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally controlled. In some embodiments, the present disclosure provides a composition of an oligonucleotide having a base sequence which comprises CUCCGGUUCUGAAGGUGUUC, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally controlled. In some embodiments, the present disclosure provides a composition of an oligonucleotide having a base sequence which is, comprises, or comprises a 15-base portion of CUCCGGUUCUGAAGGUGUUC, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally controlled. In some embodiments, the present disclosure provides a composition of an oligonucleotide having a base sequence which is or comprises CUCCGGUUCUGAAGGUGUUCC, UCCGGUUCUGAAGGUGUUC, UCCGGUUCUGAAGGUGUUC, CCGGUUCUGAAGGUGUUC, CGGUUCUGAAGGUGUUC, GGUUCUGAAGGUGUUC, GUUCUGAAGGUGUUC, CUCCGGUUCUGAAGGUGUU, CUCCGGUUCUGAAGGUGU, CUCCGGUUCUGAAGGUG, CUCCGGUUCUGAAGGU, CUCCGGUUCUGAAGG, UCCGGUUCUGAAGGUGUU, CCGGUUCUGAAGGUGUU, UCCGGUUCUGAAGGUGU, CCGGUUCUGAAGGUGU, UCCGGUUCUGAAGGUG, CGGUUCUGAAGGUGU, UCCGGUUCUGAAGGU, CCGGUUCUGAAGGUG, CGGUUCUGAAGGUGUU, UCCGGUUCUGAAGGUGUUC,UCCGGUUCUGAAGGUG,UCCGGUUCUGAAGGU, CGGUUCUGAAGGUGUU, GGUUCUGAAGGUGUU, or GGUUCUGAAGGUGUU, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally controlled. In some embodiments, the present disclosure provides a composition of an oligonucleotide having a base sequence which is, comprises, or comprises a 15-base portion of the base sequence of UUCUGAAGGUGUUCUUGUAC, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally controlled. In some embodiments, the present disclosure provides a composition of an oligonucleotide having a base sequence which is UUCUGAAGGUGUUCUUGUAC, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally controlled. In some embodiments, the present disclosure provides a composition of an oligonucleotide having a base sequence which comprises UUCUGAAGGUGUUCUUGUAC, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally controlled. In some embodiments, the present disclosure provides a composition of an oligonucleotide having a base sequence which comprises a 15-base portion of the base sequence of UUCUGAAGGUGUUCUUGUAC, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally

controlled. In some embodiments, the present disclosure provides a composition of an oligonucleotide having a base sequence which is or comprises UUCUGAAGGUGUUCUUGUAC, UCUGAAGGUGUUCUUGUAC, CUGAAGGUGUUCUUGUAC, UGAAGGUGUUCUUGUAC, GAAGGUGUUCUUGUAC, AAGGUGUUCUUGUAC, UUCUGAAGGUGUUCUUGUA, UUCUGAAGGUGUUCUUGU, UUCUGAAGGUGUUCUUG, UUCUGAAGGUGUUCUU, UUCUGAAGGUGUUCU, UCUGAAGGUGUUCUUGUA, UCUGAAGGUGUUCUUGU, UCUGAAGGUGUUCUUG, UCUGAAGGUGUUCUU, CUGAAGGUGUUCUUGUA, CUGAAGGUGUUCUUGU, CUGAAGGUGUUCUUG, UGAAGGUGUUCUUGU, or UGAAGGUGUUCUUGUA, wherein each U can be optionally and independently replaced by T, and wherein the composition is optionally chirally controlled.

[0091] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition of an oligonucleotide selected from any of the Tables. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition of an oligonucleotide selected from any of the Tables, wherein the oligonucleotide is conjugated to a lipid or a targeting moiety.

[0092] In some embodiments, an oligonucleotide is at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 bases long, and optionally no more than 25, 30, 35, 40, 45, 50, 55, or 60 bases long. In some embodiments, an oligonucleotide is no more than 25 bases long. In some embodiments, an oligonucleotide is no more than 30 bases long. In some embodiments, an oligonucleotide is no more than 35 bases long. In some embodiments, an oligonucleotide is no more than 40 bases long. In some embodiments, an oligonucleotide is no more than 45 bases long. In some embodiments, an oligonucleotide is no more than 50 bases long. In some embodiments, an oligonucleotide is no more than 55 bases long. In some embodiments, an oligonucleotide is no more than 60 bases long. In some embodiments, each base is independently optionally substituted A, T, C, G, or U, or an optionally substituted tautomer of A, T, C, G, or U

[0093] In some embodiments, provided oligonucleotides comprise additional chemical moieties besides their oligonucleotide chains (oligonucleotide backbones and bases), e.g., lipid moieties, targeting moieties, etc. In some embodiments, a lipid is a fatty acid. In some embodiments, an oligonucleotide is conjugated to a fatty acid. In some embodiments, a fatty acid comprises 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more carbon atoms.

[0094] In some embodiments, a lipid is stearic acid or turbinaric acid. In some embodiments, a lipid is stearic acid acid. In some embodiments, a lipid is turbinaric acid.

[0095] In some embodiments, a lipid comprises an optionally substituted, C_{10}-C_{80}, C_{10}-C_{60}, or C_{10}-C_{40} saturated or partially unsaturated aliphatic group, wherein one or more methylene units are

optionally and independently replaced by C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C— , a C_1–C_6 heteroaliphatic moiety, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, and –C(O)O–, wherein each variable is independently as defined and described herein.

[0096] In some embodiments, a lipid is selected from the group consisting of: lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, docosahexaenoic acid (DHA or cis-DHA), turbinaric acid and dilinoleyl.

[0097] In some embodiments, a lipid is conjugated to an oligonucleotide chain, optionally through one or more linker moieties. In some embodiments, a lipid is not conjugated to an oligonucleotide chain.

[0098] In some embodiments, a provided oligonucleotide is conjugated, optionally through a linker, to a chemical moiety, e.g., a lipid moiety, a peptide moiety, a targeting moiety, a carbohydrate moiety, a sulfonamide moiety, an antibody or a fragment thereof. In some embodiments, a provided compound, e.g., an oligonucleotide, has the structure of:

A^c–[–L^{LD}–(R^{LD})$_a$]$_b$, A^c–[–L^M–(R^D)$_a$]$_b$, [(A^c)$_a$–L^M]$_b$–R^D, (A^c)$_a$–L^M–(A^c)$_b$, or (A^c)$_a$–L^M–(R^D)$_b$,

or a slat thereof, wherein:

A^c is an oligonucleotide chain (e.g., H–A^c, [H]$_a$–A^c or [H]$_b$–A^c is an oligonucleotide);

a is 1-1000;

b is 1-1000;

each of L^{LD} and L^M is independently a linker moiety;

R^{LD} is a lipid moiety; and

each R^D is independently a lipid moiety or a targeting moiety.

[0099] In some embodiments, a provided compound, e.g., an oligonucleotide, has the structure of:

A^c–[–L^{LD}–(R^{LD})$_a$]$_b$, A^c–[–L^M–(R^D)$_a$]$_b$, [(A^c)$_a$–L^M]$_b$–R^D, (A^c)$_a$–L^M–(A^c)$_b$, or (A^c)$_a$–L^M–(R^D)$_b$,

or a salt thereof, wherein:

A^c is an oligonucleotide chain (e.g., H–A^c, [H]$_a$–A^c or [H]$_b$–A^c is an oligonucleotide);

a is 1-1000;

b is 1-1000;

each R^D is independently R^{LD}, R^{CD} or R^{TD};

R^{CD} is an optionally substituted, linear or branched group selected from a C_{1-100} aliphatic group and a C_{1-100} heteroaliphatic group having 1-30 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6

heteroaliphatic group having 1-5 heteroatoms, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–; and one or more CH or carbon atoms are optionally and independently replaced with Cy^L;

R^{LD} is an optionally substituted, linear or branched C$_{1-100}$ aliphatic group wherein one or more methylene units are optionally and independently replaced with C$_{1-6}$ alkylene, C$_{1-6}$ alkenylene, —C≡C—, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–; and one or more CH or carbon atoms are optionally and independently replaced with Cy^L;

R^{TD} is a targeting moiety;

each of L^{LD} and L^M is independently a covalent bond, or a bivalent or multivalent, optionally substituted, linear or branched group selected from a C$_{1-100}$ aliphatic group and a C$_{1-100}$ heteroaliphatic group having 1-30 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C$_{1-6}$ alkylene, C$_{1-6}$ alkenylene, —C≡C—, a bivalent C$_1$–C$_6$ heteroaliphatic group having 1-5 heteroatoms, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–; and one or more CH or carbon atoms are optionally and independently replaced with Cy^L;

each –Cy– is independently an optionally substituted bivalent group selected from a C$_{3-20}$ cycloaliphatic ring, a C$_{6-20}$ aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Cy^L is independently an optionally substituted trivalent or tetravalent group selected from a C$_{3-20}$ cycloaliphatic ring, a C$_{6-20}$ aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each R' is independently −R, −C(O)R, −C(O)OR, or $-S(O)_2R$; and

each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

two R groups are optionally and independently taken together to form a covalent bond, or

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms, or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

[00100] In some embodiments, the present disclosure provides an oligonucleotide composition comprising a plurality of oligonucleotides each having the structure of:

$A^c-[-L^{LD}-(R^{LD})_a]_b$, $A^c-[-L^M-(R^D)_a]_b$, $[(A^c)_a-L^M]_b-R^D$, $(A^c)_a-L^M-(A^c)_b$, or $(A^c)_a-L^M-(R^D)_b$,

or a salt thereof.

[00101] In some embodiments, $[H]_b$-Ac (wherein b is 1-1000) is an oligonucleotide of any one of the Tables. In some embodiments, $[H]_b$-Ac is an oligonucleotide of Table A1.

[00102] In some embodiments, a is 1-100. In some embodiments, a is 1-50. In some embodiments, a is 1-40. In some embodiments, a is 1-30. In some embodiments, a is 1-20. In some embodiments, a is 1-15. In some embodiments, a is 1-10. In some embodiments, a is 1-9. In some embodiments, a is 1-8. In some embodiments, a is 1-7. In some embodiments, a is 1-6. In some embodiments, a is 1-5. In some embodiments, a is 1-4. In some embodiments, a is 1-3. In some embodiments, a is 1-2. In some embodiments, a is 1. In some embodiments, a is 2. In some embodiments, a is 3. In some embodiments, a is 4. In some embodiments, a is 5. In some embodiments, a is 6. In some embodiments, a is 7. In some embodiments, a is 8. In some embodiments, a is 9. In some embodiments, a is 10. In some embodiments, a is more than 10. In some embodiments, b is 1-100. In some embodiments, b is 1-50. In some embodiments, b is 1-40. In some embodiments, b is 1-30. In some embodiments, b is 1-20. In some embodiments, b is 1-15. In some embodiments, b is 1-10. In some embodiments, b is 1-9. In some embodiments, b is 1-8. In some embodiments, b is 1-7. In some embodiments, b is 1-6. In some embodiments, b is 1-5. In some embodiments, b is 1-4. In some embodiments, b is 1-3. In some embodiments, b is 1-2. In some embodiments, b is 1. In some embodiments, b is 2. In some embodiments, b is 3. In some embodiments, b is 4. In some embodiments, b is 5. In some embodiments, b is 6. In some embodiments, b is 7. In some embodiments, b is 8. In

some embodiments, b is 9. In some embodiments, b is 10. In some embodiments, b is more than 10. In some embodiments, an oligonucleotide has the structure of A^c–L^{LD}–R^{LD}. In some embodiments, A^c is conjugated through one or more of its sugar, base and/or internucleotidic linkage moieties. In some embodiments, A^c is conjugated through its 5'-OH (5'-O-). In some embodiments, A^c is conjugated through its 3'-OH (3'-O-). In some embodiments, before conjugation, A^c-$(H)_b$ (b is an integer of 1-1000 depending on valency of A^c) is an oligonucleotide as described herein, for example, one of those described in any one of the Tables. In some embodiments, L^M is –L–. In some embodiments, L^M comprises a phosphorothioate group. In some embodiments, L^M is $-C(O)NH-(CH_2)_6-OP(=O)(S^-)-O-$. In some embodiments, the –C(O)NH end is connected to R^{LD}, and the –O– end is connected to the oligonucleotide, *e.g.*, through 5'- or 3'-end. In some embodiments, R^{LD} is optionally substituted C_{10}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, or C_{25} to C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, C_{25}, C_{26}, C_{27}, C_{28}, C_{29}, C_{30}, C_{35}, C_{40}, C_{45}, C_{50}, C_{60}, C_{70}, or C_{80} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-80} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-80} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-70} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-70} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-60} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-60} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-50} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-50} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-40} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-40} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-30} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-30} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, or C_{25} to C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, C_{25}, C_{26}, C_{27}, C_{28}, C_{29}, C_{30}, C_{35}, C_{40}, C_{45}, C_{50}, C_{60}, C_{70}, or C_{80} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-80} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-80} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-70} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-70} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-60} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-60} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-50} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-50} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-40} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-40} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-30} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-30} aliphatic.

[00103] In some embodiments, incorporation of a lipid moiety into an oligonucleotide improves at least one property of the oligonucleotide compared to an otherwise identical oligonucleotide without the lipid moiety. In some embodiments, improved properties include increased activity (*e.g.*, increased ability to induce desirable skipping of a deleterious exon), decreased toxicity, and/or improved distribution to a tissue. In some embodiments, a tissue is muscle tissue. In some embodiments, a tissue is

skeletal muscle, gastrocnemius, triceps, heart or diaphragm. In some embodiments, improved properties include reduced hTLR9 agonist activity. In some embodiments, improved properties include hTLR9 antagonist activity. In some embodiments, improved properties include increased hTLR9 antagonist activity.

[00104] In some embodiments, an oligonucleotide or oligonucleotide composition is: a DMD oligonucleotide or oligonucleotide composition; an oligonucleotide or oligonucleotide composition comprising a non-negatively charged internucleotidic linkage; or a DMD oligonucleotide comprising a non-negatively charged internucleotidic linkage.

[00105] In some embodiments, the present disclosure pertains to a composition comprising an a DMD oligonucleotide comprising at least one chirally controlled phosphorothioate internucleotidic linkage in the Rp or Sp configuration, at least one natural phosphate internucleotidic linkage, and at least one non-negatively charged internucleotidic linkage. In some embodiments, the present disclosure pertains to a composition comprising an a DMD oligonucleotide comprising at least one phosphorothioate internucleotidic linkage, at least one natural phosphate internucleotidic linkage, and at least one non-negatively charged internucleotidic linkage. In some embodiments, the present disclosure pertains to a composition comprising an a DMD oligonucleotide comprising at least one phosphorothioate internucleotidic linkage, at least one natural phosphate internucleotidic linkage, and at least one chirally controlled non-negatively charged internucleotidic linkage. In some embodiments, the present disclosure pertains to a composition comprising an a DMD oligonucleotide comprising at least one chirally controlled phosphorothioate internucleotidic linkage in the Rp or Sp configuration, at least one natural phosphate internucleotidic linkage, and at least one chirally controlled non-negatively charged internucleotidic linkage.

[00106] In some embodiments, a DMD oligonucleotide (e.g., an oligonucleotide whose base sequence contains no more than 5, 4, 3, 2, or 1 mismatches when hybridizing to a portion of a DMD transcript or a DMD genetic sequence having the same length) is capable of mediating skipping of one or more exons of the Dystrophin transcript.

[00107] In some embodiments, a DMD oligonucleotide has a base sequence which consists of the base sequence of an example oligonucleotide disclosed herein (e.g., an oligonucleotide listed in a Table), or a base sequence which comprises a 15-base portion of an example oligonucleotide nucleotide described herein. In some embodiments, a DMD oligonucleotide has a length of 15 to 50 bases.

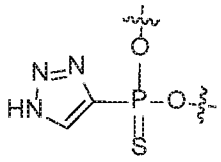
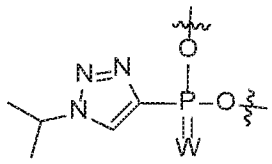
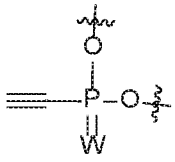
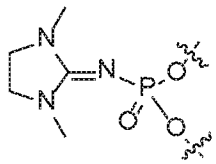
[00108] In some embodiments, an oligonucleotide comprises a nucleobase modification, a sugar modification, and/or an internucleotidic linkage. In some embodiments, a DMD oligonucleotide has a pattern of nucleobase modifications, sugar modifications, and/or internucleotidic linkages of an example oligonucleotide described herein (or any portion thereof having a length of at least 5 bases).

[00109] In some embodiments, an oligonucleotide comprises a nucleobase modification which is BrU.

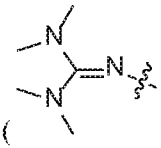
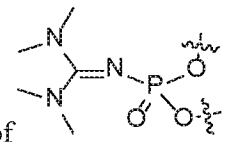
[00110] In some embodiments, an oligonucleotide comprises a sugar modification which is 2'-OMe, 2'-F, 2'-MOE, or LNA.

[00111] In some embodiments, an oligonucleotide comprises an internucleotidic linkage which is a natural phosphate linkage or a phosphorothioate internucleotidic linkage. In some embodiments, a phosphorothioate internucleotidic linkage is not chirally controlled. In some embodiments, a phosphorothioate internucleotidic linkage is a chirally controlled internucleotidic linkage (e.g., Sp or Rp).

[00112] In some embodiments, an oligonucleotide comprises a non-negatively charged internucleotidic linkage. In some embodiments, a DMD oligonucleotide comprises a neutral internucleotidic linkage. In some embodiments, a neutral internucleotidic linkage is or comprises a triazole, alkyne, or cyclic guanidine moiety.

[00113] In some embodiments, an internucleotidic linkage comprising a triazole moiety (e.g., an optionally substituted triazolyl group) in a provided oligonucleotide, e.g., a DMD oligonucleotide, has the structure of:  . In some embodiments, an internucleotidic linkage comprising a triazole moiety has the formula of  , where W is O or S. In some embodiments, an internucleotidic linkage comprising an alkyne moiety (e.g., an optionally substituted alkynyl group) has the formula of:  , wherein W is O or S. In some embodiments, an internucleotidic linkage comprises a guanidine moiety. In some embodiments, an internucleotidic linkage comprises a cyclic guanidine moiety. In some embodiments, an internucleotidic linkage comprising a cyclic guanidine moiety has the structure of:  . In some embodiments, a neutral internucleotidic linkage or internucleotidic linkage comprising a cyclic guanidine moiety is stereochemically controlled.

[00114] In some embodiments, a DMD oligonucleotide comprises a lipid moiety In some

embodiments, an internucleotidic linkage comprises a Tmg group (). In some embodiments, an internucleotidic linkage comprises a Tmg group and has the structure of  (the "Tmg internucleotidic linkage"). In some embodiments, neutral internucleotidic linkages include internucleotidic linkages of PNA and PMO, and an Tmg internucleotidic linkage.

[00115] In general, properties of oligonucleotide compositions as described herein can be assessed using any appropriate assay. Relative toxicity and/or protein binding properties for different compositions (*e.g.*, stereocontrolled vs non-stereocontrolled, and/or different stereocontrolled compositions) are typically desirably determined in the same assay, in some embodiments substantially simultaneously and in some embodiments with reference to historical results.

[00116] Those of skill in the art will be aware of and/or will readily be able to develop appropriate assays for particular oligonucleotide compositions. The present disclosure provides descriptions of certain particular assays, for example that may be useful in assessing one or more features of oligonucleotide composition behavior *e.g.*, complement activation, injection site inflammation, protein biding, *etc.*

[00117] For example, certain assays that may be useful in the assessment of toxicity and/or protein binding properties of oligonucleotide compositions may include any assay described and/or exemplified herein.

[00118] Among other things, in some embodiments, the present disclosure provides an oligonucleotide composition, comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

wherein:

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 chirally controlled internucleotidic linkages; and

the oligonucleotide composition being characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under a

reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[00119] In some embodiments, the present disclosure provides a composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

which composition is chirally controlled and it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same base sequence, pattern of backbone linkages and pattern of backbone phosphorus modifications, for oligonucleotides of the particular oligonucleotide type, wherein:

the oligonucleotide composition is characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered in that level of skipping of an exon is increased relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[00120] In some embodiments, the present disclosure provides a composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages; and

3) pattern of backbone phosphorus modifications,

wherein:

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 non-negatively charged internucleotidic linkages;

the oligonucleotide composition is characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered in that level of skipping of an exon is increased relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[00121] In some embodiments, the present disclosure provides a composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages; and

3) pattern of backbone phosphorus modifications,

wherein:

oligonucleotides of the plurality comprise:

1) a 5'-end region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleoside units comprising a 2'-F modified sugar moiety;

2) a 3'-end region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleoside units comprising a 2'-F modified sugar moiety; and

3) a middle region between the 5'-end region and the 3'-region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleotidic units comprising a phosphodiester linkage.

[00122] In some embodiments, the present disclosure provides a composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

wherein:

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 chirally controlled internucleotidic linkages; and

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 non-negatively charged internucleotidic linkages.

[00123] In some embodiments, the present disclosure provides a composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

wherein:

the oligonucleotides of the plurality comprise cholesterol; L-carnitine (amide and carbamate bond); Folic acid; Cleavable lipid (1,2-dilaurin and ester bond); Insulin receptor ligand; Gambogic acid; CPP; Glucose (tri- and hex-antennary); or Mannose (tri- and hex-antennary, alpha and beta).

[00124] In some embodiments, the present disclosure provides a pharmaceutical composition comprising an oligonucleotide or an oligonucleotide composition of the present disclosure and a pharmaceutically acceptable carrier.

[00125] In some embodiments, the present disclosure provides a method for altering splicing of a target transcript, comprising administering an oligonucleotide composition of the present disclosure. In some embodiments, the present disclosure provides a method for reducing level of a transcript or a

product thereof, comprising administering an oligonucleotide composition of the present disclosure. In some embodiments, the present disclosure provides a method for increase level of a transcript or a product thereof, comprising administering an oligonucleotide composition of the present disclosure. A method for treating muscular dystrophy, Duchenne (Duchenne's) muscular dystrophy (DMD), or Becker (Becker's) muscular dystrophy (BMD), comprising administering to a subject susceptible thereto or suffering therefrom a composition described in the present disclosure.

[00126] In some embodiments, the present disclosure provides a method for treating muscular dystrophy, Duchenne (Duchenne's) muscular dystrophy (DMD), or Becker (Becker's) muscular dystrophy (BMD), comprising administering to a subject susceptible thereto or suffering therefrom a composition comprising any DMD oligonucleotide disclosed herein.

[00127] In some embodiments, the present disclosure provides a method for treating muscular dystrophy, Duchenne (Duchenne's) muscular dystrophy (DMD), or Becker (Becker's) muscular dystrophy (BMD), comprising (a) administering to a subject susceptible thereto or suffering therefrom a composition comprising any oligonucleotide disclosed herein, and (b) administering to the subject additional treatment which is capable of preventing, treating, ameliorating or slowing the progress of muscular dystrophy, Duchenne (Duchenne's) muscular dystrophy (DMD), or Becker (Becker's) muscular dystrophy (BMD).

BRIEF DESCRIPTION OF THE DRAWINGS

[00128] *Figure 1.* Figure 1 shows an example of multiple exon skipping.

[00129] *Figure 2.* Figure 2 shows a cartoon of a method for detecting multiple exon skipping.

[00130] *Figure 3.* Figure 3 illustrates various strategies for multiple exon skipping.

DEFINITIONS

[00131] As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001.

[00132] *Aliphatic*: The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic or polycyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but

which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or "cycloalkyl"), or combinations thereof. In some embodiments, aliphatic groups contain 1-100 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-20 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-9 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-7 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1, 2, 3, or 4 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic or bicyclic or polycyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3–C_6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[00133] *Alkenyl*: As used herein, the term "alkenyl" refers to an aliphatic group, as defined herein, having one or more double bonds.

[00134] *Alkyl*: As used herein, the term "alkyl" is given its ordinary meaning in the art and may include saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In some embodiments, an alkyl has 1-100 carbon atoms. In certain embodiments, a straight chain or branched chain alkyl has about 1-20 carbon atoms in its backbone (e.g., C_1-C_{20} for straight chain, C_2-C_{20} for branched chain), and alternatively, about 1-10. In some embodiments, cycloalkyl rings have from about 3-10 carbon atoms in their ring structure where such rings are monocyclic, bicyclic, or polycyclic, and alternatively about 5, 6 or 7 carbons in the ring structure. In some embodiments, an alkyl group may be a lower alkyl group, wherein a lower alkyl group comprises 1-4 carbon atoms (e.g., C_1-C_4 for straight chain lower alkyls).

[00135] Alkynyl: As used herein, the term "alkynyl" refers to an aliphatic group, as defined herein, having one or more triple bonds.

[00136] *Animal*: As used herein, the term "animal" refers to any member of the animal kingdom. In some embodiments, "animal" refers to humans, at any stage of development. In some embodiments, "animal" refers to non-human animals, at any stage of development. In certain embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, and/or a pig). In some embodiments, animals include, but are not limited to, mammals, birds,

reptiles, amphibians, fish, and/or worms. In some embodiments, an animal may be a transgenic animal, a genetically-engineered animal, and/or a clone.

[00137] *Approximately:* As used herein, the terms "approximately" or "about" in reference to a number are generally taken to include numbers that fall within a range of 5%, 10%, 15%, or 20% in either direction (greater than or less than) of the number unless otherwise stated or otherwise evident from the context (except where such number would be less than 0% or exceed 100% of a possible value). In some embodiments, use of the term "about" in reference to dosages means ± 5 mg/kg/day.

[00138] *Aryl:* The term "aryl", as used herein, used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic, bicyclic or polycyclic ring systems having a total of, *e.g.*, five to thirty ring members, wherein at least one ring in the system is aromatic. In some embodiments, an aryl group is a monocyclic, bicyclic or polycyclic ring system having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, and wherein each ring in the system contains 3 to 7 ring members. In some embodiments, an aryl group is a biaryl group. The term "aryl" may be used interchangeably with the term "aryl ring." In certain embodiments of the present disclosure, "aryl" refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, binaphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl," as it is used herein, is an aromatic ring fused to one or more non–aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[00139] *Characteristic sequence*: A "characteristic sequence" is a sequence that is found in all members of a family of polypeptides or nucleic acids, and therefore can be used by those of ordinary skill in the art to define members of the family.

[00140] *Comparable:* The term "comparable" is used herein to describe two (or more) sets of conditions or circumstances that are sufficiently similar to one another to permit comparison of results obtained or phenomena observed. In some embodiments, comparable sets of conditions or circumstances are characterized by a plurality of substantially identical features and one or a small number of varied features. Those of ordinary skill in the art will appreciate that sets of conditions are comparable to one another when characterized by a sufficient number and type of substantially identical features to warrant a reasonable conclusion that differences in results obtained or phenomena observed under the different sets of conditions or circumstances are caused by or indicative of the variation in those features that are varied.

[00141] *Cycloaliphatic*: The term "cycloaliphatic," "carbocycle," "carbocyclyl," "carbocyclic radical," and "carbocyclic ring," are used interchangeably, and as used herein, refer to saturated or partially unsaturated, but non-aromatic, cyclic aliphatic monocyclic, bicyclic, or polycyclic ring systems,

as described herein, having, unless otherwise specified, from 3 to 30 ring members. Cycloaliphatic groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, norbornyl, adamantyl, and cyclooctadienyl. In some embodiments, a cycloaliphatic group has 3–6 carbons. In some embodiments, a cycloaliphatic group is saturated and is cycloalkyl. The term "cycloaliphatic" may also include aliphatic rings that are fused to one or more aromatic or nonaromatic rings, such as decahydronaphthyl or 1,2,3,4-tetrahydronaphth-1-yl. In some embodiments, a cycloaliphatic group is bicyclic. In some embodiments, a cycloaliphatic group is tricyclic. In some embodiments, a cycloaliphatic group is polycyclic. In some embodiments, "cycloaliphatic" refers to C_3-C_6 monocyclic hydrocarbon, or C_8-C_{10} bicyclic or polycyclic hydrocarbon, that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, or a C_9-C_{16} polycyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic.

[00142] *Dosing regimen:* As used herein, a "dosing regimen" or "therapeutic regimen" refers to a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by periods of time. In some embodiments, a given therapeutic agent has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which are separated from one another by a time period of the same length; in some embodiments, a dosing regime comprises a plurality of doses and at least two different time periods separating individual doses. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from the first dose amount. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount same as the first dose amount.

[00143] *Heteroaliphatic*: The term "heteroaliphatic" refers to an aliphatic group wherein one or more units selected from C, CH, CH_2, and CH_3 are independently replaced by one or more heteroatoms. In some embodiments, a heteroaliphatic group is heteroalkyl. In some embodiments, a heteroaliphatic group is heteroalkenyl.

[00144] *Heteroaryl*: The terms "heteroaryl" and "heteroar–", as used herein, used alone or as part of a larger moiety, e.g., "heteroaralkyl," or "heteroaralkoxy," refer to monocyclic, bicyclic or polycyclic ring systems having a total of, e.g., five to thirty ring members, wherein at least one ring in the system is aromatic and at least one aromatic ring atom is a heteroatom. In some embodiments, a heteroaryl group is a group having 5 to 10 ring atoms (i.e., monocyclic, bicyclic or polycyclic), in some embodiments 5, 6, 9, or 10 ring atoms. In some embodiments, a heteroaryl group has 6, 10, or 14 π electrons shared in a cyclic

array; and having, in addition to carbon atoms, from one to five heteroatoms. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. In some embodiments, a heteroaryl is a heterobiaryl group, such as bipyridyl and the like. The terms "heteroaryl" and "heteroar–", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Non-limiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H–quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3–b]–1,4–oxazin–3(4H)–one. A heteroaryl group may be monocyclic, bicyclic or polycyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring," "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl group, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[00145] *Heteroatom*: The term "heteroatom" means an atom that is not carbon or hydrogen. In some embodiments, a heteroatom is oxygen, sulfur, nitrogen, phosphorus, boron or silicon (including any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or a substitutable nitrogen of a heterocyclic ring (for example, N as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl); *etc.*). In some embodiments, a heteroatom is boron, nitrogen, oxygen, silicon, sulfur, or phosphorus. In some embodiments, a heteroatom is nitrogen, oxygen, silicon, sulfur, or phosphorus. In some embodiments, a heteroatom is nitrogen, oxygen, sulfur, or phosphorus. In some embodiments, a heteroatom is nitrogen, oxygen or sulfur.

[00146] *Heterocycle*: As used herein, the terms "heterocycle," "heterocyclyl," "heterocyclic radical," and "heterocyclic ring", as used herein, are used interchangeably and refer to a monocyclic, bicyclic or polycyclic ring moiety (e.g., 3-30 membered) that is saturated or partially unsaturated and has one or more heteroatom ring atoms. In some embodiments, a heterocyclyl group is a stable 5– to 7–membered monocyclic or 7– to 10–membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur and nitrogen, the nitrogen may be N (as in 3,4–dihydro–2H–pyrrolyl), NH (as in pyrrolidinyl), or $^+$NR (as in N–substituted pyrrolidinyl). A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any

of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms "heterocycle," "heterocyclyl," "heterocyclyl ring," "heterocyclic group," "heterocyclic moiety," and "heterocyclic radical," are used interchangeably herein, and also include heterocyclyl rings fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3H–indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl. A heterocyclyl group may be monocyclic, bicyclic or polycyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[00147] *Intraperitoneal:* The phrases "intraperitoneal administration" and "administered intraperitonealy" as used herein have their art-understood meaning referring to administration of a compound or composition into the peritoneum of a subject.

[00148] *In vitro*: As used herein, the term "*in vitro*" refers to events that occur in an artificial environment, *e.g.*, in a test tube or reaction vessel, in cell culture, *etc.*, rather than within an organism (*e.g.*, animal, plant, and/or microbe).

[00149] *In vivo:* As used herein, the term "*in vivo*" refers to events that occur within an organism (*e.g.*, animal, plant, and/or microbe).

[00150] *Lower alkyl:* The term "lower alkyl" refers to a C_{1-4} straight or branched alkyl group. Example lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[00151] *Lower haloalkyl:* The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

[00152] *Optionally substituted:* As described herein, compounds of the disclosure, e.g., oligonucleotides, lipids, carbohydrates, etc., may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[00153] Suitable monovalent substituents are halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; –CH=CHPh, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; –CN; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)N(R^\circ)_2$; $-N(R^\circ)C(S)N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)N(R^\circ)_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSi(R^\circ)_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$, $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)N(R^\circ)_2$; $-C(S)N(R^\circ)_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)N(R^\circ)_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2N(R^\circ)_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2N(R^\circ)_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)N(R^\circ)_2$; $-Si(R^\circ)_3$; $-OSi(R^\circ)_3$; $-P(R^\circ)_2$; $-P(OR^\circ)_2$; $-P(R^\circ)(OR^\circ)$; $-OP(R^\circ)_2$; $-OP(OR^\circ)_2$; $-OP(R^\circ)(OR^\circ)$; $-P[N(R^\circ)_2]_2$ $-P(R^\circ)[N(R^\circ)_2]$; $-P(OR^\circ)[N(R^\circ)_2]$; $-OP[N(R^\circ)_2]_2$; $-OP(R^\circ)[N(R^\circ)_2]$; $-OP(OR^\circ)[N(R^\circ)_2]$; $-N(R^\circ)P(R^\circ)_2$; $-N(R^\circ)P(OR^\circ)_2$; $-N(R^\circ)P(R^\circ)(OR^\circ)$; $-N(R^\circ)P[N(R^\circ)_2]_2$; $-N(R^\circ)P(R^\circ)[N(R^\circ)_2]$; $-N(R^\circ)P(OR^\circ)[N(R^\circ)_2]$; $-B(R^\circ)_2$; $-B(R^\circ)(OR^\circ)$; $-B(OR^\circ)_2$; $-OB(R^\circ)_2$; $-OB(R^\circ)(OR^\circ)$; $-OB(OR^\circ)_2$; $-P(O)(R^\circ)_2$; $-P(O)(R^\circ)(OR^\circ)$; $-P(O)(R^\circ)(SR^\circ)$; $-P(O)(R^\circ)[N(R^\circ)_2]$; $-P(O)(OR^\circ)_2$; $-P(O)(SR^\circ)_2$; $-P(O)(OR^\circ)[N(R^\circ)_2]$; $-P(O)(SR^\circ)[N(R^\circ)_2]$; $-P(O)(OR^\circ)(SR^\circ)$; $-P(O)[N(R^\circ)_2]_2$; $-OP(O)(R^\circ)_2$; $-OP(O)(R^\circ)(OR^\circ)$; $-OP(O)(R^\circ)(SR^\circ)$; $-OP(O)(R^\circ)[N(R^\circ)_2]$; $-OP(O)(OR^\circ)_2$; $-OP(O)(SR^\circ)_2$; $-OP(O)(OR^\circ)[N(R^\circ)_2]$; $-OP(O)(SR^\circ)[N(R^\circ)_2]$; $-OP(O)(OR^\circ)(SR^\circ)$; $-OP(O)[N(R^\circ)_2]_2$; $-SP(O)(R^\circ)_2$; $-SP(O)(R^\circ)(OR^\circ)$; $-SP(O)(R^\circ)(SR^\circ)$; $-SP(O)(R^\circ)[N(R^\circ)_2]$; $-SP(O)(OR^\circ)_2$; $-SP(O)(SR^\circ)_2$; $-SP(O)(OR^\circ)[N(R^\circ)_2]$; $-SP(O)(SR^\circ)[N(R^\circ)_2]$; $-SP(O)(OR^\circ)(SR^\circ)$; $-SP(O)[N(R^\circ)_2]_2$; $-N(R^\circ)P(O)(R^\circ)_2$; $-N(R^\circ)P(O)(R^\circ)(OR^\circ)$; $-N(R^\circ)P(O)(R^\circ)(SR^\circ)$; $-N(R^\circ)P(O)(R^\circ)[N(R^\circ)_2]$; $-N(R^\circ)P(O)(OR^\circ)_2$; $-N(R^\circ)P(O)(SR^\circ)_2$; $-N(R^\circ)P(O)(OR^\circ)[N(R^\circ)_2]$; $-N(R^\circ)P(O)(SR^\circ)[N(R^\circ)_2]$; $-N(R^\circ)P(O)(OR^\circ)(SR^\circ)$; $-N(R^\circ)P(O)[N(R^\circ)_2]_2$; $-P(R^\circ)_2[B(R^\circ)_3]$; $-P(OR^\circ)_2[B(R^\circ)_3]$; $-P(NR^\circ)_2[B(R^\circ)_3]$; $-P(R^\circ)(OR^\circ)[B(R^\circ)_3]$; $-P(R^\circ)[N(R^\circ)_2][B(R^\circ)_3]$; $-P(OR^\circ)[N(R^\circ)_2][B(R^\circ)_3]$; $-OP(R^\circ)_2[B(R^\circ)_3]$; $-OP(OR^\circ)_2[B(R^\circ)_3]$; $-OP(NR^\circ)_2[B(R^\circ)_3]$; $-OP(R^\circ)(OR^\circ)[B(R^\circ)_3]$; $-OP(R^\circ)[N(R^\circ)_2][B(R^\circ)_3]$; $-OP(OR^\circ)[N(R^\circ)_2][B(R^\circ)_3]$; $-N(R^\circ)P(R^\circ)_2[B(R^\circ)_3]$; $-N(R^\circ)P(OR^\circ)_2[B(R^\circ)_3]$; $-N(R^\circ)P(NR^\circ)_2[B(R^\circ)_3]$; $-N(R^\circ)P(R^\circ)(OR^\circ)[B(R^\circ)_3]$; $-N(R^\circ)P(R^\circ)[N(R^\circ)_2][B(R^\circ)_3]$; $-N(R^\circ)P(OR^\circ)[N(R^\circ)_2][B(R^\circ)_3]$; $-P(OR')[B(R')_3]-$; $-(C_{1-4}$ straight or branched alkylene)$O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-20} aliphatic, C_{1-20} heteroaliphatic having 1–5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus, $-CH_2-(C_{6-20}$ aryl), $-O(CH_2)_{0-1}(C_{6-20}$ aryl), $-CH_2-$(5-20 membered heteroaryl ring having 1–5 heteroatoms

independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus), a 5–20 membered, monocyclic, bicyclic, or polycyclic, saturated, partially unsaturated or aryl ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–20 membered, monocyclic, bicyclic, or polycyclic, saturated, partially unsaturated or aryl ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus, which may be substituted as defined below.

[00154] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^{\bullet}$, –(haloR•), $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^{\bullet}$, $-(CH_2)_{0-2}CH(OR^{\bullet})_2$; –O(haloR•), –CN, $-N_3$, $-(CH_2)_{0-2}C(O)R^{\bullet}$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^{\bullet}$, $-(CH_2)_{0-2}SR^{\bullet}$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^{\bullet}$, $-(CH_2)_{0-2}NR^{\bullet}_2$, $-NO_2$, $-SiR^{\bullet}_3$, $-OSiR^{\bullet}_3$, -C(O)SR•, –(C_{1-4} straight or branched alkylene)C(O)OR•, or –SSR• wherein each R• is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, and a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[00155] Suitable divalent substituents, e.g., on a suitable carbon atom, nitrogen atom, are independently the following: =O, =S, $=CR^{*}_2$, $=NNR^{*}_2$, $=NNHC(O)R^{*}$, $=NNHC(O)OR^{*}$, $=NNHS(O)_2R^{*}$, $=NR^{*}$, $=NOR^{*}$, $-O(C(R^{*}_2))_{2-3}O-$, or $-S(C(R^{*}_2))_{2-3}S-$, wherein each R* may be substituted as defined below and is independently hydrogen, C_{1-20} aliphatic, C_{1-20} heteroaliphatic having 1–5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus, $-CH_2-(C_{6-20}$ aryl), $-O(CH_2)_{0-1}(C_{6-20}$ aryl), –CH_2-(5-20 membered heteroaryl ring having 1–5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus), a 5–20 membered, monocyclic, bicyclic, or polycyclic, saturated, partially unsaturated or aryl ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus, or, notwithstanding the definition above, two independent occurrences of R*, taken together with their intervening atom(s), form a 3–20 membered, monocyclic, bicyclic, or polycyclic, saturated, partially unsaturated or aryl ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus, which may be substituted as defined below. Suitable divalent substituents that are bound to vicinal substitutable atoms of an "optionally substituted" group include: $-O(CR^{*}_2)_{2-3}O-$.

[00156] Suitable monovalent substituents on R* (or the ring formed by taking two independent occurrences of R* together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^{\bullet}$, –(haloR•), $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^{\bullet}$, $-(CH_2)_{0-2}CH(OR^{\bullet})_2$; –O(haloR•), –CN, $-N_3$, $-(CH_2)_{0-2}C(O)R^{\bullet}$, –

$(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^{\bullet}$, $-(CH_2)_{0-2}SR^{\bullet}$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^{\bullet}$, $-(CH_2)_{0-2}NR^{\bullet}_2$, $-NO_2$, $-SiR^{\bullet}_3$, $-OSiR^{\bullet}_3$, $-C(O)SR^{\bullet}$, $-(C_{1-4}$ straight or branched alkylene$)C(O)OR^{\bullet}$, or $-SSR^{\bullet}$ wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, and a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Suitable divalent substituents on a saturated carbon atom of R^* include =O and =S.

[00157] In some embodiments, suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^{\dagger}$, $-NR^{\dagger}_2$, $-C(O)R^{\dagger}$, $-C(O)OR^{\dagger}$, $-C(O)C(O)R^{\dagger}$, $-C(O)CH_2C(O)R^{\dagger}$, $-S(O)_2R^{\dagger}$, $-S(O)_2NR^{\dagger}_2$, $-C(S)NR^{\dagger}_2$, $-C(NH)NR^{\dagger}_2$, or $-N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each $R^{\dagger}$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5-6 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3-12 membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00158] In some embodiments, suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, $-R^{\bullet}$, -(halo$R^{\bullet}$), $-OH$, $-OR^{\bullet}$, $-O$(halo$R^{\bullet}$), $-CN$, $-C(O)OH$, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6 membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00159] *Oral:* The phrases "oral administration" and "administered orally" as used herein have their art-understood meaning referring to administration by mouth of a compound or composition.

[00160] *Parenteral:* The phrases "parenteral administration" and "administered parenterally" as used herein have their art-understood meaning referring to modes of administration other than enteral and topical administration, usually by injection, and include, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal, and intrasternal injection and infusion.

[00161] *Partially unsaturated:* As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[00162] *Pharmaceutical composition:* As used herein, the term "pharmaceutical composition" refers to an active agent, formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, active agent is present in unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a controlled therapeutic effect when administered to a relevant population. In some embodiments, pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, *e.g.*, those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

[00163] *Pharmaceutically acceptable:* As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00164] *Pharmaceutically acceptable carrier:* As used herein, the term "pharmaceutically acceptable carrier" means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in pharmaceutical formulations.

[00165] *Pharmaceutically acceptable salt:* The term "pharmaceutically acceptable salt", as used herein, refers to salts of such compounds that are appropriate for use in pharmaceutical contexts, i.e., salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). In some embodiments, pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts, which are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. In some embodiments, pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. In some embodiments, pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate. In some embodiments, a provided compound comprises one or more acidic groups, e.g., an oligonucleotide, and a pharmaceutically acceptable salt is an alkali, alkaline earth metal, or ammonium (e.g., an ammonium salt of $N(R)_3$, wherein each R is independently as defined and described in the present disclosure) salt. Representative alkali or alkaline earth metal salts include salts of sodium, lithium, potassium, calcium, magnesium, and the like. In some embodiments, a pharmaceutically acceptable salt is a sodium salt. In some embodiments, a pharmaceutically acceptable salt is a potassium salt. In some embodiments, a pharmaceutically acceptable salt is a calcium salt. In some embodiments, pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate. In some embodiments, a provided compound comprises more than one acid groups, for example, a provided

oligonucleotide may comprise two or more acidic groups (e.g., in natural phosphate linkages and/or modified internucleotidic linkages). In some embodiments, a pharmaceutically acceptable salt, or generally a salt, of such a compound comprises two or more cations, which can be the same or different. In some embodiments, in a pharmaceutically acceptable salt (or generally, a salt), each acidic group having sufficient acidity independently exists as its salt form (e.g., in an oligonucleotide comprising natural phosphate linkages and phosphorothioate internucleotidic linkages, each of the natural phosphate linkages and phosphorothioate internucleotidic linkages independently exists as its salt form). In some embodiments, a pharmaceutically acceptable salt of an oligonucleotide is a sodium salt of a provided oligonucleotide. In some embodiments, a pharmaceutically acceptable salt of an oligonucleotide is a sodium salt of a provided oligonucleotide, wherein each acidic linkage, e.g., each natural phosphate linkage and phosphorothioate internucleotidic linkage, exists as a sodium salt form (all sodium salt).

[00166] *Protecting group:* The term "protecting group," as used herein, is well known in the art and includes those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of which is incorporated herein by reference. Also included are those protecting groups specially adapted for nucleoside and nucleotide chemistry, e.g., those described in *Current Protocols in Nucleic Acid Chemistry*, edited by Serge L. Beaucage *et al.* 06/2012, the entirety of Chapter 2 is incorporated herein by reference. Suitable amino–protecting groups include methyl carbamate, ethyl carbamante, 9–fluorenylmethyl carbamate (Fmoc), 9–(2–sulfo)fluorenylmethyl carbamate, 9–(2,7–dibromo)fluoroenylmethyl carbamate, 2,7–di–*t*–butyl–[9–(10,10–dioxo–10,10,10,10–tetrahydrothioxanthyl)]methyl carbamate (DBD–Tmoc), 4–methoxyphenacyl carbamate (Phenoc), 2,2,2–trichloroethyl carbamate (Troc), 2–trimethylsilylethyl carbamate (Teoc), 2–phenylethyl carbamate (hZ), 1–(1–adamantyl)–1–methylethyl carbamate (Adpoc), 1,1–dimethyl–2–haloethyl carbamate, 1,1–dimethyl–2,2–dibromoethyl carbamate (DB–*t*–BOC), 1,1–dimethyl–2,2,2–trichloroethyl carbamate (TCBOC), 1–methyl–1–(4–biphenylyl)ethyl carbamate (Bpoc), 1–(3,5–di–*t*–butylphenyl)–1–methylethyl carbamate (*t*–Bumeoc), 2–(2'– and 4'–pyridyl)ethyl carbamate (Pyoc), 2–(*N,N*–dicyclohexylcarboxamido)ethyl carbamate, *t*–butyl carbamate (BOC), 1–adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1–isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4–nitrocinnamyl carbamate (Noc), 8–quinolyl carbamate, *N*–hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), *p*–methoxybenzyl carbamate (Moz), *p*–nitobenzyl carbamate, *p*–bromobenzyl carbamate, *p*–chlorobenzyl carbamate, 2,4–dichlorobenzyl carbamate, 4–methylsulfinylbenzyl carbamate (Msz), 9–anthrylmethyl carbamate, diphenylmethyl carbamate, 2–methylthioethyl carbamate, 2–methylsulfonylethyl carbamate, 2–(*p*–toluenesulfonyl)ethyl carbamate, [2–(1,3–dithianyl)]methyl carbamate (Dmoc), 4–methylthiophenyl carbamate (Mtpc), 2,4–dimethylthiophenyl carbamate (Bmpc), 2–phosphonioethyl carbamate (Peoc), 2–

triphenylphosphonioisopropyl carbamate (Ppoc), 1,1–dimethyl–2–cyanoethyl carbamate, *m*–chloro–*p*–acyloxybenzyl carbamate, *p*–(dihydroxyboryl)benzyl carbamate, 5–benzisoxazolylmethyl carbamate, 2–(trifluoromethyl)–6–chromonylmethyl carbamate (Tcroc), *m*–nitrophenyl carbamate, 3,5–dimethoxybenzyl carbamate, *o*–nitrobenzyl carbamate, 3,4–dimethoxy–6–nitrobenzyl carbamate, phenyl(*o*–nitrophenyl)methyl carbamate, phenothiazinyl–(10)–carbonyl derivative, *N'*–*p*–toluenesulfonylaminocarbonyl derivative, *N'*–phenylaminothiocarbonyl derivative, *t*–amyl carbamate, *S*–benzyl thiocarbamate, *p*–cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*–decyloxybenzyl carbamate, 2,2–dimethoxycarbonylvinyl carbamate, *o*–(*N,N*–dimethylcarboxamido)benzyl carbamate, 1,1–dimethyl–3–(*N,N*–dimethylcarboxamido)propyl carbamate, 1,1–dimethylpropynyl carbamate, di(2–pyridyl)methyl carbamate, 2–furanylmethyl carbamate, 2–iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*–(*p'*–methoxyphenylazo)benzyl carbamate, 1–methylcyclobutyl carbamate, 1–methylcyclohexyl carbamate, 1–methyl–1–cyclopropylmethyl carbamate, 1–methyl–1–(3,5–dimethoxyphenyl)ethyl carbamate, 1–methyl–1–(*p*–phenylazophenyl)ethyl carbamate, 1–methyl–1–phenylethyl carbamate, 1–methyl–1–(4–pyridyl)ethyl carbamate, phenyl carbamate, *p*–(phenylazo)benzyl carbamate, 2,4,6–tri–*t*–butylphenyl carbamate, 4–(trimethylammonium)benzyl carbamate, 2,4,6–trimethylbenzyl carbamate, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3–phenylpropanamide, picolinamide, 3–pyridylcarboxamide, *N*–benzoylphenylalanyl derivative, benzamide, *p*–phenylbenzamide, *o*–nitrophenylacetamide, *o*–nitrophenoxyacetamide, acetoacetamide, (*N'*–dithiobenzyloxycarbonylamino)acetamide, 3–(*p*–hydroxyphenyl)propanamide, 3–(*o*–nitrophenyl)propanamide, 2–methyl–2–(*o*–nitrophenoxy)propanamide, 2–methyl–2–(*o*–phenylazophenoxy)propanamide, 4–chlorobutanamide, 3–methyl–3–nitrobutanamide, *o*–nitrocinnamide, *N*–acetylmethionine derivative, *o*–nitrobenzamide, *o*–(benzoyloxymethyl)benzamide, 4,5–diphenyl–3–oxazolin–2–one, *N*–phthalimide, *N*–dithiasuccinimide (Dts), *N*–2,3–diphenylmaleimide, *N*–2,5–dimethylpyrrole, *N*–1,1,4,4–tetramethyldisilylazacyclopentane adduct (STABASE), 5–substituted 1,3–dimethyl–1,3,5–triazacyclohexan–2–one, 5–substituted 1,3–dibenzyl–1,3,5–triazacyclohexan–2–one, 1–substituted 3,5–dinitro–4–pyridone, *N*–methylamine, *N*–allylamine, *N*–[2–(trimethylsilyl)ethoxy]methylamine (SEM), *N*–3–acetoxypropylamine, *N*–(1–isopropyl–4–nitro–2–oxo–3–pyroolin–3–yl)amine, quaternary ammonium salts, *N*–benzylamine, *N*–di(4–methoxyphenyl)methylamine, *N*–5–dibenzosuberylamine, *N*–triphenylmethylamine (Tr), *N*–[(4–methoxyphenyl)diphenylmethyl]amine (MMTr), *N*–9–phenylfluorenylamine (PhF), *N*–2,7–dichloro–9–fluorenylmethyleneamine, *N*–ferrocenylmethylamino (Fcm), *N*–2–picolylamino *N'*–oxide, *N*–1,1–dimethylthiomethyleneamine, *N*–benzylideneamine, *N*–*p*–methoxybenzylideneamine, *N*–diphenylmethyleneamine, *N*–[(2–pyridyl)mesityl]methyleneamine, *N*–(*N',N'*–

dimethylaminomethylene)amine, *N,N'*–isopropylidenediamine, *N*–*p*–nitrobenzylideneamine, *N*–salicylideneamine, *N*–5–chlorosalicylideneamine, *N*–(5–chloro–2–hydroxyphenyl)phenylmethyleneamine, *N*–cyclohexylideneamine, *N*–(5,5–dimethyl–3–oxo–1–cyclohexenyl)amine, *N*–borane derivative, *N*–diphenylborinic acid derivative, *N*–[phenyl(pentacarbonylchromium– or tungsten)carbonyl]amine, *N*–copper chelate, *N*–zinc chelate, *N*–nitroamine, *N*–nitrosoamine, amine *N*–oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*–nitrobenzenesulfenamide (Nps), 2,4–dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2–nitro–4–methoxybenzenesulfenamide, triphenylmethylsulfenamide, 3–nitropyridinesulfenamide (Npys), *p*–toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,–trimethyl–4–methoxybenzenesulfonamide (Mtr), 2,4,6–trimethoxybenzenesulfonamide (Mtb), 2,6–dimethyl–4–methoxybenzenesulfonamide (Pme), 2,3,5,6–tetramethyl–4–methoxybenzenesulfonamide (Mte), 4–methoxybenzenesulfonamide (Mbs), 2,4,6–trimethylbenzenesulfonamide (Mts), 2,6–dimethoxy–4–methylbenzenesulfonamide (iMds), 2,2,5,7,8–pentamethylchroman–6–sulfonamide (Pmc), methanesulfonamide (Ms), β–trimethylsilylethanesulfonamide (SES), 9–anthracenesulfonamide, 4–(4',8'–dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[00167] Suitably protected carboxylic acids further include, but are not limited to, silyl–, alkyl–, alkenyl–, aryl–, and arylalkyl–protected carboxylic acids. Examples of suitable silyl groups include trimethylsilyl, triethylsilyl, t–butyldimethylsilyl, t–butyldiphenylsilyl, triisopropylsilyl, and the like. Examples of suitable alkyl groups include methyl, benzyl, p–methoxybenzyl, 3,4–dimethoxybenzyl, trityl, t–butyl, tetrahydropyran–2–yl. Examples of suitable alkenyl groups include allyl. Examples of suitable aryl groups include optionally substituted phenyl, biphenyl, or naphthyl. Examples of suitable arylalkyl groups include optionally substituted benzyl (*e.g.*, p–methoxybenzyl (MPM), 3,4–dimethoxybenzyl, O–nitrobenzyl, p–nitrobenzyl, p–halobenzyl, 2,6–dichlorobenzyl, p–cyanobenzyl), and 2– and 4–picolyl.

[00168] Suitable hydroxyl protecting groups include methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), *t*–butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*–methoxybenzyloxymethyl (PMBM), (4–methoxyphenoxy)methyl (*p*–AOM), guaiacolmethyl (GUM), *t*–butoxymethyl, 4–pentenyloxymethyl (POM), siloxymethyl, 2–methoxyethoxymethyl (MEM), 2,2,2–trichloroethoxymethyl, bis(2–chloroethoxy)methyl, 2–(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3–bromotetrahydropyranyl, tetrahydrothiopyranyl, 1–methoxycyclohexyl, 4–methoxytetrahydropyranyl (MTHP), 4–

methoxytetrahydrothiopyranyl, 4–methoxytetrahydrothiopyranyl S,S–dioxide, 1–[(2–chloro–4–methyl)phenyl]–4–methoxypiperidin–4–yl (CTMP), 1,4–dioxan–2–yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a–octahydro–7,8,8–trimethyl–4,7–methanobenzofuran–2–yl, 1–ethoxyethyl, 1–(2–chloroethoxy)ethyl, 1–methyl–1–methoxyethyl, 1–methyl–1–benzyloxyethyl, 1–methyl–1–benzyloxy–2–fluoroethyl, 2,2,2–trichloroethyl, 2–trimethylsilylethyl, 2–(phenylselenyl)ethyl, *t*–butyl, allyl, *p*–chlorophenyl, *p*–methoxyphenyl, 2,4–dinitrophenyl, benzyl, *p*–methoxybenzyl, 3,4–dimethoxybenzyl, *o*–nitrobenzyl, *p*–nitrobenzyl, *p*–halobenzyl, 2,6–dichlorobenzyl, *p*–cyanobenzyl, *p*–phenylbenzyl, 2–picolyl, 4–picolyl, 3–methyl–2–picolyl *N*–oxido, diphenylmethyl, *p,p'*–dinitrobenzhydryl, 5–dibenzosuberyl, triphenylmethyl, α–naphthyldiphenylmethyl, *p*–methoxyphenyldiphenylmethyl, di(*p*–methoxyphenyl)phenylmethyl, tri(*p*–methoxyphenyl)methyl, 4–(4'–bromophenacyloxyphenyl)diphenylmethyl, 4,4',4''–tris(4,5–dichlorophthalimidophenyl)methyl, 4,4',4''–tris(levulinoyloxyphenyl)methyl, 4,4',4''–tris(benzoyloxyphenyl)methyl, 3–(imidazol–1–yl)bis(4',4''–dimethoxyphenyl)methyl, 1,1–bis(4–methoxyphenyl)–1'–pyrenylmethyl, 9–anthryl, 9–(9–phenyl)xanthenyl, 9–(9–phenyl–10–oxo)anthryl, 1,3–benzodithiolan–2–yl, benzisothiazolyl S,S–dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, *t*–butyldimethylsilyl (TBDMS), *t*–butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri–*p*–xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*–butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*–chlorophenoxyacetate, 3–phenylpropionate, 4–oxopentanoate (levulinate), 4,4–(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4–methoxycrotonate, benzoate, *p*–phenylbenzoate, 2,4,6–trimethylbenzoate (mesitoate), alkyl methyl carbonate, 9–fluorenylmethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2–trichloroethyl carbonate (Troc), 2–(trimethylsilyl)ethyl carbonate (TMSEC), 2–(phenylsulfonyl) ethyl carbonate (Psec), 2–(triphenylphosphonio) ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate alkyl allyl carbonate, alkyl *p*–nitrophenyl carbonate, alkyl benzyl carbonate, alkyl *p*–methoxybenzyl carbonate, alkyl 3,4–dimethoxybenzyl carbonate, alkyl *o*–nitrobenzyl carbonate, alkyl *p*–nitrobenzyl carbonate, alkyl *S*–benzyl thiocarbonate, 4–ethoxy–1–napththyl carbonate, methyl dithiocarbonate, 2–iodobenzoate, 4–azidobutyrate, 4–nitro–4–methylpentanoate, *o*–(dibromomethyl)benzoate, 2–formylbenzenesulfonate, 2–(methylthiomethoxy)ethyl, 4–(methylthiomethoxy)butyrate, 2–(methylthiomethoxymethyl)benzoate, 2,6–dichloro–4–methylphenoxyacetate, 2,6–dichloro–4–(1,1,3,3–tetramethylbutyl)phenoxyacetate, 2,4–bis(1,1–dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)–2–methyl–2–butenoate, *o*–(methoxycarbonyl)benzoate, α–naphthoate, nitrate, alkyl *N,N,N',N'*–tetramethylphosphorodiamidate, alkyl *N*–phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4–

dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts). For protecting 1,2– or 1,3–diols, the protecting groups include methylene acetal, ethylidene acetal, 1–*t*–butylethylidene ketal, 1–phenylethylidene ketal, (4–methoxyphenyl)ethylidene acetal, 2,2,2–trichloroethylidene acetal, acetonide, cyclopentylidene ketal, cyclohexylidene ketal, cycloheptylidene ketal, benzylidene acetal, *p*–methoxybenzylidene acetal, 2,4–dimethoxybenzylidene ketal, 3,4–dimethoxybenzylidene acetal, 2–nitrobenzylidene acetal, methoxymethylene acetal, ethoxymethylene acetal, dimethoxymethylene ortho ester, 1–methoxyethylidene ortho ester, 1–ethoxyethylidine ortho ester, 1,2–dimethoxyethylidene ortho ester, α–methoxybenzylidene ortho ester, 1–(*N,N*–dimethylamino)ethylidene derivative, α–(*N,N'*–dimethylamino)benzylidene derivative, 2–oxacyclopentylidene ortho ester, di–*t*–butylsilylene group (DTBS), 1,3–(1,1,3,3–tetraisopropyldisiloxanylidene) derivative (TIPDS), tetra–*t*–butoxydisiloxane–1,3–diylidene derivative (TBDS), cyclic carbonates, cyclic boronates, ethyl boronate, and phenyl boronate.

[00169] In some embodiments, a hydroxyl protecting group is acetyl, t-butyl, tbutoxymethyl, methoxymethyl, tetrahydropyranyl, 1 -ethoxyethyl, 1 -(2-chloroethoxy)ethyl, 2- trimethylsilylethyl, p-chlorophenyl, 2,4-dinitrophenyl, benzyl, benzoyl, p-phenylbenzoyl, 2,6- dichlorobenzyl, diphenylmethyl, p-nitrobenzyl, triphenylmethyl (trityl), 4,4'-dimethoxytrityl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triphenylsilyl, triisopropylsilyl, benzoylformate, chloroacetyl, trichloroacetyl, trifiuoroacetyl, pivaloyl, 9- fluorenylmethyl carbonate, mesylate, tosylate, triflate, trityl, monomethoxytrityl (MMTr), 4,4'-dimethoxytrityl, (DMTr) and 4,4',4"-trimethoxytrityl (TMTr), 2-cyanoethyl (CE or Cne), 2-(trimethylsilyl)ethyl (TSE), 2-(2-nitrophenyl)ethyl, 2-(4-cyanophenyl)ethyl 2-(4-nitrophenyl)ethyl (NPE), 2-(4-nitrophenylsulfonyl)ethyl, 3,5-dichlorophenyl, 2,4-dimethylphenyl, 2-nitrophenyl, 4-nitrophenyl, 2,4,6-trimethylphenyl, 2-(2-nitrophenyl)ethyl, butylthiocarbonyl, 4,4',4"-tris(benzoyloxy)trityl, diphenylcarbamoyl, levulinyl, 2-(dibromomethyl)benzoyl (Dbmb), 2-(isopropylthiomethoxymethyl)benzoyl (Ptmt), 9-phenylxanthen-9-yl (pixyl) or 9-(p-methoxyphenyl)xanthine-9-y1 (MOX). In some embodiments, each of the hydroxyl protecting groups is, independently selected from acetyl, benzyl, t- butyldimethylsilyl, t-butyldiphenylsilyl and 4,4'-dimethoxytrityl. In some embodiments, the hydroxyl protecting group is selected from the group consisting of trityl, monomethoxytrityl and 4,4'-dimethoxytrityl group.

[00170] In some embodiments, a phosphorous protecting group is a group attached to the internucleotide phosphorous linkage throughout oligonucleotide synthesis. In some embodiments, the phosphorous protecting group is attached to the sulfur atom of the internucleotide phosphorothioate linkage. In some embodiments, the phosphorous protecting group is attached to the oxygen atom of the internucleotide phosphorothioate linkage. In some embodiments, the phosphorous protecting group is attached to the oxygen atom of the internucleotide phosphate linkage. In some embodiments the

phosphorous protecting group is 2-cyanoethyl (CE or Cne), 2-trimethylsilylethyl, 2-nitroethyl, 2-sulfonylethyl, methyl, benzyl, *o*-nitrobenzyl, 2-(*p*-nitrophenyl)ethyl (NPE or Npe), 2-phenylethyl, 3-(*N*-*tert*-butylcarboxamido)-1-propyl, 4-oxopentyl, 4-methylthio-1-butyl, 2-cyano-1,1-dimethylethyl, 4-*N*-methylaminobutyl, 3-(2-pyridyl)-1-propyl, 2-[*N*-methyl-*N*-(2-pyridyl)]aminoethyl, 2-(*N*-formyl,*N*-methyl)aminoethyl, 4-[*N*-methyl-*N*-(2,2,2-trifluoroacetyl)amino]butyl.

[00171] *Protein:* As used herein, the term "protein" refers to a polypeptide (*i.e.*, a string of at least two amino acids linked to one another by peptide bonds). In some embodiments, proteins include only naturally-occurring amino acids. In some embodiments, proteins include one or more non-naturally-occurring amino acids (*e.g.*, moieties that form one or more peptide bonds with adjacent amino acids). In some embodiments, one or more residues in a protein chain contain a non-amino-acid moiety (*e.g.*, a glycan, *etc*). In some embodiments, a protein includes more than one polypeptide chain, for example linked by one or more disulfide bonds or associated by other means. In some embodiments, proteins contain L-amino acids, D-amino acids, or both; in some embodiments, proteins contain one or more amino acid modifications or analogs known in the art. Useful modifications include, *e.g.*, terminal acetylation, amidation, methylation, *etc.* The term "peptide" is generally used to refer to a polypeptide having a length of less than about 100 amino acids, less than about 50 amino acids, less than 20 amino acids, or less than 10 amino acids.

[00172] *Subject:* As used herein, the term "subject" or "test subject" refers to any organism to which a provided compound or composition is administered in accordance with the present disclosure *e.g.*, for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and humans; insects; worms; *etc.*) and plants. In some embodiments, a subject may be suffering from, and/or susceptible to a disease, disorder, and/or condition.

[00173] *Substantially:* As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and/or chemical phenomena.

[00174] *Suffering from*: An individual who is "suffering from" a disease, disorder, and/or condition has been diagnosed with and/or displays one or more symptoms of a disease, disorder, and/or condition.

[00175] *Susceptible to*: An individual who is "susceptible to" a disease, disorder, and/or condition is one who has a higher risk of developing the disease, disorder, and/or condition than does a member of

the general public. In some embodiments, an individual who is susceptible to a disease, disorder and/or condition may not have been diagnosed with the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition may exhibit symptoms of the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition may not exhibit symptoms of the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

[00176] *Systemic:* The phrases "systemic administration," "administered systemically," "peripheral administration," and "administered peripherally" as used herein have their art-understood meaning referring to administration of a compound or composition such that it enters the recipient's system.

[00177] *Tautomeric forms:* The phrase "tautomeric forms," as used herein and generally understood in the art, is used to describe different isomeric forms of organic compounds that are capable of facile interconversion. Tautomers may be characterized by the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond and adjacent double bond. In some embodiments, tautomers may result from prototropic tautomerism (*i.e.*, the relocation of a proton). In some embodiments, tautomers may result from valence tautomerism (*i.e.*, the rapid reorganization of bonding electrons). All such tautomeric forms are intended to be included within the scope of the present disclosure. In some embodiments, tautomeric forms of a compound exist in mobile equilibrium with each other, so that attempts to prepare the separate substances results in the formation of a mixture. In some embodiments, tautomeric forms of a compound are separable and isolatable compounds. In some embodiments of the disclosure, chemical compositions may be provided that are or include pure preparations of a single tautomeric form of a compound. In some embodiments of the disclosure, chemical compositions may be provided as mixtures of two or more tautomeric forms of a compound. In certain embodiments, such mixtures contain equal amounts of different tautomeric forms; in certain embodiments, such mixtures contain different amounts of at least two different tautomeric forms of a compound. In some embodiments of the disclosure, chemical compositions may contain all tautomeric forms of a compound. In some embodiments of the disclosure, chemical compositions may contain less than all tautomeric forms of a compound. In some embodiments of the disclosure, chemical compositions may contain one or more tautomeric forms of a compound in amounts that vary over time as a result of interconversion. In some embodiments of the disclosure, the tautomerism is keto-enol tautomerism. One of skill in the chemical arts would recognize that a keto-enol tautomer can be "trapped" (i.e., chemically

modified such that it remains in the "enol" form) using any suitable reagent known in the chemical arts in to provide an enol derivative that may subsequently be isolated using one or more suitable techniques known in the art. Unless otherwise indicated, the present disclosure encompasses all tautomeric forms of relevant compounds, whether in pure form or in admixture with one another.

[00178] *Therapeutic agent:* As used herein, the phrase "therapeutic agent" refers to any agent that, when administered to a subject, has a therapeutic effect and/or elicits a desired biological and/or pharmacological effect. In some embodiments, a therapeutic agent is any substance that can be used to alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of, and/or reduce incidence of one or more symptoms or features of a disease, disorder, and/or condition.

[00179] *Therapeutically effective amount:* As used herein, the term "therapeutically effective amount" means an amount of a substance (*e.g.*, a therapeutic agent, composition, and/or formulation) that elicits a desired biological response when administered as part of a therapeutic regimen. In some embodiments, a therapeutically effective amount of a substance is an amount that is sufficient, when administered to a subject suffering from or susceptible to a disease, disorder, and/or condition, to treat, diagnose, prevent, and/or delay the onset of the disease, disorder, and/or condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a substance may vary depending on such factors as the desired biological endpoint, the substance to be delivered, the target cell or tissue, *etc.* For example, the effective amount of compound in a formulation to treat a disease, disorder, and/or condition is the amount that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of and/or reduces incidence of one or more symptoms or features of the disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is administered in a single dose; in some embodiments, multiple unit doses are required to deliver a therapeutically effective amount.

[00180] *Treat:* As used herein, the term "treat," "treatment," or "treating" refers to any method used to partially or completely alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of, and/or reduce incidence of one or more symptoms or features of a disease, disorder, and/or condition. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition. In some embodiments, treatment may be administered to a subject who exhibits only early signs of the disease, disorder, and/or condition, for example for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[00181] *Unit dose*: The expression "unit dose" as used herein refers to an amount administered as a single dose and/or in a physically discrete unit of a pharmaceutical composition. In many embodiments, a unit dose contains a predetermined quantity of an active agent. In some embodiments, a unit dose contains an entire single dose of the agent. In some embodiments, more than one unit dose is administered to achieve a total single dose. In some embodiments, administration of multiple unit doses

is required, or expected to be required, in order to achieve an intended effect. A unit dose may be, for example, a volume of liquid (e.g., an acceptable carrier) containing a predetermined quantity of one or more therapeutic agents, a predetermined amount of one or more therapeutic agents in solid form, a sustained release formulation or drug delivery device containing a predetermined amount of one or more therapeutic agents, etc. It will be appreciated that a unit dose may be present in a formulation that includes any of a variety of components in addition to the therapeutic agent(s). For example, acceptable carriers (e.g., pharmaceutically acceptable carriers), diluents, stabilizers, buffers, preservatives, etc., may be included as described infra. It will be appreciated by those skilled in the art, in many embodiments, a total appropriate daily dosage of a particular therapeutic agent may comprise a portion, or a plurality, of unit doses, and may be decided, for example, by the attending physician within the scope of sound medical judgment. In some embodiments, the specific effective dose level for any particular subject or organism may depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of specific active compound employed; specific composition employed; age, body weight, general health, sex and diet of the subject; time of administration, and rate of excretion of the specific active compound employed; duration of the treatment; drugs and/or additional therapies used in combination or coincidental with specific compound(s) employed, and like factors well known in the medical arts.

[00182] *Unsaturated:* The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[00183] *Wild-type:* As used herein, the term "wild-type" has its art-understood meaning that refers to an entity having a structure and/or activity as found in nature in a "normal" (as contrasted with mutant, diseased, altered, *etc*) state or context. Those of ordinary skill in the art will appreciate that wild type genes and polypeptides often exist in multiple different forms (*e.g.*, alleles).

[00184] *Nucleic acid*: The term "nucleic acid" includes any nucleotides, analogs thereof, and polymers thereof. The term "polynucleotide" as used herein refer to a polymeric form of nucleotides of any length, either ribonucleotides (RNA) or deoxyribonucleotides (DNA) or analogs thereof. These terms refer to the primary structure of the molecules and include double- and single-stranded DNA, and double- and single-stranded RNA. These terms include, as equivalents, analogs of either RNA or DNA made from nucleotide analogs and modified polynucleotides such as, though not limited to, methylated, protected and/or capped nucleotides or polynucleotides. The terms encompass poly- or oligo-ribonucleotides (RNA) and poly- or oligo-deoxyribonucleotides (DNA); RNA or DNA derived from N-glycosides or C-glycosides of nucleobases and/or modified nucleobases; nucleic acids derived from sugars and/or modified sugars; and nucleic acids derived from phosphate bridges and/or modified phosphorus-atom bridges (also referred to herein as "internucleotidic linkages"). The term encompasses

nucleic acids containing any combinations of nucleobases, modified nucleobases, sugars, modified sugars, natural natural phosphate internucleotidic linkages or non-natural internucleotidic linkages. Examples include, and are not limited to, nucleic acids containing ribose moieties, nucleic acids containing deoxy-ribose moieties, nucleic acids containing both ribose and deoxyribose moieties, nucleic acids containing ribose and modified ribose moieties. Unless otherwise specified, the prefix poly- refers to a nucleic acid containing 2 to about 10,000 nucleotide monomer units and wherein the prefix oligo- refers to a nucleic acid containing 2 to about 200 nucleotide monomer units.

[00185] *Nucleotide:* The term "nucleotide" as used herein refers to a monomeric unit of a polynucleotide that consists of a heterocyclic base, a sugar, and one or more phosphate groups or phosphorus-containing internucleotidic linkages. Naturally occurring bases, (guanine, (G), adenine, (A), cytosine, (C), thymine, (T), and uracil (U)) are derivatives of purine or pyrimidine, though it should be understood that naturally and non-naturally occurring base analogs are also included. Naturally occurring sugars include the pentose (five-carbon sugar) deoxyribose (which is found in natural DNA) or ribose (which is found in natural RNA), though it should be understood that naturally and non-naturally occurring sugar analogs are also included, such as sugars with 2'-modifications, sugars in locked nucleic acid (LNA) and phosphorodiamidate morpholino oligomer (PMO). Nucleotides are linked via internucleotidic linkages to form nucleic acids, or polynucleotides. Many internucleotidic linkages are known in the art (such as, though not limited to, natural phosphate linkage, phosphorothioate linkages, boranophosphate linkages and the like). Artificial nucleic acids include PNAs (peptide nucleic acids), phosphotriesters, phosphorothionates, *H*-phosphonates, phosphoramidates, boranophosphates, methylphosphonates, phosphonoacetates, thiophosphonoacetates and other variants of the phosphate backbone of native nucleic acids, etc. In some embodiments, a nucleotide is a natural nucleotide comprising a naturally occurring nucleobase, a natural occurring sugar and the natural phosphate linkage. In some embodiments, a nucleotide is a modified nucleotide or a nucleotide analog, which is a structural analog that can be used in lieu of a natural nucleotide.

[00186] *Modified nucleotide*: The term "modified nucleotide" includes any chemical moiety which differs structurally from a natural nucleotide but is capable of performing at least one function of a natural nucleotide. In some embodiments, a modified nucleotide comprises a modification at a sugar, base and/or internucleotidic linkage. In some embodiments, a modified nucleotide comprises a modified sugar, modified nucleobase and/or modified internucleotidic linkage. In some embodiments, a modified nucleotide is capable of at least one function of a nucleotide, e.g., forming a subunit in a polymer capable of base-pairing to a nucleic acid comprising an at least complementary sequence of bases.

[00187] *Analog*: The term "analog" includes any chemical moiety which differs structurally from a reference chemical moiety or class of moieties, but which is capable of performing at least one function

of such a reference chemical moiety or class of moieties. As non-limiting examples, a nucleotide analog differs structurally from a nucleotide but performs at least one function of a nucleotide; a nucleobase analog differs structurally from a nucleobase but performs at least one function of a nucleobase; a sugar analog differs structurally from a nucleobase but performs at least one function of a sugar, etc.

[00188] *Nucleoside*: The term "nucleoside" refers to a moiety wherein a nucleobase or a modified nucleobase is covalently bound to a sugar or modified sugar.

[00189] *Modified nucleoside*: The term "modified nucleoside" refers to a chemical moiety which is chemically distinct from a natural nucleoside, but which is capable of performing at least one function of a nucleoside. In some embodiments, a modified nucleoside is derived from or chemically similar to a natural nucleoside, but which comprises a chemical modification which differentiates it from a natural nucleoside. Non-limiting examples of modified nucleosides include those which comprise a modification at the base and/or the sugar. Non-limiting examples of modified nucleosides include those with a 2'-modification at a sugar. Non-limiting examples of modified nucleosides also include abasic nucleosides (which lack a nucleobase). In some embodiments, a modified nucleoside is capable of at least one function of a nucleoside, e.g., forming a moiety in a polymer capable of base-pairing to a nucleic acid comprising an at least complementary sequence of bases.

[00190] *Nucleoside analog*: The term "nucleoside analog" refers to a chemical moiety which is chemically distinct from a natural nucleoside, but which is capable of performing at least one function of a nucleoside. In some embodiments, a nucleoside analog comprises an analog of a sugar and/or an analog of a nucleobase. In some embodiments, a modified nucleoside is capable of at least one function of a nucleoside, e.g., forming a moiety in a polymer capable of base-pairing to a nucleic acid comprising a complementary sequence of bases.

[00191] *Sugar*: The term "sugar" refers to a monosaccharide or polysaccharide in closed and/or open form. In some embodiments, sugars are monosaccharides. In some embodiments, sugars are polysaccharides. Sugars include, but are not limited to, ribose, deoxyribose, pentofuranose, pentopyranose, and hexopyranose moieties. As used herein, the term "sugar" also encompasses structural analogs used in lieu of conventional sugar molecules, such as glycol, polymer of which forms the backbone of the nucleic acid analog, glycol nucleic acid ("GNA"), etc. As used herein, the term "sugar" also encompasses structural analogs used in lieu of natural or naturally-occurring nucleotides, such as modified sugars and nucleotide sugars. In some embodiments, a sugar is D-2-deoxyribose. In some embodiments, a sugar is beta-D-deoxyribofuranose. In some embodiments, a sugar moiety is a beta-D-deoxyribofuranose moiety. In some embodiments, a sugar is D-ribose. In some embodiments, a sugar is beta-D-ribofuranose. In some embodiments, a sugar moiety is a beta-D-ribofuranose moiety. In some embodiments, a sugar is optionally substituted beta-D-deoxyribofuranose or beta-D-ribofuranose. In

some embodiments, a sugar moiety is an optionally substituted beta-D-deoxyribofuranose or beta-D-ribofuranose moiety. In some embodiments, a sugar moiety/unit in an oligonucleotide, nucleic acid, etc. is a sugar which comprises one or more carbon atoms each independently connected to an internucleotidic linkage, e.g., optionally substituted beta-D-deoxyribofuranose or beta-D-ribofuranose whose 5`-C and/or 3`-C are each independently connected to an internucleotidic linkage (e.g., a natural phosphate linkage, a modified internucleotidic linkage, a chirally controlled internucleotidic linkage, etc.).

[00192] *Modified sugar*: The term "modified sugar" refers to a moiety that can replace a sugar. A modified sugar mimics the spatial arrangement, electronic properties, or some other physicochemical property of a sugar. In some embodiments, a modified sugar is substituted beta-D-deoxyribofuranose or beta-D-ribofuranose. In some embodiments, a modified sugar comprises a 2'-modification. In some embodiments, a modified sugar comprises a linker (e.g., optionally substituted bivalent heteroaliphatic) connecting two sugar carbon atoms (e.g., C2 and C4), e.g., as found in LNA. In some embodiments, a linker is –O–CH(R)–, wherein R is as described in the present disclosure. In some embodiments, a linker is –O–CH(R)–, wherein O is connected to C2, and –CH(R)– is connected to C4 of a sugar, and R is as described in the present disclosure. In some embodiments, R is methyl. In some embodiments, R is –H. In some embodiments, –CH(R)– is of S configuration. In some embodiments, –CH(R)– is of R configuration.

[00193] *Nucleobase*: The term "nucleobase" refers to the parts of nucleic acids that are involved in the hydrogen-bonding that binds one nucleic acid strand to another complementary strand in a sequence specific manner. The most common naturally-occurring nucleobases are adenine (A), guanine (G), uracil (U), cytosine (C), and thymine (T). In some embodiments, a modified nucleobase is a substituted nucleobase which nucleobase is selected from A, T, C, G, U, and tautomers thereof. In some embodiments, the naturally-occurring nucleobases are modified adenine, guanine, uracil, cytosine, or thymine. In some embodiments, the naturally-occurring nucleobases are methylated adenine, guanine, uracil, cytosine, or thymine. In some embodiments, a nucleobase is a "modified nucleobase," e.g., a nucleobase other than adenine (A), guanine (G), uracil (U), cytosine (C), and thymine (T). In some embodiments, the modified nucleobases are methylated adenine, guanine, uracil, cytosine, or thymine. In some embodiments, the modified nucleobase mimics the spatial arrangement, electronic properties, or some other physicochemical property of the nucleobase and retains the property of hydrogen-bonding that binds one nucleic acid strand to another in a sequence specific manner. In some embodiments, a modified nucleobase can pair with all of the five naturally occurring bases (uracil, thymine, adenine, cytosine, or guanine) without substantially affecting the melting behavior, recognition by intracellular enzymes or activity of the oligonucleotide duplex. As used herein, the term "nucleobase" also encompasses structural analogs used in lieu of natural or naturally-occurring nucleotides, such as modified nucleobases and

nucleobase analogs. In some embodiments, a nucleobase is an optionally substituted A, T, C, G, or U, or a substituted nucleobase which nucleobase is selected from A, T, C, G, U, and tautomers thereof.

[00194] *Modified nucleobase*: The terms "modified nucleobase", "modified base" and the like refer to a chemical moiety which is chemically distinct from a nucleobase, but which is capable of performing at least one function of a nucleobase. In some embodiments, a modified nucleobase is a nucleobase which comprises a modification. In some embodiments, a modified nucleobase is capable of at least one function of a nucleobase, e.g., forming a moiety in a polymer capable of base-pairing to a nucleic acid comprising an at least complementary sequence of bases. In some embodiments, a modified nucleobase is a substituted nucleobase which nucleobase is selected from A, T, C, G, U, and tautomers thereof.

[00195] *Chiral ligand*: The term "chiral ligand" or "chiral auxiliary" refers to a moiety that is chiral and can be incorporated into a reaction so that the reaction can be carried out with certain stereoselectivity. In some embodiments, the term may also refer to a compound that comprises such a moiety.

[00196] *Blocking group*: The term "blocking group" refers to a group that masks the reactivity of a functional group. The functional group can be subsequently unmasked by removal of the blocking group. In some embodiments, a blocking group is a protecting group.

[00197] *Moiety*: The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule. In some embodiments, a moiety of a compound is a monovalent, bivalent, or polyvalent group formed from the compound by removing one or more –H and/or equivalents thereof from a compound. In some embodiments, depending on its context, "moiety" may also refer to a compound or entity from which the moiety is derived from.

[00198] *Solid support*: The term "solid support" when used in the context of preparation of nucleic acids, oligonucleotides, or other compounds refers to any support which enables synthesis of nucleic acids, oligonucleotides or other compounds. In some embodiments, the term refers to a glass or a polymer, that is insoluble in the media employed in the reaction steps performed to synthesize nucleic acids, and is derivatized to comprise reactive groups. In some embodiments, the solid support is Highly Cross-linked Polystyrene (HCP) or Controlled Pore Glass (CPG). In some embodiments, the solid support is Controlled Pore Glass (CPG). In some embodiments, the solid support is hybrid support of Controlled Pore Glass (CPG) and Highly Cross-linked Polystyrene (HCP).

[00199] *Reading frame*: The term "reading frame" refers to one of the six possible reading frames, three in each direction, of a double stranded DNA molecule. The reading frame that is used determines which codons are used to encode amino acids within the coding sequence of a DNA molecule.

[00200] *Antisense*: As used herein, an "antisense" nucleic acid molecule comprises a nucleotide sequence which is complementary to a "sense" nucleic acid encoding a protein, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule, complementary to an mRNA sequence or complementary to the coding strand of a gene. Accordingly, an antisense nucleic acid molecule can associate via hydrogen bonds to a sense nucleic acid molecule. In some embodiments, transcripts may be generated from both strands. In some embodiments, transcripts may or may not encode protein products. In some embodiments, when directed or targeted to a particular nucleic acid sequence, a "antisense" sequence may refer to a sequence that is complementary to the particular nucleic acid sequence.

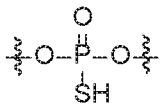
[00201] *Oligonucleotide:* the term "oligonucleotide" refers to a polymer or oligomer of nucleotide monomers, containing any combination of nucleobases, modified nucleobases, sugars, modified sugars, natural phosphate linkages, or non-natural internucleotidic linkages.

[00202] Oligonucleotides can be single-stranded or double-stranded. As used herein, the term "oligonucleotide strand" encompasses a single-stranded oligonucleotide. A single-stranded oligonucleotide can have double-stranded regions and a double-stranded oligonucleotide can have single-stranded regions. Example oligonucleotides include, but are not limited to structural genes, genes including control and termination regions, self-replicating systems such as viral or plasmid DNA, single-stranded and double-stranded siRNAs and other RNA interference reagents (RNAi agents or iRNA agents), shRNA, antisense oligonucleotides, ribozymes, microRNAs, microRNA mimics, supermirs, aptamers, antimirs, antagomirs, UI adaptors, triplex-forming oligonucleotides, G-quadruplex oligonucleotides, RNA activators, immuno-stimulatory oligonucleotides, and decoy oligonucleotides.

[00203] Double-stranded and single-stranded oligonucleotides that are effective in inducing RNA interference may also be referred to as siRNA, RNAi agent, or iRNA agent. In some embodiments, these RNA interference inducing oligonucleotides associate with a cytoplasmic multi-protein complex known as RNAi-induced silencing complex (RISC). In many embodiments, single-stranded and double-stranded RNAi agents are sufficiently long that they can be cleaved by an endogenous molecule, *e.g.*, by Dicer, to produce smaller oligonucleotides that can enter the RISC machinery and participate in RISC mediated cleavage of a target sequence, *e.g.* a target mRNA.

[00204] Oligonucleosides of the present disclosure can be of various lengths. In particular embodiments, oligonucleosides can range from about 2 to about 200 nucleosides in length. In various related embodiments, oligonucleosides, single-stranded, double-stranded, and triple-stranded, can range in length from about 4 to about 10 nucleosides, from about 10 to about 50 nucleosides, from about 20 to about 50 nucleosides, from about 15 to about 30 nucleosides, from about 20 to about 30 nucleosides in length. In some embodiments, the oligonucleoside is from about 9 to about 39 nucleosides in length. In some embodiments, the oligonucleoside is at least 15 nucleosides in length. In some embodiments, the

oligonucleoside is at least 20 nucleosides in length. In some embodiments, the oligonucleoside is at least 25 nucleosides in length. In some embodiments, the oligonucleoside is at least 30 nucleosides in length. In some embodiments, the oligonucleoside is a duplex of complementary strands of at least 18 nucleosides in length. In some embodiments, the oligonucleoside is a duplex of complementary strands of at least 21 nucleosides in length. In some embodiments, for the purpose of oligonucleotide lengths, each nucleoside counted independently comprises an optionally substituted nucleobase selected from A, T, C, G, U and their tautomers.

[00205] *Internucleotidic linkage:* As used herein, the phrase "internucleotidic linkage" refers generally to a linkage, typically a phosphorus-containing linkage, between nucleotide units of a nucleic acid or an oligonucleotide, and is interchangeable with "inter-sugar linkage", "internucleosidic linkage," and "phosphorus atom bridge," as used above and herein. As appreciated by those skilled in the art, natural DNA and RNA contain natural phosphate linkages. In some embodiments, an internucleotidic linkage is a natural phosphate linkage (–OP(O)(OH)O–, typically existing as its anionic form –OP(O)(O^-)O– at pH e.g., ~7.4), as found in naturally occurring DNA and RNA molecules. In some embodiments, an internucleotidic linkage is a modified internucleotidic linkage (or non-natural internucleotidic linkage), which is structurally different from a natural phosphate linkage but may be utilized in place of a natural phosphate linkage, e.g., phosphorothioate internucleotidic linkage, PMO linkages, etc. In some embodiments, an internucleotidic linkage is a modified internucleotidic linkage wherein one or more oxygen atoms of a natural phosphodiester linkage are independently replaced by one or more organic or inorganic moieties. In some embodiments, such an organic or inorganic moiety is selected from but not limited to =S, =Se, =NR', –SR', –SeR', $–N(R')_2$, $B(R')_3$, –S–, –Se–, and –N(R')–, wherein each R' is independently as defined and described below. In some embodiments, an internucleotidic linkage is a phosphotriester linkage. In some embodiments, an internucleotidic linkage is a phosphorothioate diester linkage (phosphorothioate internucleotidic linkage,  , typically existing as its anionic form –OP(O)(S^-)O– at pH e.g., ~7.4). It is understood by a person of ordinary skill in the art that an internucleotidic linkage may exist as an anion or cation at a given pH due to the existence of acid or base moieties in the linkage. In some embodiments, an internucleotidic linkage is a non-negatively charged internucleotidic linkage at a given pH. In some embodiments, an internucleotidic linkage is a neutral internucleotidic linkage at a given pH. In some embodiments, a given pH is pH ~7.4. In some embodiments, a given pH is in the range of pH about 0, 1, 2, 3, 4, 5, 6 or 7 to pH about 7, 8, 9, 10, 11, 12, 13 or 14. In some embodiments, a given pH is in the range of pH 5-9. In some embodiments, a given pH is in the range of pH 6-8. In some embodiments, an internucleotidic linkage has the structure

of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., as described in the present disclosure. In some embodiments, a non-negatively charged internucleotidic linkage has the structure of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., as described in the present disclosure. In some embodiments, an internucleotidic linkage is one of, e.g., PNA (peptide nucleic acid) or PMO (phosphorodiamidate Morpholino oligomer) linkage. In some embodiments, an internucleotidic linkage comprises a chiral linkage phosphorus. In some embodiments, an internucleotidic linkage is a chirally controlled internucleotidic linkage. In some embodiments, an internucleotidic linkage is selected from: s (phosphorothioate), s1, s2, s3, s4, s5, s6, s7, s8, s9, s10, s11, s12, s13, s14, s15, s16, s17 or s18, wherein each of s1, s2, s3, s4, s5, s6, s7, s8, s9, s10, s11, s12, s13, s14, s15, s16, s17 and s18 is independently as described in WO 2017/062862.

[00206] Unless otherwise specified, the Rp/Sp designations preceding an oligonucleotide sequence describe the configurations of linkage phosphorus in chirally controlled internucleotidic linkages sequentially from 5' to 3' of the oligonucleotide sequence. For instance, in (Rp, Sp)-ATsCs1GA, the phosphorus in the "s" linkage between T and C has Rp configuration and the phosphorus in "s1" linkage between C and G has Sp configuration. In some embodiments, "All-(Rp)" or "All-(Sp)" is used to indicate that all chiral linkage phosphorus atoms in chirally controlled internucleotidic linkages have the same Rp or Sp configuration, respectively. For instance, All-(*Rp*)-GsCsCsTsCsAsGsTsCsTsGsCsTsTsCsGsCsAsCsC indicates that all the chiral linkage phosphorus atoms in the oligonucleotide have *Rp* configuration; All-(*Sp*)-GsCsCsTsCsAsGsTsCsTsGsCsTsTsCsGsCsAsCsC indicates that all the chiral linkage phosphorus atoms in the oligonucleotide have *Sp* configuration.

[00207] *Oligonucleotide type:* As used herein, the phrase "oligonucleotide type" is used to define oligonucleotides that have a particular base sequence, pattern of backbone linkages (i.e., pattern of internucleotidic linkage types, for example, natural phosphate linkages, phosphorothioate internucleotidic linkages, negatively charged internucleotidic linkages, neutral internucleotidic linkages *etc*), pattern of backbone chiral centers (i.e. pattern of linkage phosphorus stereochemistry (*Rp*/*Sp*)), and pattern of backbone phosphorus modifications (*e.g.*, pattern of "$-X-L-R^1$" groups in formula **I**). In some embodiments, oligonucleotides of a common designated "type" are structurally identical to one another.

[00208] One of skill in the art will appreciate that synthetic methods of the present disclosure provide for a degree of control during the synthesis of an oligonucleotide strand such that each nucleotide unit of the oligonucleotide strand can be designed and/or selected in advance to have a particular stereochemistry at the linkage phosphorus and/or a particular modification at the linkage phosphorus, and/or a particular base, and/or a particular sugar. In some embodiments, an oligonucleotide strand is

designed and/or selected in advance to have a particular combination of stereocenters at the linkage phosphorus. In some embodiments, an oligonucleotide strand is designed and/or determined to have a particular combination of modifications at the linkage phosphorus. In some embodiments, an oligonucleotide strand is designed and/or selected to have a particular combination of bases. In some embodiments, an oligonucleotide strand is designed and/or selected to have a particular combination of one or more of the above structural characteristics. The present disclosure provides compositions comprising or consisting of a plurality of oligonucleotide molecules (*e.g.*, chirally controlled oligonucleotide compositions). In some embodiments, all such molecules are of the same type. In some embodiments, all such molecules are structurally identical to one another. In some embodiments, provided compositions comprise a plurality of oligonucleotides of different types, typically in pre-determined (non-random) relative amounts.

[00209] *Chiral control:* As used herein, "chiral control" refers to control of the stereochemical designation of a chiral linkage phosphorus in a chiral internucleotidic linkage within an oligonucleotide. In some embodiments, a control is achieved through a chiral element that is absent from the sugar and base moieties of an oligonucleotide, for example, in some embodiments, a control is achieved through use of one or more chiral auxiliaries during oligonucleotide preparation as exemplified in the present disclosure, which chiral auxiliaries often are part of chiral phosphoramidites used during oligonucleotide preparation. In contrast to chiral control, a person having ordinary skill in the art appreciates that conventional oligonucleotide synthesis which does not use chiral auxiliaries cannot control stereochemistry at a chiral internucleotidic linkage if such conventional oligonucleotide synthesis is used to form the chiral internucleotidic linkage. In some embodiments, the stereochemical designation of each chiral linkage phosphorus in a chiral internucleotidic linkage within an oligonucleotide is controlled.

[00210] *Chirally controlled oligonucleotide composition:* The terms "chirally controlled (stereocontrolled or stereodefined) oligonucleotide composition", "chirally controlled (stereocontrolled or stereodefined) nucleic acid composition", and the like, as used herein, refers to a composition that comprises a plurality of oligonucleotides (or nucleic acids, chirally controlled oligonucleotides or chirally controlled nucleic acids) which share 1) a common base sequence, 2) a common pattern of backbone linkages; 3) a common pattern of backbone chiral centers, and 4) a common pattern of backbone phosphorus modifications (oligonucleotides of a particular type), wherein the plurality of oligonucleotides (or nucleic acids) share the same stereochemistry at one or more chiral internucleotidic linkages (chirally controlled internucleotidic linkages, whose chiral linkage phosphorus is Rp or Sp, not a random Rp and Sp mixture as non-chirally controlled internucleotidic linkages). Level of the plurality of oligonucleotides (or nucleic acids) in a chirally controlled oligonucleotide composition is non-random (pre-determined, controlled). Chirally controlled oligonucleotide compositions are typically prepared through chirally

controlled oligonucleotide preparation to stereoselectively form one or more chiral internucleotidic linkages (e.g., using chiral auxiliaries as exemplified in the present disclosure, compared to non-chirally controlled (stereorandom, non-stereoselective, racemic) oligonucleotide synthesis such as traditional phosphoramidite-based oligonucleotide synthesis using no chiral auxiliaries or chiral catalysts to purposefully control stereoselectivity). A chirally controlled oligonucleotide composition is enriched, relative to a substantially racemic preparation of oligonucleotides having the common base sequence, the common pattern of backbone linkages, and the common pattern of backbone phosphorus modifications, for oligonucleotides of the plurality. In some embodiments, a chirally controlled oligonucleotide composition comprises a plurality of oligonucleotides of a particular oligonucleotide type defined by: 1) base sequence; 2) pattern of backbone linkages; 3) pattern of backbone chiral centers; and 4) pattern of backbone phosphorus modifications, wherein it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same base sequence, pattern of backbone linkages, and pattern of backbone phosphorus modifications, for oligonucleotides of the particular oligonucleotide type. As one having ordinary skill in the art readily appreciates, such enrichment can be characterized in that compared to a substantially racemic preparation, at each chirally controlled internucleotidic linkage, a higher level of the linkage phosphorus has the desired configuration. In some embodiments, each chirally controlled internucleotidic linkage independently has a diastereopurity of at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% with respect to its chiral linkage phosphorus. In some embodiments, each independently has a diastereopurity of at least 90%. In some embodiments, each independently has a diastereopurity of at least 95%. In some embodiments, each independently has a diastereopurity of at least 97%. In some embodiments, each independently has a diastereopurity of at least 98%. In some embodiments, oligonucleotides of a plurality have the same constitution. In some embodiments, oligonucleotides of a plurality have the same constitution and stereochemistry, and are structurally identical.

[00211] In some embodiments, the plurality of oligonucleotides in a chirally controlled oligonucleotide composition share the same base sequence, the same, if any, nucleobase, sugar, and internucleotidic linkage modifications, and the same stereochemistry (*R*p or *S*p) independently at linkage phosphorus chiral centers of one or more chirally controlled internucleotidic linkages, though stereochemistry of certain linkage phosphorus chiral centers may differ. In some embodiments, about 0.1%-100%, (*e.g.*, about 1%-100%, 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, or about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, or at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) of all oligonucleotides in a chirally controlled oligonucleotide composition are

oligonucleotides of the plurality. In some embodiments, about 0.1%-100%, (*e.g.*, about 1%-100%, 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, or about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, or at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) of all oligonucleotides in a chirally controlled oligonucleotide composition that share the common base sequence are oligonucleotides of the plurality. In some embodiments, about 0.1%-100%, (*e.g.*, about 1%-100%, 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, or about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, or at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) of all oligonucleotides in a chirally controlled oligonucleotide composition that share the common base sequence, the common pattern of backbone linkages, and the common pattern of backbone phosphorus modifications are oligonucleotides of the plurality. In some embodiments, about 0.1%-100%, (*e.g.*, about 1%-100%, 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, or about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, or at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) of all oligonucleotides in a chirally controlled oligonucleotide composition, or of all oligonucleotides in a composition that share a common base sequence (*e.g.*, of a plurality of oligonucleotide or an oligonucleotide type), or of all oligonucleotides in a composition that share a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone phosphorus modifications (*e.g.*, of a plurality of oligonucleotide or an oligonucleotide type), or of all oligonucleotides in a composition that share a common base sequence, a common patter of base modifications, a common pattern of sugar modifications, a common pattern of internucleotidic linkage types, and/or a common pattern of internucleotidic linkage modifications (*e.g.*, of a plurality of oligonucleotide or an oligonucleotide type), or of all oligonucleotides in a composition that share the same constitution, are oligonucleotides of the plurality. In some embodiments, a percentage is at least $(DP)^{NCI}$, wherein DP is a percentage selected from 85%-100%, and NCI is the number of chirally controlled internucleotidic linkage. In some embodiments, DP is at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. In some embodiments, DP is at least 85%. In some embodiments, DP is at least 90%. In some embodiments, DP is at least 95%. In some embodiments, DP is at least 96%. In some embodiments, DP is at least 97%. In some embodiments, DP is at least 98%. In some embodiments, DP is at least 99%. In some embodiments, DP reflects diastereopurity of linkage phosphorus chiral centers chirally controlled

internucleotidic linkages. In some embodiments, diastereopurity of a linkage phosphorus chiral center of an internucleotidic linkage may be typically assessed using an appropriate dimer comprising such an internucleotidic linkage and the two nucleoside units being linked by the internucleotidic linkage. In some embodiments, the plurality of oligonucleotides share the same stereochemistry at about 1-50 (*e.g.*, about 1-10, 1-20, 5-10, 5-20, 10-15, 10-20, 10-25, 10-30, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) chiral internucleotidic linkages. In some embodiments, the plurality of oligonucleotides share the same stereochemistry at about 0.1%-100% (*e.g.*, about 1%-100%, 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99%) of chiral internucleotidic linkages. In some embodiments, each chiral internucleotidic linkage is a chiral controlled internucleotidic linkage, and the composition is a completely chirally controlled oligonucleotide composition. In some embodiments, not all chiral internucleotidic linkages are chiral controlled internucleotidic linkages, and the composition is a partially chirally controlled oligonucleotide composition. In some embodiments, a chirally controlled oligonucleotide composition comprises predetermined levels of individual oligonucleotide or nucleic acids types. For instance, in some embodiments a chirally controlled oligonucleotide composition comprises one oligonucleotide type at a predetermined level (e.g., as described above). In some embodiments, a chirally controlled oligonucleotide composition comprises more than one oligonucleotide type, each independently at a predetermined level. In some embodiments, a chirally controlled oligonucleotide composition comprises multiple oligonucleotide types, each independently at a predetermined level. In some embodiments, a chirally controlled oligonucleotide composition is a composition of oligonucleotides of an oligonucleotide type, which composition comprises a predetermined level of a plurality of oligonucleotides of the oligonucleotide type.

[00212] *Chirally pure:* as used herein, the phrase "chirally pure" is used to describe an oligonucleotide or compositions thereof, in which all or nearly all (the rest are impurities) of the oligonucleotide molecules exist in a single diastereomeric form with respect to the linkage phosphorus atoms. In many embodiments, as appreciated by those skilled in the art, a chirally pure oligonucleotide composition is substantially pure in that substantially all of the oligonucleotides in the composition are structurally identical (being the same stereoisomer).

[00213] *Linkage phosphorus:* as defined herein, the phrase "linkage phosphorus" is used to indicate that the particular phosphorus atom being referred to is the phosphorus atom present in an internucleotidic linkage, which phosphorus atom corresponds to the phosphorus atom of a natural

phosphate linkage as occurs in naturally occurring DNA and RNA. In some embodiments, a linkage phosphorus atom is in a modified internucleotidic linkage. In some embodiments, a linkage phosphorus atom is the P of P^L of formula I. In some embodiments, a linkage phosphorus atom is chiral.

[00214] *P-modification:* as used herein, the term "P-modification" refers to any modification at the linkage phosphorus other than a stereochemical modification. In some embodiments, a P-modification comprises addition, substitution, or removal of a pendant moiety covalently attached to a linkage phosphorus. In some embodiments, the "P-modification" is W, Y, Z, or –X–L–R^1 of formula I.

[00215] *Blockmer:* the term "blockmer," as used herein, refers to an oligonucleotide whose pattern of structural features characterizing each individual nucleotide unit is characterized by the presence of at least two consecutive nucleotide units sharing a common structural feature at the nucleobase, sugar and/or internucleotidic linkage. By common structural feature is meant common chemistry and/or stereochemistry, e.g., common modifications at nucleobases, sugars, and/or internucleotidic linkages and common stereochemistry at linkage phosphorus chiral centers. In some embodiments, the at least two consecutive nucleotide units sharing a common structural feature are referred to as a "block".

[00216] In some embodiments, a blockmer is a "stereoblockmer," *e.g.*, at least two consecutive nucleotide units have the same stereochemistry at the linkage phosphorus. Such at least two consecutive nucleotide units form a "stereoblock." For instance, (*S*p, *S*p)-ATsCs1GA is a stereoblockmer because at least two consecutive nucleotide units, the Ts and the Cs1, have the same stereochemistry at the linkage phosphorus (both *S*p). In the same oligonucleotide (*S*p, *S*p)-ATsCs1GA, TsCs1 forms a block, and it is a stereoblock.

[00217] In some embodiments, a blockmer is a "P-modification blockmer," *e.g.*, at least two consecutive nucleotide units have the same modification at the linkage phosphorus. Such at least two consecutive nucleotide units form a "P-modification block". For instance, (*R*p, *S*p)-ATsCsGA is a P-modification blockmer because at least two consecutive nucleotide units, the Ts and the Cs, have the same P-modification (i.e., both are a phosphorothioate diester). In the same oligonucleotide of (*R*p, *S*p)-ATsCsGA, TsCs forms a block, and it is a P-modification block.

[00218] In some embodiments, a blockmer is a "linkage blockmer," *e.g.*, at least two consecutive nucleotide units have identical stereochemistry and identical modifications at the linkage phosphorus. At least two consecutive nucleotide units form a "linkage block". For instance, (*R*p, *R*p)-ATsCsGA is a linkage blockmer because at least two consecutive nucleotide units, the Ts and the Cs, have the same stereochemistry (both *R*p) and P-modification (both phosphorothioate). In the same oligonucleotide of (*R*p, *R*p)-ATsCsGA, TsCs forms a block, and it is a linkage block.

[00219] In some embodiments, a blockmer is a "sugar modification blockmer," e.g., at least two

consecutive nucleotide units have identical sugar modifications. In some embodiments, a sugar modification blockmer is a 2'-F blockmer wherein at least two consecutive nucleotide units have 2'-F modification at their sugars. In some embodiments, a sugar modification blockmer is a 2'-OR blockmer wherein at lead two consecutive nucleotide units independently have 2'-OR modification at their sugars, wherein each R is independent as described in the present disclosure. In some embodiments, a sugar modification blockmer is a 2'-OMe blockmer wherein at least two consecutive nucleotide units have 2'-OMe modification at their sugars. In some embodiments, a sugar modification blockmer is a 2'-MOE blockmer wherein at lead two consecutive nucleotide units have 2'-MOE modification at their sugars. In some embodiments, a sugar modification blockmer is a LNA blockmer wherein at least two consecutive nucleotide units have LNA sugars.

[00220] In some embodiments, a blockmer comprises one or more blocks independently selected from a sugar modification block, a stereoblock, a P-modification block and a linkage block. In some embodiments, a blockmer is a stereoblockmer with respect to one block, and/or a P-modification blockmer with respect to another block, and/or a linkage blockmer with respect to yet another block.

[00221] *Altmer*: the term "altmer," as used herein, refers to an oligonucleotide whose pattern of structural features characterizing each individual nucleotide unit is characterized in that no two consecutive nucleotide units of the oligonucleotide strand share a particular structural feature at the nucleobase, sugar, and/or the internucleotidic phosphorus linkage. In some embodiments, an altmer is designed such that it comprises a repeating pattern. In some embodiments, an altmer is designed such that it does not comprise a repeating pattern.

[00222] In some embodiments, an altmer is a "stereoaltmer," *e.g.*, no two consecutive nucleotide units have the same stereochemistry at the linkage phosphorus. For instance, (*R*p, *S*p, *R*p, *S*p, *R*p, *S*p, *R*p, *S*p, *R*p, *S*p *R*p, *S*p, *R*p, *S*p, *R*p, *S*p, *R*p, *S*p, *R*p)-GsCsCsTsCsAsGsTsCsTsGsCsTsTsCsGsCsAsCsC.

[00223] *Gapmer*: as used herein, the term "gapmer" refers to an oligonucleotide characterized in that one or more nucleotide units (gap) do not have the structural features (e.g., nucleobase modifications, sugar modifications, internucleotidic linkage modifications, linkage phosphours stereochemistry, etc.) contained by nucleotide units flanking such one or more nucleotide units at both ends. In some embodiments, a gapmer comprises a gap of one or more natural phosphate linkages, independently flanked at both ends by non-natural internucleotidic linkages. In some embodiments, a gapmer is a sugar modification gapmer, wherein the gapmer comprises a gap of one or more nucleotide units comprising no sugar modifications which the flanking nucleotide at both ends contain. In some embodiments, a gapmer comprises a gap, wherein each nucleotide unit in the gap region contains no 2'-modification that is contained in nucleotide units flanking the gap at both ends. In some embodiments, a provided oligonucleotide comprising a gap, wherein each nucleotide unit in the gap region contains no 2'-OR

modification, while nucleotide units flanking the gap at each end independently comprise a 2'-OR modification. In some embodiments, a provided oligonucleotide comprising a gap, wherein each nucleotide unit in the gap region contains no 2'-F modification, while nucleotide units flanking the gap at each end independently comprise a 2'-F modification.

[00224] *Skipmer*: as used herein, the term "skipmer" refers to a type of gapmer in which every other internucleotidic phosphorus linkage of the oligonucleotide strand is a phosphate diester linkage (a natural phosphate linkage), for example such as those found in naturally occurring DNA or RNA, and every other internucleotidic phosphorus linkage of the oligonucleotide strand is a modified internucleotidic linkage (a non-natural internucleotidic linkage).

[00225] For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 67th Ed., 1986-87, inside cover.

[00226] Unless otherwise specified, salts, such as pharmaceutically acceptable acid or base addition salts, stereoisomeric forms, and tautomeric forms, of compounds (e.g., oligonucleotides, agents, etc.) are included. Unless otherwise specified, singular forms "a", "an", and "the" include the plural reference unless the context clearly indicates otherwise (and vice versa). Thus, for example, a reference to "a compound" may include a plurality of such compounds.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[00227] Synthetic oligonucleotides provide useful molecular tools in a wide variety of applications. For example, oligonucleotides are useful in therapeutic, diagnostic, research, and new nanomaterials applications. The use of naturally occurring nucleic acids (*e.g.*, unmodified DNA or RNA) is limited, for example, by their susceptibility to endo- and exo-nucleases. As such, various synthetic counterparts have been developed to circumvent these shortcomings. These include synthetic oligonucleotides that contain chemical modification, *e.g.*, base modifications, sugar modifications, backbone modifications, *etc.*, which, among other things, render these molecules less susceptible to degradation and improve other properties of oligonucleotides. Chemical modifications may also lead to certain undesired effects, such as increased toxicities, *etc.* From a structural point of view, modifications to natural phosphate linkages can introduce chirality, and certain properties of oligonucleotides may be affected by the configurations of the phosphorus atoms that form the backbone of the oligonucleotides.

[00228] In some embodiments, an oligonucleotide or oligonucleotide composition is: a DMD oligonucleotide or oligonucleotide composition; an oligonucleotide or oligonucleotide composition comprising a non-negatively charged internucleotidic linkage; or a DMD oligonucleotide comprising a non-negatively charged internucleotidic linkage.

[00229] In some embodiments, the chirality of the backbone (*e.g.*, the configurations of the phosphorus atoms) or inclusion of natural phosphate linkages or non-natural internucleotidic linkages in the backbone and/or modifications of a sugar and/or nucleobase, and/or the addition of chemical moieties can affect properties and activities of oligonucleotides, e.g., the ability of a DMD oligonucleotide (e.g., an oligonucleotide antisense to a Dystrophin (DMD) transcript sequence) to skip one or more exons, and/or other properties of a DMD oligonucleotide, including but not limited to, increased stability, improved pharmacokinetics, and/or decreased immunogenicity, etc. Suitable assays for assessing properties and/or activities of provided compounds, e.g., oligonucleotides, and compositions thereof are widely known in the art and can be utilized in accordance with the present disclosure. For example, to test immunogenicity, various DMD oligonucleotides were tested in mouse serum in vivo and demonstrated minimal activation of cytokines, and various DMD oligonucleotides were tested ex vivo in human PBMC (peripheral blood mononuclear cells) for cytokine activity (e.g., IL-12p40, IL-12p70, IL-1alpha, IL-1beta, IL-6, MCP-1, MIP-1alpha, MIP-1beta, and TNF-alpha).

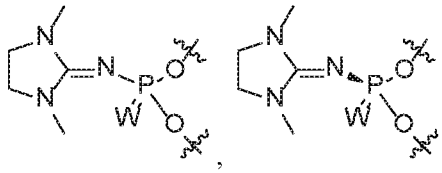
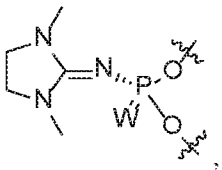
[00230] In some embodiments, technologies (e.g., oligonucleotides, compositions, and methods of use thereof) of the present disclosure can be utilized to target various nucleic acids (e.g., by hybridizing to a target sequence of a target nucleic acid, and/or providing level reduction, degradation, splicing modulation, transcription suppression, etc. of the target nucleic acid, etc.) In some embodiments, provided technologies are particularly useful for modulating splicing of transcripts, e.g., to increase levels of desired splicing products and/or to reduce levels of undesired splicing products. In some embodiments, provided technologies are particularly useful for reducing levels of transcripts, e.g., pre-mRNA, RNA, etc., and in many instances, reducing levels of products arising from or encoded by such transcripts such as mRNA, proteins, etc.

[00231] In some embodiments, a transcript is pre-mRNA. In some embodiments, a splicing product is mature RNA. In some embodiments, a splicing product is mRNA. In some embodiments, splicing modulation or alteration comprises skipping one or more exons. In some embodiments, splicing of a transcript is improved in that exon skipping increases levels of mRNA and proteins that have improved beneficial activities compared with absence of exon skipping. In some embodiments, an exon causing frameshift is skipped. In some embodiments, an exon comprising an undesired mutation is skipped. In some embodiments, an exon comprising a premature termination codon is skipped. An undesired mutation can be a mutation causing changes in protein sequences; it can also be a silent mutation. In some embodiments, a transcript is a transcript of Dystrophin (DMD).

[00232] In some embodiments, splicing of a transcript is improved in that exon skipping lowers levels of mRNA and proteins that have undesired activities compared with absence of exon skipping. In some embodiments, a target is knocked down through exon skipping which, by skipping one or more

exons, causes premature stop codon and/or frameshift mutations. In some embodiments, provided oligonucleotides in provided compositions, *e.g.*, oligonucleotides of a plurality, comprise base modifications, sugar modifications, and/or internucleotidic linkage modifications. In some embodiments, provided oligonucleotides comprise base modifications and sugar modifications. In some embodiments, provided oligonucleotides comprise base modifications and internucleotidic linkage modifications. In some embodiments, provided oligonucleotides comprise sugar modifications and internucleotidic modifications. In some embodiments, provided compositions comprise base modifications, sugar modifications, and internucleotidic linkage modifications. Example chemical modifications, such as base modifications, sugar modifications, internucleotidic linkage modifications, *etc.* are widely known in the art including but not limited to those described in this disclosure. In some embodiments, a modified base is substituted A, T, C, G or U. In some embodiments, a sugar modification is 2'-modification. In some embodiments, a 2'-modification is 2-F modification. In some embodiments, a 2'-modification is 2'-OR^1, wherein R^1 is not hydrogen. In some embodiments, a 2'-modification is 2'-OR^1, wherein R^1 is optionally substituted alkyl. In some embodiments, a 2'-modification is 2'-OMe. In some embodiments, a 2'-modification is 2'-MOE. In some embodiments, a modified sugar moiety is a bridged bicyclic or polycyclic ring. In some embodiments, a modified sugar moiety is a bridged bicyclic or polycyclic ring having 5-20 ring atoms wherein one or more ring atoms are optionally and independently heteroatoms. Example ring structures are widely known in the art, such as those found in BNA, LNA, *etc.* In some embodiments, provided oligonucleotides comprise both one or more modified internucleotidic linkages and one or more natural phosphate linkages. In some embodiments, oligonucleotides comprising both modified internucleotidic linkage and natural phosphate linkage and compositions thereof provide improved properties, *e.g.*, activities and toxicities, *etc.* In some embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphorothioate linkage. In some embodiments, a modified internucleotidic linkage is a substituted phosphorothioate linkage.

[00233] In some embodiments, provided oligonucleotides comprise one or more non-negatively charged internucleotidic linkages. In some embodiments, a non-negatively charged internucleotidic linkage is a positively charged internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a modified internucleotidic linkage (e.g., a non-negatively charged internucleotidic linkage) comprises optionally substituted triazolyl. In some embodiments, a modified internucleotidic linkage (e.g., a non-negatively charged internucleotidic linkage) comprises optionally substituted alkynyl. In some embodiments, a modified internucleotidic linkage comprises a triazole or alkyne moiety. In some embodiments, a triazole moiety, e.g., a triazolyl group, is optionally substituted. In some embodiments, a triazole moiety, e.g., a

triazolyl group) is substituted. In some embodiments, a triazole moiety is unsubstituted. In some embodiments, a modified internucleotidic linkage comprises an optionally substituted guanidine moiety. In some embodiments, a modified internucleotidic linkage comprises an optionally substituted cyclic guanidine moiety. In some embodiments, a modified internucleotidic linkage comprises an optionally substituted cyclic guanidine moiety and has the structure of:  , or  , wherein W is O or S. In some embodiments, W is O. In some embodiments, W is S. In some embodiments, a non-negatively charged internucleotidic linkage is stereochemically controlled.

[00234] In some embodiments, an internucleotidic linkage comprising an optionally substituted guanidine moiety is an internucleotidic linkage of formula **I-n-2**, **I-n-3**, **I-n-4**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, or **II-d-2** as described herein. In some embodiments, an internucleotidic linkage comprising an optionally substituted cyclic guanidine moiety is an internucleotidic linkage of formula **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, or **II-d-2**.

[00235] Among other things, the present disclosure encompasses the recognition that stereorandom oligonucleotide preparations contain a plurality of distinct chemical entities that differ from one another, *e.g.*, in the stereochemical structure of individual backbone linkage phosphorus chiral centers within the oligonucleotide chain. Without control of stereochemistry of backbone chiral centers, stereorandom oligonucleotide preparations provide uncontrolled compositions comprising undetermined levels of oligonucleotide stereoisomers with respect to the uncontrolled chiral centers, e.g., chiral linkage phosphorus. Even though these stereoisomers may have the same base sequence, they are different chemical entities at least due to their different backbone stereochemistry, and they can have, as demonstrated herein, different properties, *e.g.*, activities, toxicities, *etc.* Among other things, the present disclosure provides new oligonucleotide compositions wherein stereochemistry of one or more linkage phosphorus chiral centers are independently controlled (e.g., in chirally controlled internucleotidic linkages). In some embodiments, the present disclosure provides chirally controlled oligonucleotide compositions which are or contain particular stereoisomers of oligonucleotides of interest.

[00236] In some embodiments, provided oligonucleotides contain increased levels of one or more isotopes. In some embodiments, provided oligonucleotides are labeled, *e.g.*, by one or more isotopes of one or more elements, *e.g.*, hydrogen, carbon, nitrogen, *etc.* In some embodiments, provided

oligonucleotides in provided compositions, *e.g.*, oligonucleotides of a plurality, comprise base modifications, sugar modifications, and/or internucleotidic linkage modifications, wherein the oligonucleotides contain an enriched level of deuterium. In some embodiments, provided oligonucleotides are labeled with deuterium (replacing $-^{1}H$ with $-^{2}H$) at one or more positions. In some embodiments, one or more ^{1}H of an oligonucleotide or any moiety conjugated to the oligonucleotide (*e.g.*, a targeting moiety, lipid, *etc.*) is substituted with ^{2}H. Such oligonucleotides can be used in any composition or method described herein.

[00237] In some embodiments, in an oligonucleotide, a pattern of backbone chiral centers can provide improved activity(s) or characteristic(s), including but not limited to: improved skipping of one or more exons, increased stability, increased activity, increased stability and activity, low toxicity, low immune response, improved protein binding profile, increased binding to certain proteins, and/or enhanced delivery.

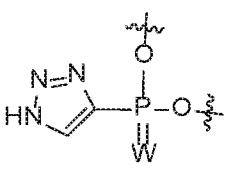
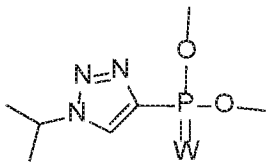
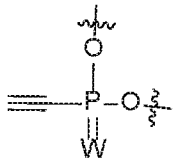
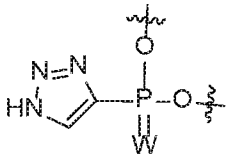
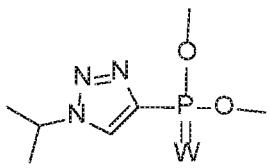
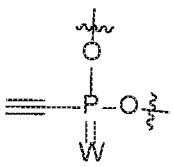
[00238] In some embodiments, a pattern of backbone chiral centers is or comprises S, SS, SSS, SSSS, SSSSS, SSSSSS, SSSSSSS, SOS, SSOSS, SSSOSSS, SSSSOSSSS, SSSSSOSSSSS, SSSSSSOSSSSSS, SSSSSSSOSSSSSSS, SSSSSSSSOSSSSSSSS, SSSSSSSSSOSSSSSSSSS, SOSOSOSOS, SSOSOSOSOSS, SSSOSOSOSOSSS, SSSSOSOSOSOSSSS, SSSSSOSOSOSOSSSSS, SSSSSSOSOSOSOSSSSSS, SOSOSSOOS, SSOSOSSOOSS, SSSOSOSSOOSSS, SSSSOSOSSOOSSSSS, SSSSSSOSOSSOOSSSSSS, SOSOOSOOS, SSOSOOSOOSS, SSSOSOOSOOSSS, SSSSOSOOSOOSSSSS, SSSSSOSOOSOOSSSSSS, SSSSSSOSOOSOOSSSSSSS, SOSOSSOOS, SSOSOSSOOSO, SSSOSOSSOOSOS, SSSSOSOSSOOSOSS, SSSSSOSOSSOOSOSSSS, SSSSSSOSOSSOOSOSSSSS, SOSOOSOOSO, SSOSOOSOOSOS, SSSOSOOSOOSOS, SSSSOSOOSOOSOSS, SSSSSOSOOSOOSOSSS, SSSSSSOSOOSOOSOSSSSS, SSOSOSSOO, SSSOSOSSOOS, SSSSOSOSSOOS, SSSSSOSOSSOOSS, SSSSSSOSOSSOOSSSS, OSSSSSSOSOSSOOSSS, OOSSSSSSOSOSSOOS, OOSSSSSSOSOSSOOSS, OOSSSSSSOSOSSOOSSS, OOSSSSSSOSOSSOOSSSS, OOSSSSSSOSOSSOOSSSSS, and/or OOSSSSSSOSOSSOOSSSSSS, RS, SR, SRS, SRSS, SSRS, RR, RRR, RRRR, RRRRR, SRR, RRS, SRRS, SSRRS, SRRSS, SRRR, RRRS, SRRRS, SSRRRS, SSRRRS, RSRRR, SRRRSR, SSSRSSS, SSSSRSSSS, SSSSSRSSSSS, SSSSSSRSSSSSS, SSSSSSSRSSSSSSS, SSSSSSSSRSSSSSSSS, SSSSSSSSSRSSSSSSSSS, SRSRSRSRS, SSRSRSRSRSS, SSSRSRSRSRSSS, SSSSRSRSRSRSSSS, SSSSSRSRSRSRSSSSS, SSSSSSRSRSRSRSSSSSS, SRSRSSRRS, SSRSRSSRRSS, SSSRSRSSRRSSS, SSSSRSRSSRRSSSS, SSSSSRSRSSRRSSSSS, SSSSSSRSRSSRRSSSSSS, SRSRRSRRS, SSRSRRSRRSS, SSSRSRRSRRSSS, SSSSRSRRSRRSSSS, SSSSSRSRRSRRSSSSS, SSSSSSRSRRSRRSSSSSS, SRSRSSRRS, SSRSRSSRRSR, SSSRSRSSRRSRS, SSSSRSRSSRRSRSS, SSSSSRSRSSRRSRSSS, SSSSSSRSRSSRRSRSSSS, SRSRRSRRSR, SSRSRRSRRSRS,

SSSRSRRSRRSRS, SSSSRSRRSRRSRSS, SSSSSRSRRSRRSRSSS, SSSSSSRSRRSRRSRSSSS, SSRSRSSRR, SSSRSRSSRRS, SSSSRSRSSRRS, SSSSSRSRSSRRSS, SSSSSSRSRSSRRSSS, RSSSSSSRSRSSRRSSS, RRSSSSSSRSRSSRRS, RRSSSSSSRSRSSRRSS, RRSSSSSSRSRSSRRSSS, RRSSSSSSRSRSSRRSSSS, RRSSSSSSRSRSSRRSSSSS, $(R)_n(S)_m$, $(S)_t(R)_n$, $(O)_t(R)_n(S)_m$, $(S)_t(O)_m$, $(O)_m(S)_t$, $(S)_t(R)_n(S)_m$, $(S)_t(O)_m(S)_n$, $(S)_t(O)_m$, wherein t, m and n are independently 1 to 20, O is a non-chiral internucleotidic linkage, R is a Rp chiral internucleotidic linkage, and S is an *Sp* chiral internucleotidic linkage. In some embodiments, the non-chiral center is a phosphodiester linkage. In some embodiments, the chiral center in a *Sp* configuration is a phosphorothioate linkage.

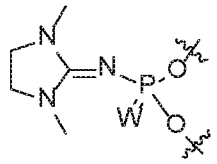
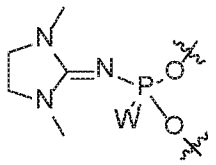
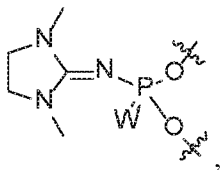
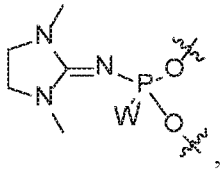
[00239] In some embodiments, the 5'-end region of provided oligonucleotides, *e.g.*, a 5'-wing, comprises a stereochemistry pattern of S, SS, SSS, SSSS, SSSSS, SSSSSS, or SSSSSS. In some embodiments, each S is or represents an *Sp* phosphorothioate internucleotidic linkage. In some embodiments, the 5'-end region of provided oligonucleotides, *e.g.*, a 5'-wing, comprises a stereochemistry pattern of S, SS, SSS, SSSS, SSSSS, SSSSSS, or SSSSSS, wherein the first S represents the first (the 5'-end) internucleotidic linkage of a provided oligonucleotide. In some embodiments, one or more nucleotidic units comprising an *Sp* internucleotidic linkage in the 5'-end region independently comprise −F. In some embodiments, each nucleotidic unit comprising an *Sp* internucleotidic linkage in the 5'-end region independently comprises −F. In some embodiments, one or more nucleotidic units comprising an *Sp* internucleotidic linkage in the 5'-end region independently comprise a sugar modification. In some embodiments, each nucleotidic unit comprising an *Sp* internucleotidic linkage in the 5'-end region independently comprises a sugar modification. In some embodiments, each 2'-modification is the same. In some embodiments, a sugar modification is a 2'-modification. In some embodiments, a 2'-modification is 2'-OR^1. In some embodiments, a 2'-modification is 2'-F. In some embodiments, the 3'-end region of provided oligonucleotides, *e.g.*, a 3'-wing, comprises a stereochemistry pattern of S, SS, SSS, SSSS, SSSSS, SSSSSS, or SSSSSS. In some embodiments, each S is or represents an *Sp* phosphorothioate internucleotidic linkage. In some embodiments, the 3'-end region of provided oligonucleotides, *e.g.*, a 3'-wing, comprises a stereochemistry pattern of S, SS, SSS, SSSS, SSSSS, SSSSSS, or SSSSSS, wherein the last S represents the last (the 3'-end) internucleotidic linkage of a provided oligonucleotide. In some embodiments, each S represents an *Sp* phosphorothioate internucleotidic linkage. In some embodiments, one or more nucleotidic units comprising an *Sp* internucleotidic linkage in the 3'-end region independently comprise −F. In some embodiments, each nucleotidic unit comprising an *Sp* internucleotidic linkage in the 3'-end region independently comprises −F. In some embodiments, one or more nucleotidic units comprising an *Sp* internucleotidic linkage in the 3'-end region independently comprise a sugar modification. In some embodiments, each nucleotidic unit comprising an *Sp* internucleotidic linkage in the 3'-end region independently comprises a sugar

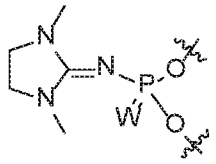
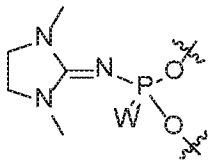
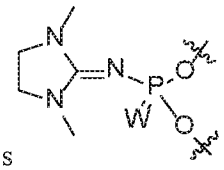
modification. In some embodiments, each 2'-modification is the same. In some embodiments, a sugar modification is a 2'-modification. In some embodiments, a 2'-modification is 2'-OR^1. In some embodiments, a 2'-modification is 2'-F. In some embodiments, provided oligonucleotides comprise both a 5'-end region, *e.g.*, a 5'-wing, and a 3'-end region, *e.g.*, a 3'-end wing, as described herein. In some embodiments, the 5'-end region comprises a stereochemistry pattern of SS, wherein the first S represents the first internucleotidic linkage of a provided oligonucleotide, the 3'-end region comprises a stereochemistry pattern of SS, wherein one or more nucleotidic unit comprising an *Sp* internucleotidic linkage in the 5'- or 3'-end region comprise −F. In some embodiments, the 5'-end region comprises a stereochemistry pattern of SS, wherein the first S represents the first internucleotidic linkage of a provided oligonucleotide, the 3'-end region comprises a stereochemistry pattern of SS, wherein one or more nucleotidic unit comprising an *Sp* internucleotidic linkage in the 5'- or 3'-end region comprise a 2'-F sugar modification. In some embodiments, provided oligonucleotides further comprise a middle region between the 5'-end and 3'-end regions, *e.g.*, a core region, which comprises one or more natural phosphate linkages. In some embodiments, provided oligonucleotides further comprise a middle region between the 5'-end and 3'-end regions, *e.g.*, a core region, which comprises one or more natural phosphate linkages and one or more internucleotidic linkages. In some embodiments, a middle region comprises one or more sugar moieties, wherein each sugar moiety independently comprises a 2'-OR^1 modification. In some embodiments, a middle region comprises one or more sugar moieties comprising no 2'-F modification. In some embodiments, a middle region comprises one or more *Sp* internucleotidic linkages. In some embodiments, a middle region comprises one or more *Sp* internucleotidic linkages and one or more natural phosphate linkages. In some embodiments, a middle region comprises one or more *Rp* internucleotidic linkages. In some embodiments, a middle region comprises one or more *Rp* internucleotidic linkages and one or more natural phosphate linkages. In some embodiments, a middle region comprises one or more *Rp* internucleotidic linkages and one or more *Sp* internucleotidic linkages.

[00240] In some embodiments, provided oligonucleotides comprise one or more modified internucleotidic linkages. In some embodiments, provided oligonucleotides comprise one or more chiral modified internucleotidic linkages. In some embodiments, provided oligonucleotides comprise one or more chirally controlled chiral modified internucleotidic linkages. In some embodiments, provided oligonucleotides comprise one or more natural phosphate linkages. In some embodiments, provided oligonucleotides comprise one or more modified internucleotidic linkages and one or more natural phosphate linkages. In some embodiments, a modified internucleotidic linkage is a phosphorothioate linkage. In some embodiments, each modified internucleotidic linkage is a phosphorothioate linkage. In some embodiments, a modified internucleotidic linkage comprises a triazole, substituted triazole, alkyne or Tmg.

[00241] In some embodiments, the present disclosure pertains to a nucleic acid which comprises a modified internucleotidic linkage comprising a triazole or alkyne moiety. In some embodiments, the present disclosure pertains to a nucleic acid which comprises a modified internucleotidic linkage comprising an optionally substituted triazolyl or alkynyl. In some embodiments, such a nucleic acid is a siRNA, double-straned siRNA, single-stranded siRNA, oligonucleotide, gapmer, skipmer, blockmer, antisense oligonucleotide, antagomir, microRNA, pre-microRNA, antimir, supermir, ribozyme, Ul adaptor, RNA activator, RNAi agent, decoy oligonucleotide, triplex forming oligonucleotide, aptamer or adjuvant. In some embodiments, the present disclosure pertains to an oligonucleotide which comprises a modified internucleotidic linkage comprising a triazole or alkyne moiety. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which comprises a modified internucleotidic linkage comprising a triazole or alkyne moiety. In some embodiments, the present disclosure pertains to a nucleic acid which comprises a modified internucleotidic linkage comprising a triazole moiety. In some embodiments, the present disclosure pertains to a nucleic acid which comprises a modified internucleotidic linkage comprising optionally substituted triazolyl. In some embodiments, the present disclosure pertains to a nucleic acid which comprises a modified internucleotidic linkage comprising a substituted triazole moiety. In some embodiments, the present disclosure pertains to a nucleic acid which comprises a modified internucleotidic linkage comprising an alkyne moiety. In some embodiments, the present disclosure pertains to a nucleic acid or oligonucleotide which comprises, at a 5' end, a structure of the formula:  ,  , or  , wherein W is O or S. In some embodiments, an oligonucleotide is a single-stranded siRNA which comprises, at a 5' end, a structure of the formula:  ,  , or  , wherein W is O or S. In some embodiments, a modified internucleotidic linkage is any modified internucleotidic linkage described in Krishna et al. 2012 J. Am. Chem. Soc. 134: 11618–11631.

[00242] In some embodiments, the present disclosure pertains to a nucleic acid which comprises a modified internucleotidic linkage which comprises a guanidine moiety. In some embodiments, the present disclosure pertains to a nucleic acid which comprises a modified internucleotidic linkage which comprises a cyclic guanidine moiety. In some embodiments, the present disclosure pertains to a nucleic acid which comprises a modified internucleotidic linkage which comprises a cyclic guanidine moiety and

has the structure of:  , wherein W is O or S. In some embodiments, a neutral internucleotidic linkage or internucleotidic linkage comprising a cyclic guanidine is chirally controlled. In some embodiments, a nucleic acid comprising a non-negatively charged internucleotidic linkage or a modified internucleotidic linkage comprising a cyclic guanidine moiety is a siRNA, double-straned siRNA, single-stranded siRNA, oligonucleotide, gapmer, skipmer, blockmer, antisense oligonucleotide, antagomir, microRNA, pre-microRNA, antimir, supermir, ribozyme, Ul adaptor, RNA activator, RNAi agent, decoy oligonucleotide, triplex forming oligonucleotide, aptamer or adjuvant. In some embodiments, the present disclosure pertains to an oligonucleotide which comprises a modified internucleotidic linkage which comprises a cyclic guanidine moiety. In some embodiments, the present disclosure pertains to an oligonucleotide which comprises a modified internucleotidic linkage which has the structure of:  , wherein W is O or S. In some embodiments, a neutral internucleotidic linkage or internucleotidic linkage comprising a cyclic guanidine moiety is chirally controlled. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which comprises a modified internucleotidic linkage comprising a cyclic guanidine moiety. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which comprises a modified internucleotidic linkage which has the structure of:  , wherein W is O or S. In some embodiments, a neutral internucleotidic linkage or internucleotidic linkage comprising a cyclic guanidine moiety is chirally controlled. In some embodiments, the present disclosure pertains to a nucleic acid which comprises a modified internucleotidic linkage comprising a cyclic guanidine moiety. In some embodiments, the present disclosure pertains to a nucleic acid which comprises a modified internucleotidic linkage which has the structure of:  , wherein W is O or S. In some embodiments, the present disclosure pertains to a nucleic acid or oligonucleotide which comprises, at a 5' end, a structure comprising a cyclic guanidine moiety. In some embodiments, the present disclosure

pertains to a nucleic acid or oligonucleotide which comprises, at a 5' end, a structure of the formula:  , wherein W is O or S. In some embodiments, the oligonucleotide is a single-stranded siRNA which comprises, at a 5' end, a structure comprising a cyclic guanidine moiety. In some embodiments, the oligonucleotide is a single-stranded siRNA which comprises, at a 5' end, a structure of the formula:  , wherein W is O or S. In some embodiments, the internucleotidic linkage comprises  (wherein W is O or S) and is chirally controlled.

[00243] In some embodiments, provided oligonucleotides can bind to a transcript, and change the splicing pattern of the transcript. In some embodiments, provided oligonucleotides provides exon-skipping of an exon, with efficiency greater than a comparable oligonucleotide under one or more suitable conditions, *e.g.*, as described herein. In some embodiments, a provided skipping efficiency is at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190% more than, or 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or more fold of, that of a comparable oligonucleotide under one or more suitable conditions, *e.g.*, as described herein. In some embodiments, a comparable oligonucleotide is an oligonucleotide which has fewer or no chirally controlled internucleotidic linkages and/or fewer or no non-negatively charged internucleotidic linkages but is otherwise identical.

[00244] In some embodiments, the present disclosure demonstrates that 2'-F modifications, among other things, can improve exon-skipping efficiency. In some embodiments, the present disclosure demonstrates that *Sp* internucleotidic linkages, among other things, at the 5'- and 3'-ends can improve oligonucleotide stability. In some embodiments, the present disclosure demonstrates that, among other things, natural phosphate linkages and/or *Rp* internucleotidic linkages can improve removal of oligonucleotides from a system. As appreciated by a person having ordinary skill in the art, various assays known in the art can be utilized to assess such properties in accordance with the present disclosure.

[00245] In some embodiments, provided oligonucleotides comprise one or more modified sugar moieties. In some embodiments, a modified sugar moiety comprises a 2'-modification. In some embodiments, a modified sugar moiety comprises a 2'-modification. In some embodiments, a 2'-

modification is 2'-OR^1. In some embodiments, a 2'-modification is a 2'-OMe. In some embodiments, a 2'-modification is a 2'-MOE. In some embodiments, a 2'-modification is an LNA sugar modification. In some embodiments, a 2'-modification is 2'-F. In some embodiments, each sugar modification is independently a 2'-modification. In some embodiments, each sugar modification is independently 2'-OR^1 or 2'-F. In some embodiments, each sugar modification is independently 2'-OR^1 or 2'-F, wherein R^1 is optionally substituted C_{1-6} alkyl. In some embodiments, each sugar modification is independently 2'-OR^1 or 2'-F, wherein at least one is 2'-F. In some embodiments, each sugar modification is independently 2'-OR^1 or 2'-F, wherein R^1 is optionally substituted C_{1-6} alkyl, and wherein at least one is 2'-OR^1. In some embodiments, each sugar modification is independently 2'-OR^1 or 2'-F, wherein at least one is 2'-F, and at least one is 2'-OR^1. In some embodiments, each sugar modification is independently 2'-OR^1 or 2'-F, wherein R^1 is optionally substituted C_{1-6} alkyl, and wherein at least one is 2'-F, and at least one is 2'-OR^1.

[00246] In some embodiments, 5% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, each sugar moiety of provided oligonucleotides is modified. In some embodiments, a modified sugar moiety comprises a 2'-modification. In some embodiments, a modified sugar moiety comprises a 2'-modification. In some embodiments, a 2'-modification is 2'-OR^1. In some embodiments, a 2'-modification is a 2'-OMe. In some embodiments, a 2'-modification is a 2'-MOE. In some embodiments, a 2'-modification is an LNA sugar modification. In some embodiments, a 2'-modification is 2'-F. In some embodiments, each sugar modification is independently a 2'-modification. In some embodiments, each sugar modification is independently 2'-OR^1 or 2'-F. In some embodiments, each sugar modification is independently 2'-OR^1 or 2'-F, wherein R^1 is optionally substituted C_{1-6} alkyl. In some embodiments, each sugar modification is independently 2'-OR^1 or 2'-F, wherein at least one is 2'-F. In some embodiments, each sugar modification is independently 2'-OR^1 or 2'-F, wherein R^1 is optionally substituted C_{1-6} alkyl, and wherein at least one is 2'-OR^1. In some embodiments, each sugar modification is independently 2'-OR^1 or 2'-F, wherein at least one is 2'-F, and at least one is 2'-OR^1. In some embodiments, each sugar modification is independently 2'-OR^1 or 2'-F, wherein R^1 is optionally substituted C_{1-6} alkyl, and wherein at least one is 2'-F, and at least one is 2'-OR^1.

[00247] In some embodiments, provided oligonucleotides comprise one or more 2'-F. In some embodiments, provided oligonucleotides comprise two or more 2'-F.

[00248] In some embodiments, provided oligonucleotides comprise alternating 2'-F modified sugar moieties and 2'-OR^1 modified sugar moieties. In some embodiments, provided oligonucleotides comprise alternating 2'-F modified sugar moieties and 2'-OMe modified sugar moieties, *e.g.*, [(2'-F)(2'-OMe)]x, [(2'-OMe)(2'-F)]x, *etc.*, wherein x is 1-50. In some embodiments, provided oligonucleotides

comprise at least two pairs of alternating 2'-F and 2'-OMe modifications. In some embodiments, provided oligonucleotides comprises alternating phosphodiester and phosphorothioate internucleotidic linkages, *e.g.*, [(PO)(PS)]x, [(PS)(PO)]x, *etc.*, wherein x is 1-50. In some embodiments, provided oligonucleotides comprise at least two pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages.

[00249] In some embodiments, provided oligonucleotides comprise one or more natural phosphate linkages and one or more modified internucleotidic linkages. In some embodiments, provided oligonucleotides comprise one or more natural phosphate linkages and one or more modified internucleotidic linkages and one or more non-negatively charged internucleotidic linkages.

[00250] In some embodiments, the present disclosure provides an oligonucleotide composition comprising a plurality of oligonucleotides, wherein:

oligonucleotides of the plurality have the same base sequence; and

oligonucleotides of the plurality comprise one or more modified sugar moieties, or comprise one or more natural phosphate linkages and one or more modified internucleotidic linkages.

[00251] In some embodiments, oligonucleotides of a plurality comprise one or more modified sugar moieties. In some embodiments, provided oligonucleotides comprise one or more modified sugar moieties. In some embodiments, provided oligonucleotides comprise 2 or more modified sugar moieties. In some embodiments, provided oligonucleotides comprise 3 or more modified sugar moieties.

[00252] In some embodiments, provided compositions alter transcript splicing so that an undesired target and/or biological function are suppressed.

[00253] In some embodiments, provided compositions alter transcript splicing so a desired target and/or biological function is enhanced.

[00254] In some embodiments, each oligonucleotide of a plurality comprises one or more modified sugar moieties and modified internucleotidic linkages.

[00255] In some embodiments, each oligonucleotide of a plurality comprises no more than about 25 consecutive unmodified sugar moieties

[00256] In some embodiments, each oligonucleotide of a plurality comprises no more than about 95% unmodified sugar moieties. In some embodiments, each oligonucleotide of a plurality comprises no more than about 90% unmodified sugar moieties. In some embodiments, each oligonucleotide of a plurality comprises no more than about 85% unmodified sugar moieties. In some embodiments, each oligonucleotide of a plurality comprises no more than about 15 consecutive unmodified sugar moieties.

[00257] In some embodiments, each oligonucleotide of a plurality comprises no more than about 95% unmodified sugar moieties.

[00258] In some embodiments, each oligonucleotide of a plurality comprises two or more

modified internucleotidic linkages.

[00259] In some embodiments, about 5% of the internucleotidic linkages in each oligonucleotide of a plurality are modified internucleotidic linkages.

[00260] In some embodiments, each oligonucleotide of a plurality comprises no more than about 25 consecutive natural phosphate linkages. In some embodiments, each oligonucleotide of a plurality comprises no more than about 20 natural phosphate linkages.

[00261] In some embodiments, oligonucleotides of a plurality comprise no natural DNA nucleotide units. In some embodiments, oligonucleotides of a plurality comprise no more than 30 natural DNA nucleotides. In some embodiments, oligonucleotides of a plurality comprise no more than 30 consecutive DNA nucleotides.

[00262] In some embodiments, compared to a reference condition, provided chirally controlled oligonucleotide compositions are surprisingly effective. In some embodiments, desired biological effects (*e.g.*, as measured by increased levels of desired mRNA, proteins, *etc.*, decreased levels of undesired mRNA, proteins, *etc.*) can be enhanced by more than 5, 10, 15, 20, 25, 30, 40, 50, or 100 fold. In some embodiments, a change is measured by increase of a desired mRNA level compared to a reference condition. In some embodiments, a change is measured by decrease of an undesired mRNA level compared to a reference condition. In some embodiments, a reference condition is absence of oligonucleotide treatment. In some embodiments, a reference condition is a stereorandom composition of oligonucleotides having the same base sequence and chemical modifications.

[00263] In some embodiments, a desired biological effect is: improved skipping of one or more exons, increased stability, increased activity, increased stability and activity, low toxicity, low immune response, improved protein binding profile, increased binding to certain proteins, and/or enhanced delivery. In some embodiments, a desired biological effect is enhanced by more than 2 fold, 3 fold, 4 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 11 fold, 12 fold, 13 fold, 14 fold, 15 fold, 20 fold, 25 fold, 30 fold, 35 fold, 40 fold, 45 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, 100 fold, 200 fold, or 500 fold.

[00264] In some embodiments, the structure of a DMD oligonucleotide is or comprises a wing-core-wing, wing-core, or core-wing structure. In some embodiments, a 5'-wing is a 5'-end region. In some embodiments, a 3'-wing is a 3'-end region. In some embodiments, a core is a middle region. In some embodiments, a 5'-end region is a 5'-wing region. In some embodiments, a 3'-end region is a 3'-wing region. In some embodiments, a middle region is a core region.

[00265] In some embodiments, an oligonucleotide having a wing-core-wing structure is designated a gapmer. In some embodiments, a gapmer is asymmetric, in that the chemistry of one wing is different from the chemistry of the other wing. In some embodiments, a gapmer is asymmetric, in that the

chemistry of one wing is different from the chemistry of the other wing, wherein the wings differ in sugar modifications and/or internucleotidic linkages, or patterns thereof. In some embodiments, a gapmer is asymmetric, in that the chemistry of one wing is different from the chemistry of the other wing, wherein the wings differ in sugar modifications, wherein one wing comprises a sugar modification not present in the other wing; or both wings each comprise a sugar modification not found in the other wing; or both wings comprise different patterns of the same types of sugar modifications; or one wing comprises only one type of sugar modification, while the other wing comprises two types of sugar modifications; etc.

[00266] In some embodiments, an internucleotidic linkage between a wing region and a core region is considered part of the wing region. In some embodiments, an internucleotidic linkage between a 5'-wing region and a core region is considered part of the wing region. In some embodiments, an internucleotidic linkage between a 3'-wing region and a core region is considered part of the wing region. In some embodiments, an internucleotidic linkage between a wing region and a core region is considered part of the core region. In some embodiments, an internucleotidic linkage between a 5'-wing region and a core region is considered part of the core region. In some embodiments, an internucleotidic linkage between a 3'-wing region and a core region is considered part of the core region.

[00267] In some embodiments, a region (e.g., a wing region, a core region, a 5'-end region, a middle region, a 3'-end region, etc.) comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more nucleoside units.

[00268] In some embodiments, provided oligonucleotides comprise two wing and one core regions. In some embodiments, provided oligonucleotides comprises a 5'-wing-core-wing-3' structure. In some embodiments, provided oligonucleotides are of a 5'-wing-core-wing-3' gapmer structure. In some embodiments, the two wing regions are identical. In some embodiments, the two wing regions are different. In some embodiments, the two wing regions are identical in chemical modifications. In some embodiments, the two wing regions are identical in 2'-modifications. In some embodiments, the two wing regions are identical in internucleotidic linkage modifications. In some embodiments, the two wing regions are identical in patterns of backbone chiral centers. In some embodiments, the two wing regions are identical in pattern of backbone linkages. In some embodiments, the two wing regions are identical in pattern of backbone linkage types. In some embodiments, the two wing regions are identical in pattern of backbone phosphorus modifications.

[00269] A wing region can be differentiated from a core region in that a wing region contains a different structure feature than a core region. For example, in some embodiments, a wing region differs from a core region in that they have different sugar modifications, base modifications, internucleotidic linkages, internucleotidic linkage stereochemistry, *etc.* In some embodiments, a wing region differs from a core region in that they have different 2'-modifications of the sugars.

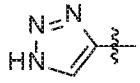
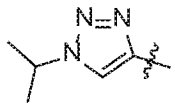
[00270] In some embodiments, a region (e.g., a wing region, a core region, a 5'-end region, a middle region, a 3'-end region, etc.) comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more modified internucleotidic linkages. In some embodiments, a region comprises 2 or more modified internucleotidic linkages. In some embodiments, a region comprises 3 or more modified internucleotidic linkages. In some embodiments, a region comprises 4 or more modified internucleotidic linkages. In some embodiments, a region comprises 5 or more modified internucleotidic linkages. In some embodiments, a region comprises 6 or more modified internucleotidic linkages. In some embodiments, a region comprises 7 or more modified internucleotidic linkages. In some embodiments, a region comprises 8 or more modified internucleotidic linkages. In some embodiments, a region comprises 9 or more modified internucleotidic linkages. In some embodiments, a region comprises 10 or more modified internucleotidic linkages.

[00271] In some embodiments, provided oligonucleotides comprise consecutive nucleoside units each of which comprises no 2'-OR^1 modifications (wherein R^1 is not hydrogen). In some embodiments, provided oligonucleotides comprise consecutive nucleoside units whose 2'-positions are independently unsubstituted or substituted with 2'-F. In some embodiments, such an oligonucleotide is a DMD oligonucleotide. In some embodiments, each of the consecutive nucleoside units is independently preceded and/or followed by a modified internucleotidic linkage. In some embodiments, each of the consecutive nucleoside units is independently preceded and/or followed by a phosphorothioate linkage. In some embodiments, each of the consecutive nucleoside units is independently preceded and/or followed by a chirally controlled modified internucleotidic linkage. In some embodiments, each of the consecutive nucleoside units is independently preceded and/or followed by a chirally controlled phosphorothioate linkage.

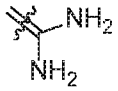
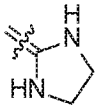
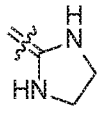
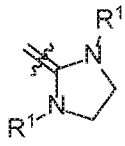
[00272] In some embodiments, a modified internucleotidic linkage has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, **III**, etc., or a salt form thereof. In some embodiments, a modified internucleotidic linkage has a structure of formula **I** or a salt form thereof. In some embodiments, a modified internucleotidic linkage has a structure of formula **I-a** or a salt form thereof.

[00273] In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a positively-charged internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., or a salt form thereof. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 3-20 membered heterocyclyl or heteroaryl

group having 1-10 heteroatoms. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 3-20 membered heterocyclyl or heteroaryl group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, such a heterocyclyl or heteroaryl group is of a 5-membered ring. In some embodiments, such a heterocyclyl or heteroaryl group is of a 6-membered ring.

[00274] In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heteroaryl group having 1-10 heteroatoms. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heteroaryl group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-6 membered heteroaryl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-membered heteroaryl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a heteroaryl group is directly bonded to a linkage phosphorus. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted triazolyl group. In some embodiments, a non-negatively charged internucleotidic linkage comprises an unsubstituted triazolyl group, e.g.,  . In some embodiments, a non-negatively charged internucleotidic linkage comprises a substituted triazolyl group, e.g.,  .

[00275] In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heterocyclyl group having 1-10 heteroatoms. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heterocyclyl group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-6 membered heterocyclyl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-membered heterocyclyl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, at least two heteroatoms are nitrogen. In some embodiments, a heterocyclyl group is directly bonded to a linkage phosphorus. In some embodiments, a heterocyclyl group is bonded to a linkage phosphorus through a linker, e.g., =N− when the heterocyclyl group is part of a guanidine moiety who directed bonded to a linkage phosphorus through its =N−. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted

 group. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted  group. In some embodiments, a non-negatively charged internucleotidic linkage comprises an substituted  group. In some embodiments, a non-negatively charged internucleotidic linkage comprises a  group. In some embodiments, each R^1 is independently optionally substituted C_{1-20} alkyl. In some embodiments, each R^1 is independently optionally substituted C_{1-6} alkyl. In some embodiments, each R^1 is independently methyl. In some embodiments, the two R^1 groups are different; for example, in some embodiments, one R^1 is methyl, and the other is $-CH_2(CH_2)_{10}CH_3$.

[00276] In some embodiments, a modified internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, comprises a triazole or alkyne moiety, each of which is optionally substituted. In some embodiments, a modified internucleotidic linkage comprises a triazole moiety. In some embodiments, a modified internucleotidic linkage comprises a unsubstituted triazole moiety. In some embodiments, a modified internucleotidic linkage comprises a substituted triazole moiety. In some embodiments, a modified internucleotidic linkage comprises an alkyl moiety. In some embodiments, a modified internucleotidic linkage comprises an optionally substituted alkynyl group. In some embodiments, a modified internucleotidic linkage comprises an unsubstituted alkynyl group. In some embodiments, a modified internucleotidic linkage comprises a substituted alkynyl group. In some embodiments, an alkynyl group is directly bonded to a linkage phosphorus.

[00277] In some embodiments, an oligonucleotide comprising a non-negatively charged internucleotidic linkage can comprise any structure, format, or portion thereof described herein. In some embodiments, an oligonucleotide comprising a non-negatively charged internucleotidic linkage can comprise any structure, format, or portion thereof described herein as being a component of a DMD oligonucleotide. In some embodiments, any structure, format, or portion thereof described as being a component of any DMD oligonucleotide can be used in any oligonucleotide comprising a non-negatively charged internucleotidic linkage, whether or not that oligonucleotide targets DMD or not, or whether the oligonucleotide is capable of mediating skipping of a DMD exon or not. In some embodiments, an

oligonucleotide comprising a non-negatively charged internucleotidic is double-stranded or single-stranded.

[00278] In some embodiments, a provided oligonucleotide composition is characterized in that, when it is contacted with the transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under reference conditions selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof. In some embodiments, a desired splicing product is increased 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 fold or more. In some embodiments, a desired splicing reference is absent (*e.g.*, cannot be reliably detected by quantitative PCR) under reference conditions. In some embodiments, as exemplified in the present disclosure, levels of the plurality of oligonucleotides, *e.g.*, a plurality of oligonucleotides, in provided compositions are pre-determined.

[00279] In some embodiments, provided oligonucleotides, e.g., oligonucleotides of a plurality in a provided composition, comprise two or more regions. In some embodiments, provided comprise a 5'-end region, a 3'-end region, and a middle region in between. In some embodiments, provided oligonucleotides have two wing and one core regions. In some embodiments, provided oligonucleotides are of a wing-core-wing structure. In some embodiments, the two wing regions are identical. In some embodiments, the two wing regions are different. In some embodiments, a 5'-end region is a 5'-wing region. In some embodiments, a 5'-wing region is a 5'-end region. In some embodiments, a 3'-end region is a 3'-wing region. In some embodiments, a 3'-wing region is a 3'-end region. In some embodiments, a core region is a middle region.

[00280] In some embodiments, a region (e.g., a 5'-wing region, a 3'-wing, a core region, a 5'-end region, a middle region, etc.) comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more nucleoside units. In some embodiments, a region comprises 2 or more nucleoside units. In some embodiments, a region comprises 3 or more nucleoside units. In some embodiments, a region comprises 4 or more nucleoside units. In some embodiments, a region comprises 5 or more nucleoside units. In some embodiments, a region comprises 6 or more nucleoside units. In some embodiments, a region comprises 7 or more nucleoside units. In some embodiments, a region comprises 8 or more nucleoside units. In some embodiments, a region comprises 9 or more nucleoside units. In some embodiments, a region comprises 10 or more nucleoside units.

[00281] In some embodiments, a region (e.g., a 5'-wing region, a 3'-wing, a core region, a 5'-end region, a middle region, etc.) comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more modified internucleotidic linkages. In some embodiments, a region comprises 2 or more modified internucleotidic linkages. In some embodiments, the one or more modified

internucleotidic linkages are consecutive. In some embodiments, a region comprises 2 or more consecutive modified internucleotidic linkages. In some embodiments, each internucleotidic linkage in a region is independently a modified internucleotidic linkage, wherein each chiral internucleotidic linkage is optionally and independently chirally controlled. In some embodiments, a chiral internucleotidic linkage or a modified internucleotidic linkage has the structure of formula **I** or a salt form thereof. In some embodiments, a chiral internucleotidic linkage or a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, each chiral internucleotidic linkage or a modified internucleotidic linkage independently has the structure of formula **I** or a salt form thereof. In some embodiments, each chiral internucleotidic linkage or a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a region comprises 3 or consecutive modified internucleotidic linkages.

[00282] In some embodiments, a wing region comprises one or more natural phosphate linkages. In some embodiments, a core region comprises one or more natural phosphate linkages. In some embodiments, a 5'-end region comprises one or more natural phosphate linkages. In some embodiments, a 3'-end region comprises one or more natural phosphate linkages. In some embodiments, a middle region comprises one or more natural phosphate linkages. In some embodiments, the one or more natural phosphate linkages are consecutive.

[00283] In some embodiments, a natural phosphate linkage follows (e.g., connected to a 3'-position of a sugar moiety) or precedes (e.g., connected to a 5'-position of a sugar moiety) a nucleoside unit whose sugar moiety comprises a 2'-OR^1 modification, wherein R^1 is not hydrogen. In some embodiments, R^1 is optionally substituted C_{1-6} aliphatic. In some embodiments, a modified internucleotidic linkage follows (e.g., connected to a 3'-position of a sugar moiety) or precedes (e.g., connected to a 5'-position of a sugar moiety) all or most (e.g., more than 55%, 60%, 70%, 80%, 90%, 95%, etc.) nucleoside units whose sugar moiety comprises no 2'-OR^1 modification, wherein R^1 is not hydrogen (e.g., those having two 2'-H at the 2'-position, those having a 2'-H and a 2'-F at the 2'-position (2'-F modified), etc.).

[00284] In some embodiments, a region comprises one or more nucleoside units comprising sugar modifications, e.g., 2'-F, 2'-OR^1, LNA sugar modifications, etc. In some embodiments, each sugar in a region is independently modified. In some embodiments, each sugar moiety in a wing, a 5'-end region, and/or a 3'-end region is modified. In some embodiments, a modification is a 2'-modification. In some embodiments, a modification can increase stability, e.g., 2'-OR^1 where in R^1 is not –H (e.g., is optionally substituted C_{1-6} aliphatic), LNA sugar modifications, etc. In some embodiments, a region, e.g., a core region or a middle region, comprise no sugar modifications (or no 2'-OR^1 sugar modifications/LNA modifications etc.). In some embodiments, such a core/middle region can form a duplex with a RNA for

recognition/binding of a protein, e.g., RNase H, for the protein to perform one or more of its functions (e.g., in the case of RNase H, its binding and cleavage of DNA/RNA duplex).

[00285] A region and/or a provided oligonucleotide may have various patterns of backbone chiral centers. In some embodiments, each internucleotidic linkage in a region is a chirally controlled internucleotidic linkage and is *Sp*. In some embodiments, the 5'-end and/or the 3'-end internucleotidic linkage is a chirally controlled internucleotidic linkage and is *Sp*. In some embodiments, the pattern of backbone chiral centers of a wing region, a 5'-end region, and/or a 3'-end region is or comprises a 5'-end and/or a 3'-end internucleotidic linkage which is a chirally controlled internucleotidic linkage and is *Sp*, with the other internucleotidic linkages in the region independently being an natural phosphate linkage, a modified internucleotidic linkage, or a chirally controlled internucleotidic linkage (*Sp* or *Rp*). In some embodiments, such patterns provide stability. Many example patterns of backbone chiral centers are described in the present disclosure.

[00286] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides defined by having:

1) a common base sequence;

2) a common pattern of backbone linkages; and

3) a common pattern of backbone chiral centers, which composition is a substantially pure preparation of a single oligonucleotide in that a controlled level of the oligonucleotides in the composition have the common base sequence and length, the common pattern of backbone linkages, and the common pattern of backbone chiral centers.

[00287] In some embodiments, oligonucleotides having a common base sequence may have the same pattern of nucleoside modifications, *e.g.*, sugar modifications, base modifications, *etc.* In some embodiments, a pattern of nucleoside modifications may be represented by a combination of locations and modifications. In some embodiments, all non-chiral linkages (*e.g.*, PO) may be omitted. In some embodiments, oligonucleotides having the same base sequence have the same constitution.

[00288] As understood by a person having ordinary skill in the art, a stereorandom or racemic preparation of oligonucleotides is prepared by non-stereoselective and/or low-stereoselective coupling of nucleotide monomers, typically without using any chiral auxiliaries, chiral modification reagents, and/or chiral catalysts. In some embodiments, in a substantially racemic (or chirally uncontrolled) preparation of oligonucleotides, all or most coupling steps are not chirally controlled in that the coupling steps are not specifically conducted to provide enhanced stereoselectivity. An example substantially racemic preparation of oligonucleotides is the preparation of phosphorothioate oligonucleotides through sulfurizing phosphite triesters from commonly used phosphoramidite oligonucleotide synthesis with either tetraethylthiuram disulfide or (TETD) or 3H-1, 2-bensodithiol-3-one 1, 1-dioxide (BDTD), a well-

known process in the art. In some embodiments, substantially racemic preparation of oligonucleotides provides substantially racemic oligonucleotide compositions (or chirally uncontrolled oligonucleotide compositions). In some embodiments, at least one coupling of a nucleotide monomer has a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9, 92:8, 97:3, 98:2, or 99:1. In some embodiments, each internucleotidic linkage independently has a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9, 92:8, 97:3, 98:2, or 99:1. In some embodiments, a diastereoselectivity is lower than about 60:40. In some embodiments, a diastereoselectivity is lower than about 70:30. In some embodiments, a diastereoselectivity is lower than about 80:20. In some embodiments, a diastereoselectivity is lower than about 90:10. In some embodiments, a diastereoselectivity is lower than about 91:9. In some embodiments, at least one internucleotidic linkage has a diastereoselectivity lower than about 90:10. In some embodiments, at least two internucleotidic linkages have a diastereoselectivity lower than about 90:10. In some embodiments, at least three internucleotidic linkages have a diastereoselectivity lower than about 90:10. In some embodiments, at least four internucleotidic linkages have a diastereoselectivity lower than about 90:10. In some embodiments, at least five internucleotidic linkages have a diastereoselectivity lower than about 90:10. In some embodiments, each internucleotidic linkage independently has a diastereoselectivity lower than about 90:10. In some embodiments, a non-chirally controlled internucleotidic linkage has a diastereomeric purity no more than 90%, 85%, 80%, 75%, 70%, 65%, 60%, or 55%. In some embodiments, the purity is no more than 90%. In some embodiments, the purity is no more than 85%. In some embodiments, the purity is no more than 80%.

[00289] In contrast, in chirally controlled oligonucleotide composition, at least one and typically each chirally controlled internucleotidic linkage, such as those of oligonucleotides of chirally controlled oligonucleotide compositions, independently has a diastereomeric purity of 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more with respect to the chiral linkage phosphorus. In some embodiments, a diastereomeric purity is 95% or more. In some embodiments, a diastereomeric purity is 96% or more. In some embodiments, a diastereomeric purity is 97% or more. In some embodiments, a diastereomeric purity is 98% or more. In some embodiments, a diastereomeric purity is 99% or more. Among other things, technologies of the present disclosure routinely provide chirally controlled internucleotidic linkages with high diastereomeric purity.

[00290] As appreciated by a person having ordinary skill in the art, diastereoselectivity of a coupling or diastereomeric purity (diastereopurity) of an internucleotidic linkage can be assessed through the diastereoselectivity of a dimer formation/diastereomeric purity of the internucleotidic linkage of a dimer formed under the same or comparable conditions, wherein the dimer has the same 5'- and 3'-nucleosides and internucleotidic linkage.

[00291] In some embodiments, the present disclosure provides chirally controlled (and/or stereochemically pure) oligonucleotide compositions comprising a plurality of oligonucleotides defined by having:

1) a common base sequence;

2) a common pattern of backbone linkages; and

3) a common pattern of backbone chiral centers, which composition is a substantially pure preparation of a single oligonucleotide in that at least about 10% of the oligonucleotides in the composition have the common base sequence and length, the common pattern of backbone linkages, and the common pattern of backbone chiral centers.

[00292] In some embodiments, the present disclosure provides chirally controlled oligonucleotide composition of a plurality of oligonucleotides, wherein the composition is enriched, relative to a substantially racemic preparation of the same oligonucleotides, for oligonucleotides of a single oligonucleotide type. In some embodiments, the present disclosure provides chirally controlled oligonucleotide composition of a plurality of oligonucleotides wherein the composition is enriched, relative to a substantially racemic preparation of the same oligonucleotides, for oligonucleotides of a single oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications.

[00293] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications.

wherein the composition is enriched, relative to a substantially racemic preparation of oligonucleotides having the same base sequence and length, for oligonucleotides of the particular oligonucleotide type.

[00294] In some embodiments, oligonucleotides having a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of base modifications. In some embodiments, oligonucleotides having a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus

modifications and a common pattern of nucleoside modifications. In some embodiments, oligonucleotides having a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have identical structures.

[00295] In some embodiments, oligonucleotides of an oligonucleotide type have a common pattern of backbone phosphorus modifications and a common pattern of sugar modifications. In some embodiments, oligonucleotides of an oligonucleotide type have a common pattern of backbone phosphorus modifications and a common pattern of base modifications. In some embodiments, oligonucleotides of an oligonucleotide type have a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments, oligonucleotides of a particular type have the same constitution. In some embodiments, oligonucleotides of an oligonucleotide type are identical.

[00296] In some embodiments, a chirally controlled oligonucleotide composition is a substantially pure preparation of an oligonucleotide type in that oligonucleotides in the composition that are not of the oligonucleotide type are impurities form the preparation process of said oligonucleotide type, in some case, after certain purification procedures.

[00297] In some embodiments, at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95% of the oligonucleotides in the composition have a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers.

[00298] In some embodiments, oligonucleotides having a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications. In some embodiments, oligonucleotides having a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments, oligonucleotides having a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of sugar modifications. In some embodiments, oligonucleotides having a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of base modifications. In some embodiments, oligonucleotides having a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers are identical.

[00299] In some embodiments, purity of a chirally controlled oligonucleotide composition of an oligonucleotide type is expressed as the percentage of oligonucleotides in the composition that are of the oligonucleotide type. In some embodiments, at least about 10% of the oligonucleotides in a chirally

controlled oligonucleotide composition are of the oligonucleotide type. In some embodiments, at least about 20% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the oligonucleotide type. In some embodiments, at least about 30% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the oligonucleotide type. In some embodiments, at least about 40% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the oligonucleotide type. In some embodiments, at least about 50% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the oligonucleotide type. In some embodiments, at least about 60% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the oligonucleotide type. In some embodiments, at least about 70% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the oligonucleotide type. In some embodiments, at least about 80% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the oligonucleotide type. In some embodiments, at least about 90% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the oligonucleotide type. In some embodiments, at least about 92% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the oligonucleotide type. In some embodiments, at least about 94% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the oligonucleotide type. In some embodiments, at least about 95% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the oligonucleotide type. In some embodiments, at least about 96% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the same oligonucleotide type. In some embodiments, at least about 97% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the oligonucleotide type. In some embodiments, at least about 98% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the oligonucleotide type. In some embodiments, at least about 99% of the oligonucleotides in a chirally controlled oligonucleotide composition are of the oligonucleotide type.

[00300] In some embodiments, purity of a chirally controlled oligonucleotide composition can be controlled by stereoselectivity of each coupling step in its preparation process. In some embodiments, a coupling step has a stereoselectivity (*e.g.*, diastereoselectivity) of 60% (60% of the new internucleotidic linkage formed from the coupling step has the intended stereochemistry). After such a coupling step, the new internucleotidic linkage formed may be referred to have a 60% purity. In some embodiments, each coupling step has a stereoselectivity of at least 60%. In some embodiments, each coupling step has a stereoselectivity of at least 70%. In some embodiments, each coupling step has a stereoselectivity of at least 80%. In some embodiments, each coupling step has a stereoselectivity of at least 85%. In some embodiments, each coupling step has a stereoselectivity of at least 90%. In some embodiments, each coupling step has a stereoselectivity of at least 91%. In some embodiments, each coupling step has a

stereoselectivity of at least 92%. In some embodiments, each coupling step has a stereoselectivity of at least 93%. In some embodiments, each coupling step has a stereoselectivity of at least 94%. In some embodiments, each coupling step has a stereoselectivity of at least 95%. In some embodiments, each coupling step has a stereoselectivity of at least 96%. In some embodiments, each coupling step has a stereoselectivity of at least 97%. In some embodiments, each coupling step has a stereoselectivity of at least 98%. In some embodiments, each coupling step has a stereoselectivity of at least 99%. In some embodiments, each coupling step has a stereoselectivity of at least 99.5%. In some embodiments, each coupling step has a stereoselectivity of virtually 100%. In some embodiments, a coupling step has a stereoselectivity of virtually 100% in that all detectable product from the coupling step by an analytical method (*e.g.*, NMR, HPLC, use of a nuclease which stereoselectively cleaves phosphorothioates, *etc*) has the intended stereoselectivity. In some embodiments, stereoselectivity of a chiral internucleotidic linkage in an oligonucleotide may be measured through a model reaction, *e.g.* formation of a dimer under essentially the same or comparable conditions wherein the dimer has the same internucleotidic linkage as the chiral internucleotidic linkage, the 5'-nucleoside of the dimer is the same as the nucleoside to the 5'-end of the chiral internucleotidic linkage, and the 3'-nucleoside of the dimer is the same as the nucleoside to the 3'-end of the chiral internucleotidic linkage (*e.g.*, for fU*S**fU*SfC***SfU, through the dimer of fU*SfC). As appreciated by a person having ordinary skill in the art, percentage of oligonucleotides of a particular type having n chirally controlled internucleotidic linkages in a preparation may be calculated as $DP^1*DP^2*DP^3*...DP^n$, wherein each of DP^1, DP^2, DP^3, ... , and DP^n is independently the diastereomeric purity of the 1st, 2nd, 3rd, ..., and nth chirally controlled internucleotidic linkage. In some embodiments, each of DP^1, DP^2, DP^3, ... , and DP^n is independently 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 97% or 99% or more. . In some embodiments, each of DP^1, DP^2, DP^3, ... , and DP^n is independently 95% or more.

[00301] In some embodiments, in provided compositions, at least 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 97% or 99% of oligonucleotides that have the base sequence of a particular oligonucleotide type (defined by 1) base sequence; 2) pattern of backbone linkages; 3) pattern of backbone chiral centers; and 4) pattern of backbone phosphorus modifications) are oligonucleotides of the particular oligonucleotide type. In some embodiments, at least 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 97% or 99% of oligonucleotides that have the base sequence, the pattern of backbone linkages, and the pattern of backbone phosphorus modifications of a particular oligonucleotide type are oligonucleotides of the particular oligonucleotide type.

[00302] In some embodiments, oligonucleotides of a particular type in a chirally controlled oligonucleotide composition is enriched at least 5 fold (oligonucleotides of the particular type have a fraction of $5*(1/2^n)$ of oligonucleotides that have the base sequence, the pattern of backbone linkages, and the pattern of backbone phosphorus modifications of the particular oligonucleotide type, wherein n is the number of chiral internucleotidic linkages; or oligonucleotides that have the base sequence, the pattern of backbone linkages, and the pattern of backbone phosphorus modifications of the particular oligonucleotide type but are not of the particular oligonucleotide type are no more than $[1-(1/2^n)]/5$ of oligonucleotides that have the base sequence, the pattern of backbone linkages, and the pattern of backbone phosphorus modifications of the particular oligonucleotide type) compared to a stereorandom preparation of the oligonucleotides (oligonucleotides of the particular type are typically considered to have a fraction of $1/2^n$ of oligonucleotides that have the base sequence, the pattern of backbone linkages, and the pattern of backbone phosphorus modifications of the particular oligonucleotide type, wherein n is the number of chiral internucleotidic linkages, and oligonucleotides that have the base sequence, the pattern of backbone linkages, and the pattern of backbone phosphorus modifications of the particular oligonucleotide type but are not of the particular oligonucleotide type are typically considered to have a fraction of $[1-(1/2^n)]$ of oligonucleotides that have the base sequence, the pattern of backbone linkages, and the pattern of backbone phosphorus modifications of the particular oligonucleotide type). In some embodiments, the enrichment is at least 20 fold. In some embodiments, the enrichment is at least 30 fold. In some embodiments, the enrichment is at least 40 fold. In some embodiments, the enrichment is at least 50 fold. In some embodiments, the enrichment is at least 60 fold. In some embodiments, the enrichment is at least 70 fold. In some embodiments, the enrichment is at least 80 fold. In some embodiments, the enrichment is at least 90 fold. In some embodiments, the enrichment is at least 100 fold. In some embodiments, the enrichment is at least 20,000 fold. In some embodiments, the enrichment is at least $(1.5)^n$. In some embodiments, the enrichment is at least $(1.6)^n$. In some embodiments, the enrichment is at least $(1.7)^n$. In some embodiments, the enrichment is at least $(1.1)^n$. In some embodiments, the enrichment is at least $(1.8)^n$. In some embodiments, the enrichment is at least $(1.9)^n$. In some embodiments, the enrichment is at least 2^n. In some embodiments, the enrichment is at least 3^n. In some embodiments, the enrichment is at least 4^n. In some embodiments, the enrichment is at least 5^n. In some embodiments, the enrichment is at least 6^n. In some embodiments, the enrichment is at least 7^n. In some embodiments, the enrichment is at least 8^n. In some embodiments, the enrichment is at least 9^n. In some embodiments, the enrichment is at least 10^n. In some embodiments, the enrichment is at least 15^n. In some embodiments, the enrichment is at least 20^n. In some embodiments, the enrichment is at least 25^n. In some embodiments, the enrichment is at least 30^n. In some embodiments, the enrichment is at least 40^n. In some embodiments, the enrichment is at least 50^n. In some embodiments, the enrichment is at

least 100^n. In some embodiments, enrichment is measured by increase of the fraction of oligonucleotides of the particular oligonucleotide type in oligonucleotides that have the base sequence, the pattern of backbone linkages, and the pattern of backbone phosphorus modifications of the particular oligonucleotide type. In some embodiments, an enrichment is measured by decrease of the fraction of oligonucleotides that have the base sequence, the pattern of backbone linkages, and the pattern of backbone phosphorus modifications of the particular oligonucleotide type but are not of the particular oligonucleotide type in oligonucleotides that have the base sequence, the pattern of backbone linkages, and the pattern of backbone phosphorus modifications of the particular oligonucleotide type.

[00303] In some embodiments, provided oligonucleotides are antisense oligonucleotides. In some embodiments, provided oligonucleotides are siRNA oligonucleotides. In some embodiments, a provided chirally controlled oligonucleotide composition is of oligonucleotides that can be antisense oligonucleotide, antagomir, microRNA, pre-microRNA, antimir, supermir, ribozyme, Ul adaptor, RNA activator, RNAi agent, decoy oligonucleotide, triplex forming oligonucleotide, aptamer or adjuvant. In some embodiments, a chirally controlled oligonucleotide composition is of antisense oligonucleotides. In some embodiments, a chirally controlled oligonucleotide composition is of siRNA oligonucleotides. In some embodiments, a chirally controlled oligonucleotide composition is of antagomir oligonucleotides. In some embodiments, a chirally controlled oligonucleotide composition is of microRNA oligonucleotides. In some embodiments, a chirally controlled oligonucleotide composition is of pre-microRNA oligonucleotides. In some embodiments, a chirally controlled oligonucleotide composition is of antimir oligonucleotides. In some embodiments, a chirally controlled oligonucleotide composition is of supermir oligonucleotides. In some embodiments, a chirally controlled oligonucleotide composition is of ribozyme oligonucleotides. In some embodiments, a chirally controlled oligonucleotide composition is of Ul adaptor oligonucleotides. In some embodiments, a chirally controlled oligonucleotide composition is of RNA activator oligonucleotides. In some embodiments, a chirally controlled oligonucleotide composition is of RNAi agent oligonucleotides. In some embodiments, a chirally controlled oligonucleotide composition is of decoy oligonucleotides. In some embodiments, a chirally controlled oligonucleotide composition is of triplex forming oligonucleotides. In some embodiments, a chirally controlled oligonucleotide composition is of aptamer oligonucleotides. In some embodiments, a chirally controlled oligonucleotide composition is of adjuvant oligonucleotides.

[00304] In some embodiments, a provided oligonucleotide comprises one or more chiral, modified phosphate linkages. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of oligonucleotides that include one or more modified backbone linkages, bases, and/or sugars.

[00305] In some embodiments, provided chirally controlled (and/or stereochemically pure)

preparations are of a stereochemical purity of greater than about 80%. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of a stereochemical purity of greater than about 85%. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of a stereochemical purity of greater than about 90%. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of a stereochemical purity of greater than about 91%. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of a stereochemical purity of greater than about 92%. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of a stereochemical purity of greater than about 93%. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of a stereochemical purity of greater than about 94%. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of a stereochemical purity of greater than about 95%. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of a stereochemical purity of greater than about 96%. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of a stereochemical purity of greater than about 97%. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of a stereochemical purity of greater than about 98%. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of a stereochemical purity of greater than about 99%.

[00306] In some embodiments, at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the internucleotidic linkages of an oligonucleotide are independently chiral internucleotidic linkages. In some embodiments, all chiral, modified internucleotidic linkages are chiral phosphorothioate internucleotidic linkages. In some embodiments, all chiral, modified internucleotidic linkages except non-negatively charged internucleotidic linkages are chiral phosphorothioate internucleotidic linkages. In some embodiments, each chiral internucleotidic linkage is chirally controlled. In some embodiments, at least about 10, 20, 30, 40, 50, 60, 70, 80, or 90% chiral internucleotidic linkages of an oligonucleotide are chirally controlled and are of the *Sp* conformation. In some embodiments, at least about 10, 20, 30, 40, 50, 60, 70, 80, or 90% phosphorothioate internucleotidic linkages of an oligonucleotide are chirally controlled and are of the *Sp* conformation. In some embodiments, the percentage is at least about 10%. In some embodiments, the percentage is at least about 20%. In some embodiments, the percentage is at least about 30%. In some embodiments, the percentage is at least about 40%. In some embodiments, the percentage is at least about 50%. In some embodiments, the percentage is at least about 60%. In some embodiments, the percentage is at least about 70%. In some embodiments, the percentage is at least about 80%. In some embodiments, the percentage is at least about 90%.

[00307] In some embodiments, at least about 10, 20, 30, 40, 50, 60, 70, 80, or 90% chiral internucleotidic linkages of an oligonucleotide are chirally controlled and are of the *Rp* conformation. In some embodiments, at least about 10, 20, 30, 40, 50, 60, 70, 80, or 90% chiral phosphorothioate internucleotidic linkages of an oligonucleotide are chirally controlled and are of the *Rp* conformation. In some embodiments, the percentage is at least about 10%. In some embodiments, the percentage is at least about 20%. In some embodiments, the percentage is at least about 30%. In some embodiments, no more than 10, 20, 30, 40, 50, 60, 70, 80, or 90% chiral internucleotidic linkages of an oligonucleotide are chirally controlled and are of the *Rp* conformation. In some embodiments, no more than 10, 20, 30, 40, 50, 60, 70, 80, or 90% phosphorothioate internucleotidic linkages of an oligonucleotide are of the *Rp* conformation. In some embodiments, the percentage is no more than 10%. In some embodiments, the percentage is no more than 20%. In some embodiments, the percentage is no more than 30%.

[00308] In some embodiments, provided chirally controlled (and/or stereochemically pure) compositions are of oligonucleotides that contain one or more modified bases. In some embodiments, provided chirally controlled (and/or stereochemically pure) compositions are of oligonucleotides that contain no modified bases. As appreciated by those skilled in the art, many types of modified bases can be utilized in accordance with the present disclosure. Example modified bases are described herein.

[00309] In some embodiments, oligonucleotides of provided compositions comprise at least 2, 3, 4, 5, 6, 7, 8, 9 or 10 natural phosphate linkages. In some embodiments, oligonucleotides of provided compositions comprise at least one natural phosphate linkage. In some embodiments, oligonucleotides of provided compositions comprise at least two natural phosphate linkages. In some embodiments, oligonucleotides of provided compositions comprise at least three natural phosphate linkages.

[00310] In some embodiments, oligonucleotides of provided compositions comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 natural phosphate linkages. In some embodiments, oligonucleotides of provided compositions comprise one natural phosphate linkage. In some embodiments, oligonucleotides of provided compositions comprise two natural phosphate linkages. In some embodiments, oligonucleotides of provided compositions comprise three natural phosphate linkages. In some embodiments, oligonucleotides of provided compositions comprise four natural phosphate linkages. In some embodiments, oligonucleotides of provided compositions comprise five natural phosphate linkages. In some embodiments, oligonucleotides of provided compositions comprise six natural phosphate linkages. In some embodiments, oligonucleotides of provided compositions comprise seven natural phosphate linkages. In some embodiments, oligonucleotides of provided compositions comprise eight natural phosphate linkages. In some embodiments, oligonucleotides of provided compositions comprise nine natural phosphate linkages. In some embodiments, oligonucleotides of provided compositions comprise ten natural phosphate linkages.

[00311] In some embodiments, oligonucleotides of provided compositions comprise at least 2, 3, 4, 5, 6, 7, 8, 9 or 10 consecutive natural phosphate linkages. In some embodiments, oligonucleotides of provided compositions comprise at least two consecutive natural phosphate linkages. In some embodiments, oligonucleotides of provided compositions comprise at least three consecutive natural phosphate linkages.

[00312] In some embodiments, oligonucleotides of the present disclosure have at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, or 75 nucleobases in length. In some embodiments, oligonucleotides of the present disclosure comprises at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, or 75 nucleobases in length, wherein each nucleobase is independently optionally substituted A, T, C, G, U, or a tautomer thereof.

[00313] In some embodiments, provided compositions comprise oligonucleotides containing one or more residues which are modified at the sugar moiety. In some embodiments, provided compositions comprise oligonucleotides containing one or more residues which are modified at the 2' position of the sugar moiety (referred to herein as a "2'-modification"). Examples of such modifications are described herein and include, but are not limited to, 2'-OMe, 2'-MOE, 2'-LNA, 2'-F, FRNA, FANA, *S*-cEt, *etc*. In some embodiments, provided compositions comprise oligonucleotides containing one or more residues which are 2'-modified. For example, in some embodiments, provided oligonucleotides contain one or more residues which are 2'-O-methoxyethyl (2'-MOE)-modified residues. In some embodiments, provided compositions comprise oligonucleotides which do not contain any 2'-modifications. In some embodiments, provided compositions are oligonucleotides which do not contain any 2'-MOE residues. That is, in some embodiments, provided oligonucleotides are not MOE-modified. Additional example sugar modifications are described in the present disclosure.

[00314] In some embodiments, one or more is one. In some embodiments, one or more is two. In some embodiments, one or more is three. In some embodiments, one or more is four. In some embodiments, one or more is five. In some embodiments, one or more is six. In some embodiments, one or more is seven. In some embodiments, one or more is eight. In some embodiments, one or more is nine. In some embodiments, one or more is ten. In some embodiments, one or more is at least one. In some embodiments, one or more is at least two. In some embodiments, one or more is at least three. In some embodiments, one or more is at least four. In some embodiments, one or more is at least five. In some embodiments, one or more is at least six. In some embodiments, one or more is at least seven. In some embodiments, one or more is at least eight. In some embodiments, one or more is at least nine. In some embodiments, one or more is at least ten.

[00315] In some embodiments, a base sequence, e.g., a common base sequence of a plurality of

oligonucleotide, a base sequence of a particular oligonucleotide type, etc., comprises or is a sequence complementary to a gene or transcript (e.g., of Dystrophin or DMD). In some embodiments, a common base sequence comprises or is a sequence 100% complementary to a gene. In some embodiments, a common base sequence comprises or is a sequence complementary to a characteristic sequence element of a gene, which characteristic sequences differentiate the gene from a similar sequence sharing homology with the gene. In some embodiments, a common base sequence comprises or is a sequence 100% complementary to a characteristic sequence element of a gene, which characteristic sequences differentiate the gene from another allele of the gene. In some embodiments, a common base sequence comprises or is a sequence 100% complementary to a characteristic sequence element of a gene, which characteristic sequences differentiate the gene from a similar sequence sharing homology with the gene. In some embodiments, a common base sequence comprises or is a sequence complementary to characteristic sequence element of a target gene, which characteristic sequences comprises a mutation that is not found in other copies of the gene, *e.g.*, the wild-type copy of the gene, another mutant copy the gene, *etc.* In some embodiments, a common base sequence comprises or is a sequence 100% complementary to characteristic sequence element of a target gene, which characteristic sequences comprises a mutation that is not found in other copies of the gene, *e.g.*, the wild-type copy of the gene, another mutant copy the gene, *etc.* In some embodiments, a common base sequence comprises or is a sequence 100% complementary to a characteristic sequence element of a gene, which characteristic sequences differentiate the gene from another allele of the gene. In some embodiments, a characteristic sequence element is a mutation. In some embodiments, a characteristic sequence element is a SNP.

[00316] In some embodiments, a chiral internucleotidic linkage has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, **III**, etc., or a salt form thereof. In some embodiments, linkage phosphorus of chiral internucleotidic linkages are chirally controlled. In some embodiments, a chiral internucleotidic linkage is phosphorothioate internucleotidic linkage. In some embodiments, each chiral internucleotidic linkage in an oligonucleotide of a provided composition independently has the structure of formula **I**. In some embodiments, each chiral internucleotidic linkage in an oligonucleotide of a provided composition independently has the structure of formula **II**. In some embodiments, each chiral internucleotidic linkage in an oligonucleotide of a provided composition independently has the structure of formula **III**. In some embodiments, each chiral internucleotidic linkage in an oligonucleotide of a provided composition is a phosphorothioate internucleotidic linkage.

[00317] As appreciated by those skilled in the art, internucleotidic linkages, e.g., those of formula **I**, natural phosphate linkages, phosphorothioate internucleotidic linkages, etc. may exist in their salt forms depending on pH of their environment. Unless otherwise indicated, such salt forms are included in the

present application when such internucleotidic linkages are referred to.

[00318] In some embodiments, oligonucleotides of the present disclosure comprise one or more modified sugar moieties. In some embodiments, oligonucleotides of the present disclosure comprise one or more modified base moieties. As known by a person of ordinary skill in the art and described in the disclosure, various modifications can be introduced to sugar and base moieties. For example, in some embodiments, a modification is a modification described in US9006198, WO2014/012081, WO/2015/107425, and WO/2017/062862, the sugar and base modifications of each of which are incorporated herein by reference.

[00319] In some embodiments, a sugar modification is a 2'-modification. Commonly used 2'-modifications include but are not limited to 2'–OR^1, wherein R^1 is not hydrogen. In some embodiments, a modification is 2'–OR, wherein R is optionally substituted aliphatic. In some embodiments, a modification is 2'–OMe. In some embodiments, a modification is 2'-*O*-MOE. In some embodiments, the present disclosure demonstrates that inclusion and/or location of particular chirally pure internucleotidic linkages can provide stability improvements comparable to or better than those achieved through use of modified backbone linkages, bases, and/or sugars. In some embodiments, a provided single oligonucleotide of a provided composition has no modifications on the sugars. In some embodiments, a provided single oligonucleotide of a provided composition has no modifications on 2'-positions of the sugars (i.e., the two groups at the 2'-position are either –H/–H or –H/–OH). In some embodiments, a provided single oligonucleotide of a provided composition does not have any 2'-MOE modifications.

[00320] In some embodiments, a 2'-modification is –O–L– or –L– which connects the 2'-carbon of a sugar moiety to another carbon of a sugar moiety. In some embodiments, a 2'-modification is –O–L– or –L– which connects the 2'-carbon of a sugar moiety to the 4'-carbon of a sugar moiety. In some embodiments, a 2'-modification is *S*-cEt. In some embodiments, a modified sugar moiety is an LNA sugar moiety.

[00321] In some embodiments, a 2'-modification is –F. In some embodiments, a 2'-modification is FANA. In some embodiments, a 2'-modification is FRNA.

[00322] In some embodiments, a sugar modification is a 5'-modification. In some embodiments, a modification is 5'-R^1, wherein R^1 is not hydrogen. In some embodiments, a sugar modification is 5'-R, wherein R is not hydrogen and is otherwise as described in the present disclosure. In some embodiments, a sugar modification is 5'-R, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a sugar modification is 5'-R, wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, a sugar modification is 5'-R, wherein R is optionally substituted methyl. In some embodiments, a sugar modification is 5'-R, wherein R is optionally substituted methyl, wherein no substituents of the methyl group comprises a carbon atom. In some embodiments, a 5'-modification is methyl. In some

embodiments, each substituent is independently halogen. In some embodiments, a substituted 5'-carbon is diastereomerically pure. In some embodiments, a substituted 5'-carbon has the *R* configuration. In some embodiments, a substituted 5'-carbon has the *S* configuration. In some embodiments, a 5'-modification is 5'-(*R*)-Me. In some embodiments, a 5'-modification is 5'-(*S*)-Me.

[00323] In some embodiments, a sugar moiety has one and no more than one modification at a position, *e.g.*, a 2'-position, 5'-position, *etc.* In some embodiments, a 2'-modification takes the position corresponding to the position of the 2'-OH in a natural RNA sugar moiety. In some embodiments, a 2'-modification takes the position corresponding to the position of the 2'-H in a natural RNA sugar moiety.

[00324] In some embodiments, a sugar modification changes the size of the sugar ring. In some embodiments, a sugar modification changes the conformation of the sugar ring. In some embodiments, a sugar modification is the sugar moiety in FHNA.

[00325] In some embodiments, a sugar modification replaces a sugar moiety with another cyclic or acyclic moiety. Examples of such moieties are widely known in the art, including but not limited to those used in Morpholino, glycol nucleic acids, *etc*.

Certain Embodiments of Internucleotidic Linkages, Chirally Controlled Oligonucleotides and Chirally Controlled Oligonucleotide Compositions

[00326] Among other things, the present disclosure provides chirally controlled oligonucleotides and chirally controlled oligonucleotide compositions. In some embodiments, the present disclosure provides chirally controlled oligonucleotides and chirally controlled oligonucleotide compositions which are of high crude purity. In some embodiments, the present disclosure provides chirally controlled oligonucleotides, and chirally controlled oligonucleotide compositions which are of high diastereomeric purity. Chirally controlled oligonucleotides are oligonucleotides comprise one or more chirally controlled internucleotidic linkages, such as oligonucleotides of a plurality in chirally controlled oligonucleotide compositions. In some embodiments, chirally controlled oligonucleotides comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or more chirally controlled internucleotidic linkages. In some embodiments, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or more chiral internucleotidic linkages of a chirally controlled oligonucleotide are independently chirally controlled internucleotidic linkages. In some embodiments, each chiral internucleotidic linkage in a chirally controlled oligonucleotide is a chirally controlled internucleotidic linkage, and a chirally controlled oligonucleotide is diastereomerically pure.

[00327] In some embodiments, a chirally controlled oligonucleotide composition is a substantially pure composition of an oligonucleotide type in that oligonucleotides in the composition that are not of the oligonucleotide type are impurities. In some embodiments, such impurities are formed during the

preparation process of oligonucleotides of said oligonucleotide type, in some case, after certain purification procedures.

[00328] In some embodiments, the present disclosure provides oligonucleotides comprising one or more diastereomerically pure internucleotidic linkages with respect to the chiral linkage phosphorus (e.g., linkage phosphorus of chirally controlled internucleotidic linkages). In some embodiments, the present disclosure provides oligonucleotides comprising one or more diastereomerically pure internucleotidic linkages having the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, **III**, etc., or a salt form thereof. In some embodiments, the present disclosure provides oligonucleotides comprising one or more diastereomerically pure internucleotidic linkages with respect to the chiral linkage phosphorus, and one or more natural phosphate linkages (unless otherwise indicated, reference in the present application to internucleotidic linkages, such as natural phosphate linkages and other types of internucleotidic linkages when applicable, includes salt forms of such linkages).Thus, diastereomerically pure internucleotidic linkages here include salt forms of diastereomerically pure internucleotidic linkages; natural phosphate linkages here include salt forms of natural phosphate linkages. A person having ordinary skill in the art appreciates that many internucleotidic linkages, such as natural phosphate linkages, exist as salt forms when at physiological pH, in many buffers (e.g., PBS buffers having a pH around 7, e.g., PH 7.4), etc.). In some embodiments, the present disclosure provides oligonucleotides comprising one or more diastereomerically pure internucleotidic linkages having the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, **III**, etc., or a salt form thereof, and one or more natural phosphate linkages. In some embodiments, the present disclosure provides oligonucleotides comprising one or more diastereomerically pure internucleotidic linkages having the structure of formula **I-c**, and one or more phosphate diester linkages. In some embodiments, such oligonucleotides are prepared by using stereoselective oligonucleotide synthesis, as described in this application, to form designed diastereomerically pure internucleotidic linkages with respect to the chiral linkage phosphorus.

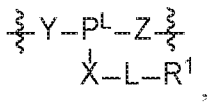
[00329] In some embodiments, an oligonucleotide of the present disclosure comprises at least one internucleotidic linkage, e.g., a modified (non-natural) internucleotidic linkage (e.g., non-negatively charged internucleotidic linkage) within or at the terminus (e.g. 5' or 3') of the oligonucleotide. In some embodiments, an oligonucleotide comprises a P-modification moiety within or at the terminus (e.g. 5' or 3') of the oligonucleotide.

[00330] In some embodiments, an oligonucleotide of the present disclosure comprises at least one chirally controlled internucleotidic linkage within the oligonucleotide. In some embodiments, an

oligonucleotide of the present disclosure comprises at least one chirally controlled internucleotidic linkage within the oligonucleotide, and at least one natural phosphate linkage. In some embodiments, an oligonucleotide of the present disclosure comprises at least one chirally controlled internucleotidic linkage within the oligonucleotide, at least one natural phosphate linkage, and at least one phosphorothioate internucleotidic linkage. In some embodiments, an oligonucleotide of the present disclosure comprises at least one chirally controlled internucleotidic linkage within the oligonucleotide, and at least one phosphorothioate triester internucleotidic linkage. In some embodiments, an oligonucleotide of the present disclosure comprises at least one chirally controlled internucleotidic linkage within the oligonucleotide, at least one natural phosphate linkage, and at least one phosphorothioate triester internucleotidic linkage.

[00331] In some embodiments, an oligonucleotide of the present disclosure comprises at least two chirally controlled internucleotidic linkages within the oligonucleotide that have different stereochemistry and/or different P-modifications relative to one another. In some embodiments, such at least two internucleotidic linkages have different stereochemistry. In some embodiments, such at least two internucleotidic linkages have different P-modifications. In some embodiments, an oligonucleotide of the present disclosure comprises at least two chirally controlled internucleotidic linkages within the oligonucleotide that have different P-modifications relative to one another, and at least one natural phosphate linkage. In some embodiments, an oligonucleotide of the present disclosure comprises at least two chirally controlled internucleotidic linkages within the oligonucleotide that have different P-modifications relative to one another, at least one natural phosphate linkage, and at least one phosphorothioate internucleotidic linkage. In some embodiments, an oligonucleotide of the present disclosure comprises at least two chirally controlled internucleotidic linkages within the oligonucleotide that have different P-modifications relative to one another, and at least one phosphorothioate triester internucleotidic linkage. In some embodiments, an oligonucleotide of the present disclosure comprises at least two chirally controlled internucleotidic linkages within the oligonucleotide that have different P-modifications relative to one another, at least one natural phosphate linkage, and at least one phosphorothioate triester internucleotidic linkage.

[00332] In certain embodiments, an internucleotidic linkage (e.g., a modified (non-natural) internucleotidic linkage when formula I is not a natural phosphate linkage) has the structure of formula I:



I

or a salt form thereof, wherein:

P^L is P(=W), P, or P→B(R')$_3$;

W is O, N(–L–R^5), S or Se;

each of R^1 and R^5 is independently –H, –L–R', halogen, –CN, –NO_2, –L–Si(R')$_3$, –OR', –SR', or –N(R')$_2$;

each of X, Y and Z is independently –O–, –S–, –N(–L–R^5)–, or L;

each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, –C≡C–, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L;

each –Cy– is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Cy^L is independently an optionally substituted trivalent or tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each R' is independently –R, –C(O)R, –C(O)OR, or –S(O)$_2$R;

each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

two R groups are optionally and independently taken together to form a covalent bond, or

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms, or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

[00333] In some embodiments, a linkage of formula I is chiral at the linkage phosphorus (P in P^L).

In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising one or more modified internucleotidic linkages of formula I. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising one or more modified internucleotidic linkages of formula I, and wherein individual internucleotidic linkages of formula I within the oligonucleotide have different P-modifications relative to one another. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising one or more modified internucleotidic linkages of formula I, and wherein individual internucleotidic linkages of formula I within the oligonucleotide have different $-X-L-R^1$ relative to one another. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising one or more modified internucleotidic linkages of formula I, and wherein individual internucleotidic linkages of formula I within the oligonucleotide have different X relative to one another. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising one or more modified internucleotidic linkages of formula I, and wherein individual internucleotidic linkages of formula I within the oligonucleotide have different $-L-R^1$ relative to one another. In some embodiments, a chirally controlled oligonucleotide is an oligonucleotide in a provided composition that is of the particular oligonucleotide type. In some embodiments, a chirally controlled oligonucleotide is an oligonucleotide in a provided composition that has the common base sequence and length, the common pattern of backbone linkages, and the common pattern of backbone chiral centers.

[00334] As extensively described herein, in some embodiments, $-X-L-R^1$ is a moiety useful for oligonucleotide preparation. For example, in some embodiments, $-X-L-R^1$ is $-OCH_2CH_2CN$ (*e.g.*, in non-chirally controlled internucleotidic linkages); in some embodiments, $-X-L-R^1$ is of such a structure that $H-X-L-R^1$ is a chiral auxiliary, optionally capped, as described herein (*e.g.*, DPSE, PSM, *etc.*; particularly in chirally controlled internucleotidic linkages, although may also in non-chirally controlled internucleotidic linkages (*e.g.*, precursors of natural phosphate linkages)).

[0001] In some embodiments, a chirally controlled oligonucleotide is an oligonucleotide in a chirally controlled composition that is of a particular oligonucleotide type, and the chirally controlled oligonucleotide is of the type. In some embodiments, a chirally controlled oligonucleotide is an oligonucleotide in a provided composition that comprises a controlled level of a plurality of oligonucleotides that share a common base sequence, a common pattern of backbone linkages, a common pattern of backbone chiral centers, and a common pattern of backbone phosphorus modifications, and the chirally controlled oligonucleotide shares the common base sequence, the common pattern of backbone linkages, the common pattern of backbone chiral centers, and the common pattern of backbone phosphorus modifications.

[00335] In some embodiments, the present disclosure provides a chirally controlled

oligonucleotide, wherein at least two chirally controlled internucleotidic linkages within the oligonucleotide have different P-modifications relative to one another, in that they have different X atoms in their $-XLR^1$ moieties, and/or in that they have different L groups in their $-XLR^1$ moieties, and/or that they have different R^1 atoms in their $-XLR^1$ moieties, and/or in that they have different $-XLR^1$ moieties.

[00336] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide, wherein at least two of the individual internucleotidic linkages within the oligonucleotide have different stereochemistry and/or different P-modifications relative to one another and the oligonucleotide has a structure represented by the following formula:

$$[S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny]$$

wherein:

each R^B independently represents a block of nucleotide units having the R configuration at the linkage phosphorus;

each S^B independently represents a block of nucleotide units having the S configuration at the linkage phosphorus;

each of n1-ny is zero or an integer, with the requirement that at least one odd n and at least one even n must be non-zero so that the oligonucleotide includes at least two individual internucleotidic linkages with different stereochemistry relative to one another; and

wherein the sum of n1-ny is between 2 and 200, and in some embodiments is between a lower limit selected from the group consisting of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or more and an upper limit selected from the group consisting of 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, and 200, the upper limit being larger than the lower limit.

[00337] In some such embodiments, each n has the same value; in some embodiments, each even n has the same value as each other even n; in some embodiments, each odd n has the same value each other odd n; in some embodiments, at least two even ns have different values from one another; in some embodiments, at least two odd ns have different values from one another.

[00338] In some embodiments, at least two adjacent ns are equal to one another, so that a provided oligonucleotide includes adjacent blocks of S stereochemistry linkages and R stereochemistry linkages of equal lengths. In some embodiments, provided oligonucleotides include repeating blocks of S and R stereochemistry linkages of equal lengths. In some embodiments, provided oligonucleotides include repeating blocks of S and R stereochemistry linkages, where at least two such blocks are of different lengths from one another; in some such embodiments each S stereochemistry block is of the same length, and is of a different length from each R stereochemistry length, which may optionally be of

the same length as one another.

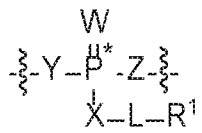
[00339] In some embodiments, at least two skip-adjacent ns are equal to one another, so that a provided oligonucleotide includes at least two blocks of linkages of a first stereochemistry that are equal in length to one another and are separated by a block of linkages of the other stereochemistry, which separating block may be of the same length or a different length from the blocks of first stereochemistry.

[00340] In some embodiments, ns associated with linkage blocks at the ends of a provided oligonucleotide are of the same length. In some embodiments, provided oligonucleotides have terminal blocks of the same linkage stereochemistry. In some such embodiments, the terminal blocks are separated from one another by a middle block of the other linkage stereochemistry.

[00341] In some embodiments, a provided oligonucleotide of formula $[S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny]$ is a stereoblockmer. In some embodiments, a provided oligonucleotide of formula $[S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny]$ is a stereoskipmer. In some embodiments, a provided oligonucleotide of formula $[S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny]$ is a stereoaltmer. In some embodiments, a provided oligonucleotide of formula $[S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny]$ is a gapmer.

[00342] In some embodiments, a provided oligonucleotide of formula $[S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny]$ is of any of the above described patterns and further comprises patterns of P-modifications. For instance, in some embodiments, a provided oligonucleotide of formula $[S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny]$ and is a stereoskipmer and P-modification skipmer. In some embodiments, a provided oligonucleotide of formula $[S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny]$ and is a stereoblockmer and P-modification altmer. In some embodiments, a provided oligonucleotide of formula $[S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny]$ and is a stereoaltmer and P-modification blockmer.

[00343] In some embodiments, an internucleotidic linkage of formula **I** has the structure of:



wherein:

P* is an asymmetric phosphorus atom and is either *R*p or *S*p;

W is O, S or Se;

each of X, Y and Z is independently –O–, –S–, –N(–L–R^1)–, or L;

L is a covalent bond or an optionally substituted, linear or branched C_1–C_{10} alkylene, wherein one or more methylene units of L are optionally and independently replaced by C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, a C_1–C_6 heteroaliphatic moiety, $-C(R')_2-$, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')-, –N(R')C(O)–, –N(R')C(O)O–, –OC(O)N(R')–, –S(O)–, $-S(O)_2-$, $-S(O)_2N(R')-$, $-N(R')S(O)_2-$ –SC(O)–, –C(O)S–, –OC(O)–, and –C(O)O–;

R^1 is halogen, R, or an optionally substituted C_1–C_{50} aliphatic wherein one or more methylene units are optionally and independently replaced by C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, a C_1–C_6 heteroaliphatic moiety, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$– –SC(O)–, –C(O)S–, –OC(O)–, and –C(O)O–;

each R′ is independently –R, -C(O)R, -CO$_2$R, or –SO$_2$R, or:

two R′ are taken together with their intervening atoms to form an optionally substituted aryl, carbocyclic, heterocyclic, or heteroaryl ring;

–Cy– is an optionally substituted bivalent ring selected from phenylene, carbocyclylene, arylene, heteroarylene, and heterocyclylene;

each R is independently hydrogen, or an optionally substituted group selected from C_1–C_6 aliphatic, carbocyclyl, aryl, heteroaryl, and heterocyclyl; and

each independently represents a connection to a nucleoside.

[00344] In some embodiments, L is a covalent bond or an optionally substituted, linear or branched C_1–C_{10} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–;

R^1 is halogen, R, or an optionally substituted C_1–C_{50} aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–;

each R′ is independently –R, -C(O)R, -CO$_2$R, or –SO$_2$R, or:

two R′ on the same nitrogen are taken together with their intervening atoms to form an optionally substituted heterocyclic or heteroaryl ring, or

two R′ on the same carbon are taken together with their intervening atoms to form an optionally substituted aryl, carbocyclic, heterocyclic, or heteroaryl ring;

–Cy– is an optionally substituted bivalent ring selected from phenylene, carbocyclylene, arylene, heteroarylene, or heterocyclylene;

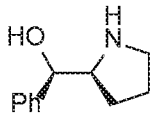
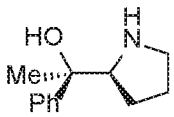
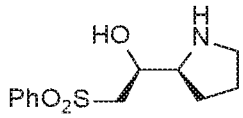
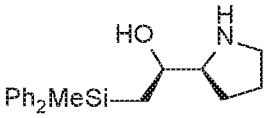
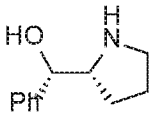
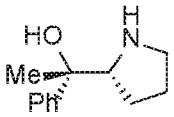
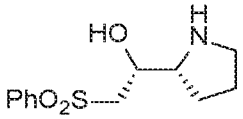
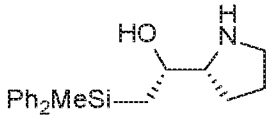
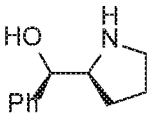
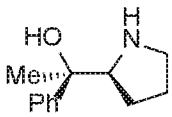
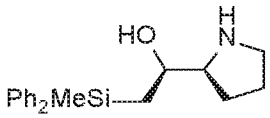
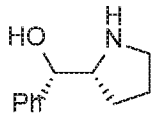
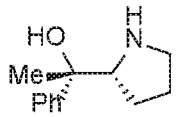
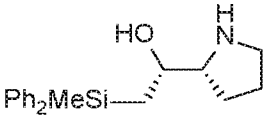
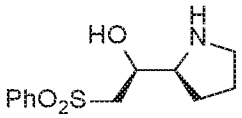
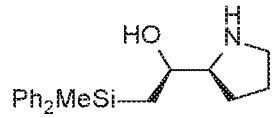
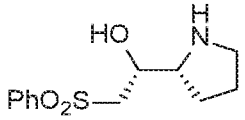
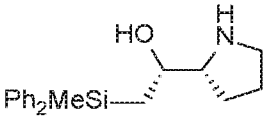
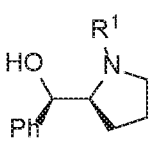
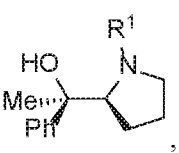
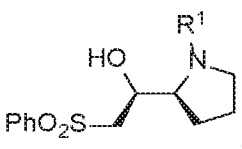
each R is independently hydrogen, or an optionally substituted group selected from C_1–C_6 aliphatic, phenyl, carbocyclyl, aryl, heteroaryl, or heterocyclyl; and

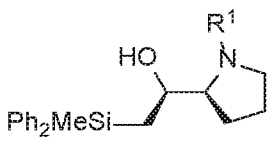
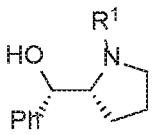
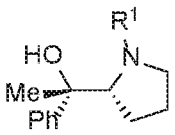
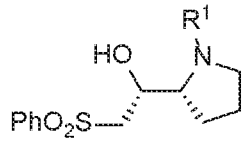
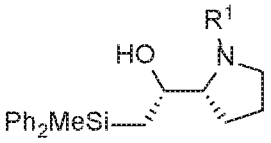
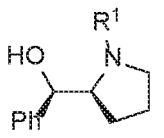
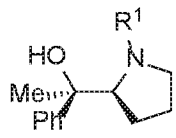
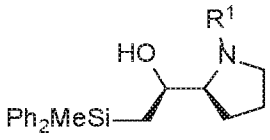
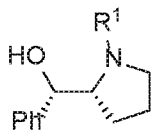
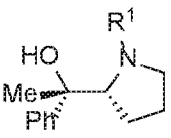
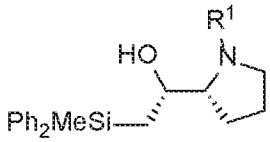
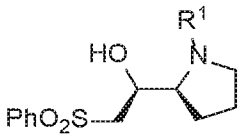
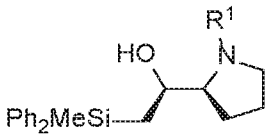
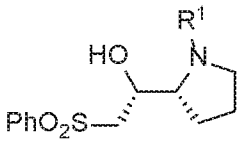
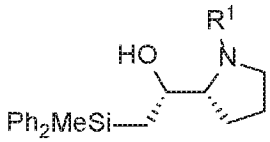
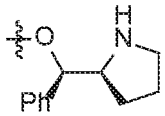
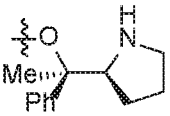
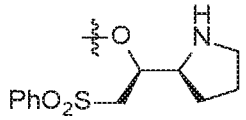
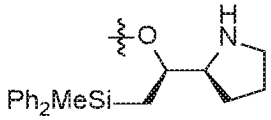
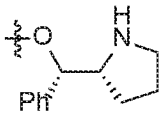
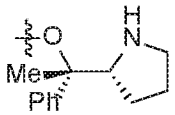
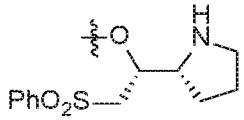
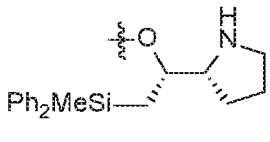
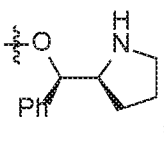
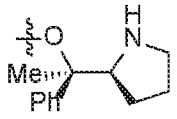
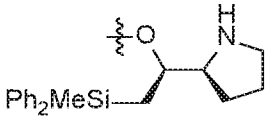
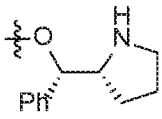
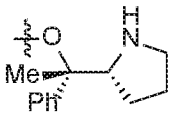
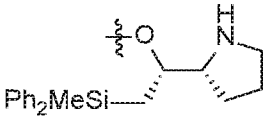
each independently represents a connection to a nucleoside.

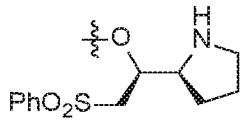
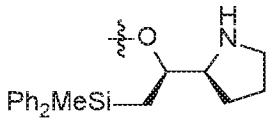
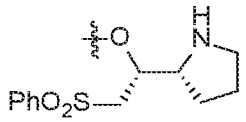
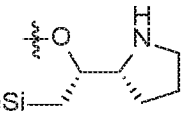
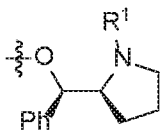
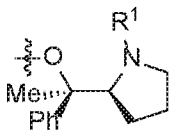
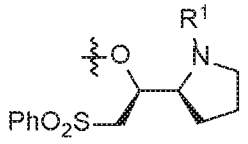
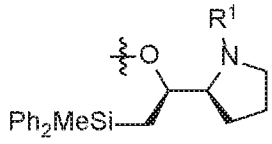
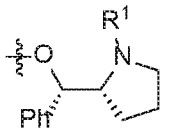
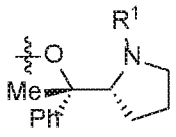
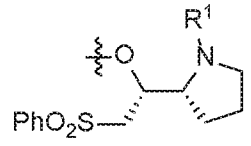
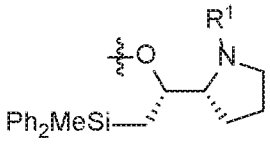
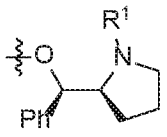
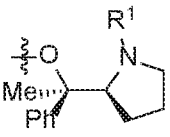
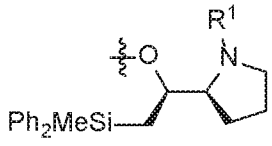
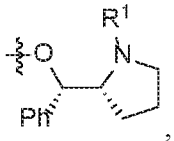
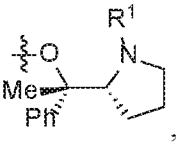
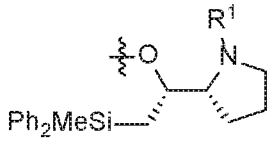
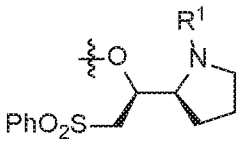
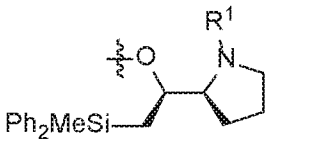
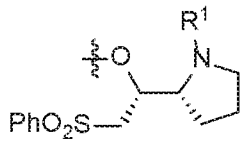
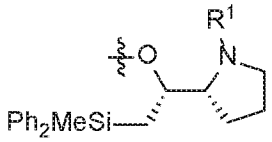
[00345] In some embodiments, a chirally controlled oligonucleotide comprises one or more modified internucleotidic linkages. In some embodiments, a chirally controlled oligonucleotide comprises, *e.g.*, a phosphorothioate or a phosphorothioate triester internucleotidic linkage. In some embodiments, a chirally controlled oligonucleotide comprises a chirally controlled phosphorothioate triester linkage. In some embodiments, a chirally controlled oligonucleotide comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 chirally controlled phosphorothioate triester internucleotidic linkages. In some embodiments, a chirally controlled oligonucleotide comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 chirally controlled phosphorothioate internucleotidic linkages (−O−P(O)(SH)−O− or salt forms thereof).

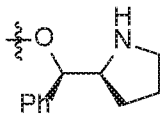
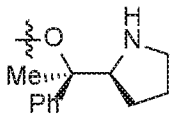
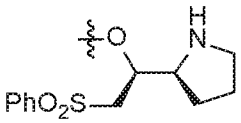
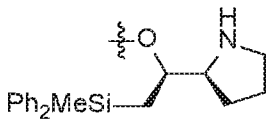
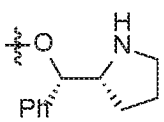
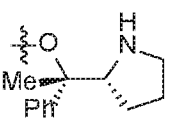
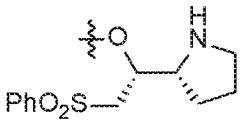
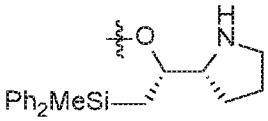
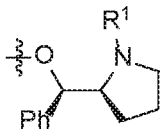
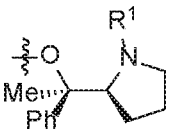
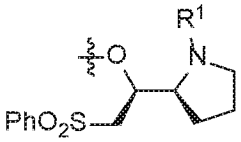
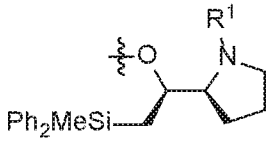
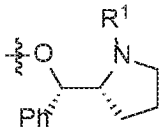
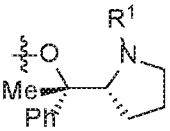
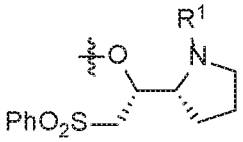
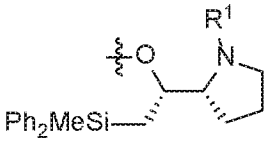
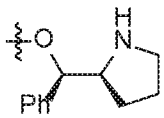
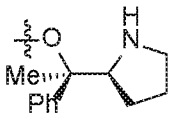
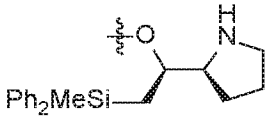
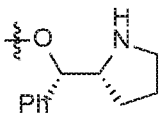
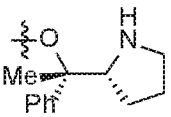
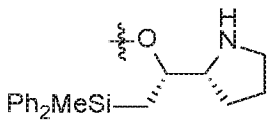
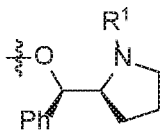
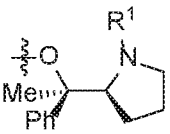
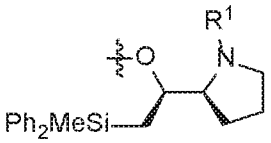
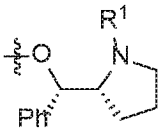
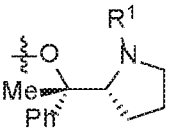
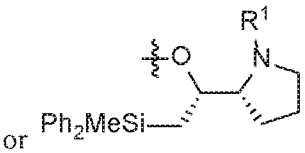
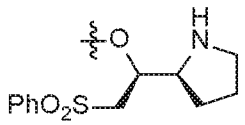
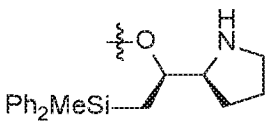
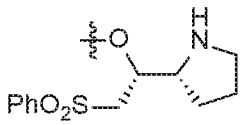
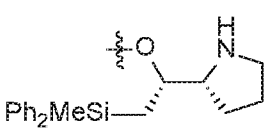
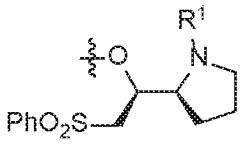
[00346] In some embodiments, an oligonucleotide comprises different types of internucleotidic phosphorus linkages. In some embodiments, a chirally controlled oligonucleotide comprises at least one natural phosphate linkage and at least one modified (non-natural) internucleotidic linkage. In some embodiments, an oligonucleotide comprises at least one natural phosphate linkage and at least one phosphorothioate. In some embodiments, an oligonucleotide comprises at least one non-negatively charged internucleotidic linkage. In some embodiments, an oligonucleotide comprises at least one natural phosphate linkage and at least one non-negatively charged internucleotidic linkage. In some embodiments, an oligonucleotide comprises at least one phosphorothioate internucleotidic linkage and at least one non-negatively charged internucleotidic linkage. In some embodiments, an oligonucleotide comprises at least one phosphorothioate internucleotidic linkage, at least one natural phosphate linkage, and at least one non-negatively charged internucleotidic linkage.

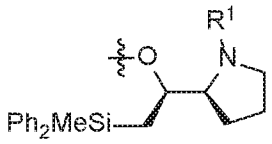
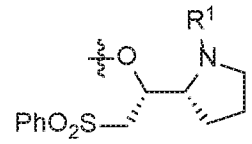
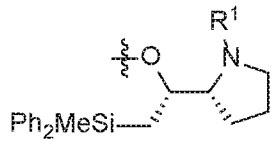
[00347] In some embodiments, an internucleotidic linkage comprises a chiral auxiliary. In some embodiments, an internucleotidic linkage of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., comprises a chiral auxiliary, wherein P^L is P=S. In some embodiments, an internucleotidic linkage of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., comprises a chiral auxiliary, wherein P^L is P=O. In some embodiments, a phosphorothioate triester linkage comprises a chiral auxiliary, which, for example, is used to control the stereoselectivity of a reaction. In some embodiments, a phosphorothioate triester linkage does not comprise a chiral auxiliary. Example chiral auxiliaries that can be utilized in accordance with the present disclosure include those described in US 9394333, US 9744183, US 9605019, US 20130178612, US 20150211006, US 9598458, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2018/237194, WO 2019/055951, the chiral auxiliaries of each of which is incorporated

herein by reference. In some embodiments, one or more $-X-L-R^1$ independently comprise or are an optionally substituted chiral auxiliary. In some embodiments, one or more $-X-L-R^1$ are each independently of such a structure that $H-X-L-R^1$ is a chiral reagent/chiral auxiliary described herein (e.g., one having the structure of formula 3-I, formula 3-AA, etc.). In some embodiments, $H-X-L-R^1$ is a capped chiral reagent/chiral auxiliary described herein (e.g., one having the structure of formula 3-I, formula 3-AA, etc.), which is capped in that an amino group of the chiral reagent/chiral auxiliary (e.g., $H-W^1$ and $H-W^2$ is or comprises $H-NG^5-$) is capped (e.g., forming R^1-NG^5- (e.g., $R'C(O)-NG^5-$, $RS(O)_2-NG^5-$, etc.)). In some embodiments, R' is optionally substituted C_{1-6} alkyl. In some embodiments, R' is methyl. In some embodiments, one or more $-X-L-R^1$ are each independently of such a structure that $H-X-L-R^1$ is  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, one or more $-X-L-R^1$ are each independently of such a structure that $H-X-L-R^1$ is  ,  ,  ,  ,  , or  . In some embodiments, one or more $-X-L-R^1$ are each independently of such a structure that $H-X-L-R^1$ is  ,  ,  , or  . In some embodiments, one or more $-X-L-R^1$ are each independently of such a structure that $H-X-L-R^1$ is a compound selected from Tables CA-1, CA-2, CA-3, CA-4, CA-5, CA-6, CA-7, CA-8, CA-9, CA-10, CA-11, CA-12, or CA-13, or a related (having the same constitution) diastereomer or enantiomer thereof. In some embodiments, one or more $-X-L-R^1$ are each independently of such a structure that $H-X-L-R^1$ is  ,  ,  ,





, or  . In some embodiments, one or more −X−L−R^1 are each independently of such a structure that H−X−L−R^1 is 




, or  . In some embodiments, one or more −X−L−R^1 are each independently of such a structure that H−X−L−R^1 is 


, or  . In some embodiments, one or more −X−L−R^1 are each independently of such a structure that H−X−L−R^1 is a compound selected from Tables CA-1, CA-2, CA-3, CA-4, CA-5, CA-6, CA-7, CA-8, CA-9, CA-10, CA-11, CA-12, or CA-13, or a related (having the same constitution) diastereomer or enantiomer thereof, wherein the −NH− of the 5-membered pyrrolidinyl is replaced with −N(R^1)−. In some embodiments, one or more −X−L−R^1 are independently 

, 




, or  . In some embodiments, one or more −X−L−R^1 are independently 
, 



, or  . In

some embodiments, one or more –X–L–R^1 are independently  ,  ,  or  . In some embodiments, one or more –X–L–R^1 are each independently of such a structure that H–X–L–R^1 is a compound selected from Tables CA-1, CA-2, CA-3, CA-4, CA-5, CA-6, CA-7, CA-8, CA-9, CA-10, CA-11, CA-12, or CA-13, or a related (having the same constitution) diastereomer or enantiomer thereof, wherein the connection to the linkage phosphorus is through the alcohol hydroxyl group. In some embodiments, one or more –X–L–R^1 are independently  ,  ,  ,  ,  ,  ,  or  . In some embodiments, one or more –X–L–R^1 are independently  ,  ,  ,  ,  , or  . In some embodiments, one or more –X–L–R^1 are independently  ,  ,  or  . In some embodiments, one or more –X–L–R^1 are each independently of such a structure that H–X–L–R^1 is a compound selected from Tables CA-1, CA-2, CA-3, CA-4, CA-5, CA-6, CA-7, CA-8, CA-9, CA-10, CA-11, CA-12, or CA-13, or a related (having the same constitution) diastereomer or enantiomer thereof, wherein the –NH– of the 5-membered pyrrolidinyl is replaced with –N(R^1)–, and wherein the connection to the linkage phosphorus is through the alcohol hydroxyl group.

In some embodiments, one or more $-X-L-R^1$ are independently  ,  ,  ,  ,  ,  ,  or  , and one or more $-X-L-R^1$ are independently  ,  ,  ,  ,  ,  ,  or  . In some embodiments, one or more $-X-L-R^1$ are independently  ,  ,  ,  ,  , or  , and one or more $-X-L-R^1$ are independently  ,  ,  ,  ,  , or  . In some embodiments, one or more $-X-L-R^1$ are independently  ,  ,  or  , and one or more $-X-L-R^1$ are independently  ,



or  . In some embodiments, R^1 is a capping group utilized in oligonucleotide synthesis. In some embodiments, R^1 is $-C(O)-R'$. In some embodiments, R^1 is $-C(O)-R'$, wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^1 is $-C(O)CH_3$.

[00348] In some embodiments, an oligonucleotide, e.g., a chirally controlled oligonucleotide, an oligonucleotide of a plurality, etc. is linked to a solid support. In some embodiments, an oligonucleotide is not linked to a solid support.

[00349] In some embodiments, an oligonucleotide comprises at least one natural phosphate linkage and at least two consecutive chirally controlled modified internucleotidic linkages. In some embodiments, a chirally controlled oligonucleotide comprises at least one natural phosphate linkage and at least two consecutive chirally controlled phosphorothioate internucleotidic linkages.

[00350] In some embodiments, a chirally controlled oligonucleotide is a blockmer. In some embodiments, a chirally controlled oligonucleotide is a stereoblockmer. In some embodiments, a chirally controlled oligonucleotide is a P-modification blockmer. In some embodiments, a chirally controlled oligonucleotide is a linkage blockmer.

[00351] In some embodiments, a chirally controlled oligonucleotide is an altmer. In some embodiments, a chirally controlled oligonucleotide is a stereoaltmer. In some embodiments, a chirally controlled oligonucleotide is a P-modification altmer. In some embodiments, a chirally controlled oligonucleotide is a linkage altmer.

[00352] In some embodiments, a chirally controlled oligonucleotide is a unimer.

[00353] In some embodiments, in a unimer, all nucleotide units within a strand share at least one common structural feature at the internucleotidic phosphorus linkage. In some embodiments, a common structural feature is a common stereochemistry at the linkage phosphorus or a common modification at the linkage phosphorus. In some embodiments, a chirally controlled oligonucleotide is a stereounimer. In some embodiments, a chirally controlled oligonucleotide is a P-modification unimer. In some embodiments, a chirally controlled oligonucleotide is a linkage unimer.

[00354] In some embodiments, a chirally controlled oligonucleotide is a gapmer.

[00355] In some embodiments, a chirally controlled oligonucleotide is a skipmer.

[00356] In some embodiments, the present disclosure provides oligonucleotides comprising one or more modified internucleotidic linkages independently having the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, **III**, or a salt form

thereof.

[00357] In some embodiments, L is a covalent bond or an optionally substituted, linear or branched C_1–C_{10} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–;

R^1 is halogen, R, or an optionally substituted C_1–C_{50} aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–;

each R′ is independently –R, -C(O)R, -CO$_2$R, or –SO$_2$R, or:

two R′ on the same nitrogen are taken together with their intervening atoms to form an optionally substituted heterocyclic or heteroaryl ring, or

two R′ on the same carbon are taken together with their intervening atoms to form an optionally substituted aryl, carbocyclic, heterocyclic, or heteroaryl ring;

–Cy– is an optionally substituted bivalent ring selected from phenylene, carbocyclylene, arylene, heteroarylene, or heterocyclylene;

each R is independently hydrogen, or an optionally substituted group selected from C_1–C_6 aliphatic, phenyl, carbocyclyl, aryl, heteroaryl, or heterocyclyl; and

each —≋— independently represents a connection to a nucleoside.

[00358] In some embodiments, a chirally controlled oligonucleotide comprises one or more modified internucleotidic phosphorus linkages. In some embodiments, a chirally controlled oligonucleotide comprises, *e.g.*, a phosphorothioate or a phosphorothioate triester linkage. In some embodiments, a chirally controlled oligonucleotide comprises a phosphorothioate triester linkage. In some embodiments, a chirally controlled oligonucleotide comprises at least two phosphorothioate triester linkages. In some embodiments, a chirally controlled oligonucleotide comprises at least three phosphorothioate triester linkages. Example modified internucleotidic phosphorus linkages are described further herein. In some embodiments, a chirally controlled oligonucleotide comprises different internucleotidic phosphorus linkages. In some embodiments, a chirally controlled oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least one modified internucleotidic linkage. In some embodiments, a chirally controlled oligonucleotide comprises at least

one phosphate diester internucleotidic linkage and at least one phosphorothioate triester linkage. In some embodiments, a chirally controlled oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least two phosphorothioate triester linkages. In some embodiments, a chirally controlled oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least three phosphorothioate triester linkages.

[00359] In some embodiments, P* is an asymmetric phosphorus atom and is either *R*p or *S*p. In some embodiments, P* is *R*p. In other embodiments, P* is *S*p. In some embodiments, an oligonucleotide comprises one or more internucleotidic linkages of formula I wherein each P* is independently *R*p or *S*p. In some embodiments, an oligonucleotide comprises one or more internucleotidic linkages of formula I wherein each P* is *R*p. In some embodiments, an oligonucleotide comprises one or more internucleotidic linkages of formula I wherein each P* is *S*p. In some embodiments, an oligonucleotide comprises at least one internucleotidic linkage of formula I wherein P* is *R*p. In some embodiments, an oligonucleotide comprises at least one internucleotidic linkage of formula I wherein P* is *S*p. In some embodiments, an oligonucleotide comprises at least one internucleotidic linkage of formula I wherein P* is *R*p, and at least one internucleotidic linkage of formula I wherein P* is *S*p.

[00360] In some embodiments, W is O, S, or Se. In some embodiments, W is O. In some embodiments, W is S. In some embodiments, W is Se. In some embodiments, an oligonucleotide comprises at least one internucleotidic linkage of formula I wherein W is O. In some embodiments, an oligonucleotide comprises at least one internucleotidic linkage of formula I wherein W is S. In some embodiments, an oligonucleotide comprises at least one internucleotidic linkage of formula I wherein W is Se.

[00361] In some embodiments, an oligonucleotide comprises at least one internucleotidic linkage of formula I wherein W is O. In some embodiments, an oligonucleotide comprises at least one internucleotidic linkage of formula I wherein W is S.

[00362] In some embodiments, X is –O–. In some embodiments, X is –S–. In some embodiments, X is –O– or –S–. In some embodiments, an oligonucleotide comprises at least one internucleotidic linkage of formula I wherein X is –O–. In some embodiments, an oligonucleotide comprises at least one internucleotidic linkage of formula I wherein X is –S–. In some embodiments, an oligonucleotide comprises at least one internucleotidic linkage of formula I wherein X is –O–, and at least one internucleotidic linkage of formula I wherein X is –S–. In some embodiments, an oligonucleotide comprises at least one internucleotidic linkage of formula I wherein X is –O–, and at least one internucleotidic linkage of formula I wherein X is –S–, and at least one internucleotidic linkage of formula I wherein L is an optionally substituted, linear or branched C_1–C_{10} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1–C_6

alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–.

[00363] In some embodiments, X is –N(–L–R^1)–. In some embodiments, X is –N(R^1)–. In some embodiments, X is –N(R’)–. In some embodiments, X is –N(R)–. In some embodiments, X is –NH–.

[00364] In some embodiments, X is L. In some embodiments, X is a covalent bond. In some embodiments, X is or an optionally substituted, linear or branched C_1–C_{10} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–. In some embodiments, X is an optionally substituted C_1–C_{10} alkylene or C_1–C_{10} alkenylene. In some embodiments, X is methylene.

[00365] In some embodiments, Y is –O–. In some embodiments, Y is –S–.

[00366] In some embodiments, Y is –N(–L–R^1)–. In some embodiments, Y is –N(R^1)–. In some embodiments, Y is –N(R’)–. In some embodiments, Y is –N(R)–. In some embodiments, Y is –NH–.

[00367] In some embodiments, Y is L. In some embodiments, Y is a covalent bond. In some embodiments, Y is or an optionally substituted, linear or branched C_1–C_{10} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–. In some embodiments, Y is an optionally substituted C_1–C_{10} alkylene or C_1–C_{10} alkenylene. In some embodiments, Y is methylene.

[00368] In some embodiments, Z is –O–. In some embodiments, Z is –S–.

[00369] In some embodiments, Z is –N(–L–R^1)–. In some embodiments, Z is –N(R^1)–. In some embodiments, Z is –N(R’)–. In some embodiments, Z is –N(R)–. In some embodiments, Z is –NH–.

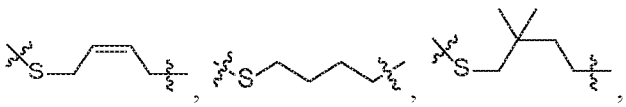
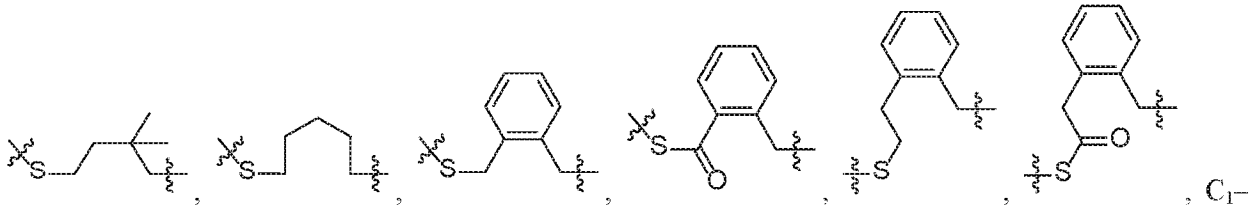
[00370] In some embodiments, Z is L. In some embodiments, Z is a covalent bond. In some embodiments, Z is or an optionally substituted, linear or branched C_1–C_{10} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–. In some

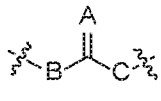
embodiments, Z is an optionally substituted C_1–C_{10} alkylene or C_1–C_{10} alkenylene. In some embodiments, Z is methylene.

[00371] In some embodiments, L is a covalent bond or an optionally substituted, linear or branched C_1–C_{10} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–.

[00372] In some embodiments, L is a covalent bond. In some embodiments, L is an optionally substituted, linear or branched C_1–C_{10} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–.

[00373] In some embodiments, L has the structure of –L^1–V–, wherein:

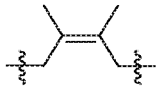
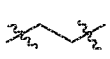
L^1 is an optionally substituted group selected from  ,  , C_1–C_6 alkylene, C_1-C_6 alkenylene, carbocyclylene, arylene, C_1–C_6 heteroalkylene, heterocyclylene, and heteroarylene;

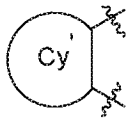
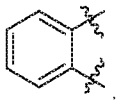
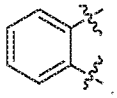
V is selected from –O–, –S–, –NR’–, C(R’)$_2$, –S–S–, –B–S–S–C–,  , or an optionally substituted group selected from C_1–C_6 alkylene, arylene, C_1–C_6 heteroalkylene, heterocyclylene, and heteroarylene;

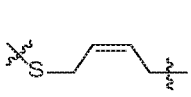
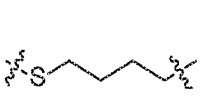
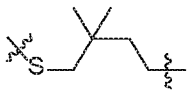
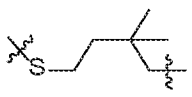
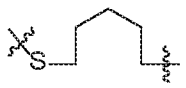
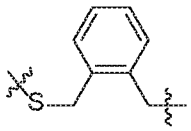
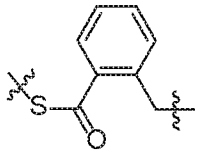
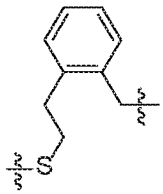
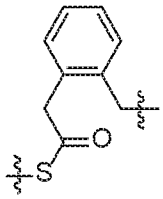
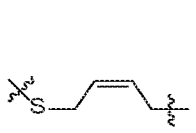
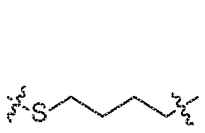
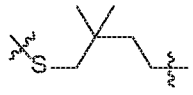
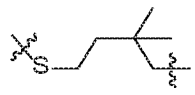
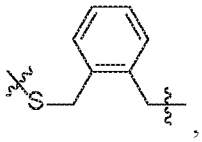
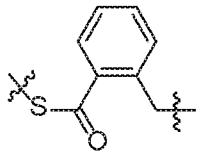
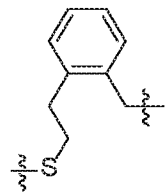
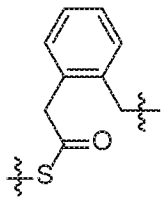
A is =O, =S, =NR’, or =C(R’)$_2$;

each of B and C is independently –O–, –S–, –NR’–, –C(R’)$_2$–, or an optionally substituted group selected from C_1–C_6 alkylene, carbocyclylene, arylene, heterocyclylene, or heteroarylene; and

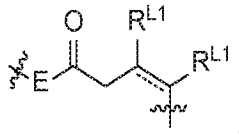
each R’ is independently as defined above and described herein.

[00374] In some embodiments, L^1 is  , , , ,  , , or .

[00375] In some embodiments, L^1 is  , wherein Ring Cy' is an optionally substituted arylene, carbocyclylene, heteroarylene, or heterocyclylene. In some embodiments, L^1 is optionally substituted  . In some embodiments, L^1 is  .

[00376] In some embodiments, L^1 is connected to X. In some embodiments, L^1 is an optionally substituted group selected from  ,  ,  ,  ,  ,  ,  ,  ,and  , and the sulfur atom is connect to V. In some embodiments, L^1 is an optionally substituted group selected from  ,  ,  ,  , ,  ,  ,  ,and  , and the carbon atom is connect to X.

[00377] In some embodiments, L has the structure of:

 ,

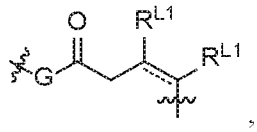
wherein:

E is –O–, –S–, –NR'– or –$C(R')_2$–;

═══ is a single or double bond;

the two R^{L1} are taken together with the two carbon atoms to which they are bound to form an optionally substituted aryl, carbocyclic, heteroaryl or heterocyclic ring; and each R' is independently as defined above and described herein.

[00378] In some embodiments, L has the structure of:



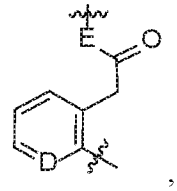
wherein:

G is –O–, –S–, or –NR';

----- is a single or double bond; and

the two R^{L1} are taken together with the two carbon atoms to which they are bound to form an optionally substituted aryl, C_3-C_{10} carbocyclic, heteroaryl or heterocyclic ring.

[00379] In some embodiments, L has the structure of:



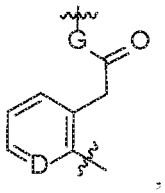
wherein:

E is –O–, –S–, –NR'– or –$C(R')_2$–;

D is =N–, =C(F)–, =C(Cl)–, =C(Br)–, =C(I)–, =C(CN)–, =$C(NO_2)$–, =$C(CO_2$–(C_1-C_6 aliphatic))–, or =$C(CF_3)$–; and

each R' is independently as defined above and described herein.

[00380] In some embodiments, L has the structure of:

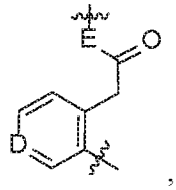


wherein:

G is –O–, –S–, or –NR';

D is =N–, =C(F)–, =C(Cl)–, =C(Br)–, =C(I)–, =C(CN)–, =$C(NO_2)$–, =$C(CO_2$–(C_1-C_6 aliphatic))–, or =$C(CF_3)$–.

[00381] In some embodiments, L has the structure of:



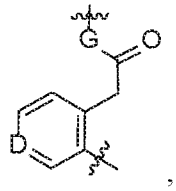
wherein:

E is –O–, –S–, –NR'– or –C(R')$_2$–;

D is =N–, =C(F)–, =C(Cl)–, =C(Br)–, =C(I)–, =C(CN)–, =C(NO$_2$)–, =C(CO$_2$–(C$_1$-C$_6$ aliphatic))–, or =C(CF$_3$)–; and

each R' is independently as defined above and described herein.

[00382] In some embodiments, L has the structure of:

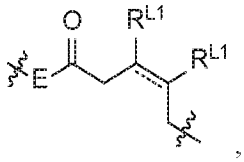


wherein:

G is –O–, –S–, or –NR';

D is =N–, =C(F)–, =C(Cl)–, =C(Br)–, =C(I)–, =C(CN)–, =C(NO$_2$)–, =C(CO$_2$–(C$_1$-C$_6$ aliphatic))–, or =C(CF$_3$)–.

[00383] In some embodiments, L has the structure of:



wherein:

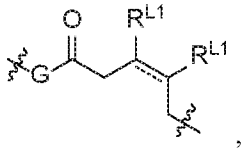
E is –O–, –S–, –NR'– or –C(R')$_2$–;

----- is a single or double bond;

the two R^{L1} are taken together with the two carbon atoms to which they are bound to form an optionally substituted aryl, C$_3$-C$_{10}$ carbocyclic, heteroaryl or heterocyclic ring;

and each R' is independently as defined above and described herein.

[00384] In some embodiments, L has the structure of:



wherein:

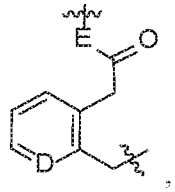
G is –O–, –S–, or –NR';

---- is a single or double bond;

the two R^{L1} are taken together with the two carbon atoms to which they are bound to form an optionally substituted aryl, C_3-C_{10} carbocyclic, heteroaryl or heterocyclic ring;

and each R' is independently as defined above and described herein.

[00385] In some embodiments, L has the structure of:



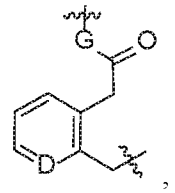
wherein:

E is –O–, –S–, –NR'– or –C(R')$_2$–;

D is =N–, =C(F)–, =C(Cl)–, =C(Br)–, =C(I)–, =C(CN)–, =C(NO_2)–, =C(CO_2–(C_1-C_6 aliphatic))–, or =C(CF_3)–; and

each R' is independently as defined above and described herein.

[00386] In some embodiments, L has the structure of:



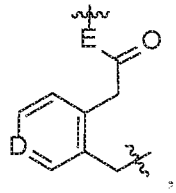
wherein:

G is –O–, –S–, or –NR';

D is =N–, =C(F)–, =C(Cl)–, =C(Br)–, =C(I)–, =C(CN)–, =C(NO_2)–, =C(CO_2–(C_1-C_6 aliphatic))–, or =C(CF_3)–; and

each R' is independently as defined above and described herein.

[00387] In some embodiments, L has the structure of:



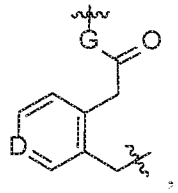
wherein:

E is –O–, –S–, –NR'– or –C(R')$_2$–;

D is =N–, =C(F)–, =C(Cl)–, =C(Br)–, =C(I)–, =C(CN)–, =C(NO_2)–, =C(CO_2–(C_1-C_6 aliphatic))–, or =C(CF_3)–; and

each R' is independently as defined above and described herein.

[00388] In some embodiments, L has the structure of:



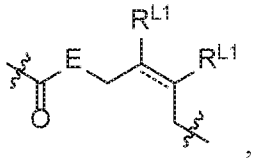
wherein:

G is –O–, –S–, or –NR';

D is =N–, =C(F)–, =C(Cl)–, =C(Br)–, =C(I)–, =C(CN)–, =C(NO_2)–, =C(CO_2–(C_1-C_6 aliphatic))–, or =C(CF_3)–; and

each R' is independently as defined above and described herein.

[00389] In some embodiments, L has the structure of:



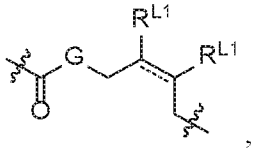
wherein:

E is –O–, –S–, –NR'– or –C(R')$_2$–;

⎯⎯ is a single or double bond;

the two R^{L1} are taken together with the two carbon atoms to which they are bound to form an optionally substituted aryl, C_3-C_{10} carbocyclic, heteroaryl or heterocyclic ring; and each R' is independently as defined above and described herein.

[00390] In some embodiments, L has the structure of:



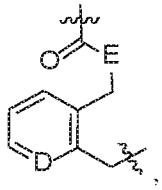
wherein:

G is –O–, –S–, or –NR';

⎯⎯ is a single or double bond;

the two R^{L1} are taken together with the two carbon atoms to which they are bound to form an optionally substituted aryl, C_3-C_{10} carbocyclic, heteroaryl or heterocyclic ring; and each R' is independently as defined above and described herein.

[00391] In some embodiments, L has the structure of:



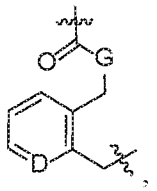
wherein:

E is –O–, –S–, –NR'– or –C(R')$_2$–;

D is =N–, =C(F)–, =C(Cl)–, =C(Br)–, =C(I)–, =C(CN)–, =C(NO$_2$)–, =C(CO$_2$–(C$_1$-C$_6$ aliphatic))–, or =C(CF$_3$)–; and

each R' is independently as defined above and described herein.

[00392] In some embodiments, L has the structure of:



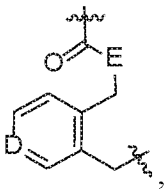
wherein:

G is –O–, –S–, or –NR';

D is =N–, =C(F)–, =C(Cl)–, =C(Br)–, =C(I)–, =C(CN)–, =C(NO$_2$)–, =C(CO$_2$–(C$_1$-C$_6$ aliphatic))–, or =C(CF$_3$)–; and

R' is as defined above and described herein.

[00393] In some embodiments, L has the structure of:



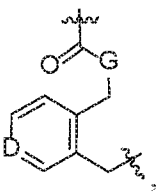
wherein:

E is –O–, –S–, –NR'– or –C(R')$_2$–;

D is =N–, =C(F)–, =C(Cl)–, =C(Br)–, =C(I)–, =C(CN)–, =C(NO$_2$)–, =C(CO$_2$–(C$_1$-C$_6$ aliphatic))–, or =C(CF$_3$)–; and

each R' is independently as defined above and described herein.

[00394] In some embodiments, L has the structure of:



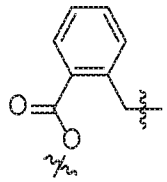
wherein:

G is –O–, –S–, or –NR’;

D is =N–, =C(F)–, =C(Cl)–, =C(Br)–, =C(I)–, =C(CN)–, =C(NO_2)–, =C(CO_2–(C_1-C_6 aliphatic))–, or =C(CF_3)–; and

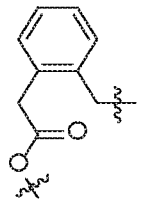
R’ is as defined above and described herein.

[00395] In some embodiments, L has the structure of:



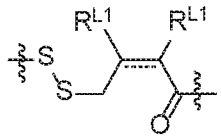
wherein the phenyl ring is optionally substituted. In some embodiments, the phenyl ring is not substituted. In some embodiments, the phenyl ring is substituted.

[00396] In some embodiments, L has the structure of:



wherein the phenyl ring is optionally substituted. In some embodiments, the phenyl ring is not substituted. In some embodiments, the phenyl ring is substituted.

[00397] In some embodiments, L has the structure of:

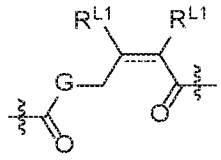


wherein:

==== is a single or double bond; and

the two R^{L1} are taken together with the two carbon atoms to which they are bound to form an optionally substituted aryl, C_3-C_{10} carbocyclic, heteroaryl or heterocyclic ring.

[00398] In some embodiments, L has the structure of:



wherein:

G is –O–, –S–, or –NR';

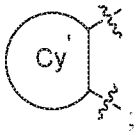
---- is a single or double bond; and

the two R^{L1} are taken together with the two carbon atoms to which they are bound to form an optionally substituted aryl, C_3-C_{10} carbocyclic, heteroaryl or heterocyclic ring.

[00399] In some embodiments, E is –O–, –S–, –NR'– or $–C(R')_2–$, wherein each R' independently as defined above and described herein. In some embodiments, E is –O–, –S–, or –NR'–. In some embodiments, E is –O–, –S–, or –NH–. In some embodiments, E is –O–. In some embodiments, E is –S–. In some embodiments, E is –NH–.

[00400] In some embodiments, G is –O–, –S–, or –NR', wherein each R' independently as defined above and described herein. In some embodiments, G is –O–, –S–, or –NH–. In some embodiments, G is –O–. In some embodiments, G is –S–. In some embodiments, G is –NH–.

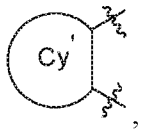
[00401] In some embodiments, L is $–L^3–G–$, wherein:

L^3 is an optionally substituted C_1–C_5 alkylene or alkenylene, wherein one or more methylene units are optionally and independently replaced by –O–, –S–,–N(R')–, –C(O)–, –C(S)–, –C(NR')–, –S(O)–, –$S(O)_2$–, or 

; and

wherein each of G, R' and Ring Cy' is independently as defined above and described herein.

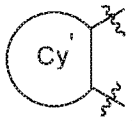
[00402] In some embodiments, L is $–L^3–S–$, wherein L^3 is as defined above and described herein. In some embodiments, L is $–L^3–O–$, wherein L^3 is as defined above and described herein. In some embodiments, L is $–L^3–N(R')–$, wherein each of L^3 and R' is independently as defined above and described herein. In some embodiments, L is $–L^3–NH–$, wherein each of L^3 and R' is independently as defined above and described herein.

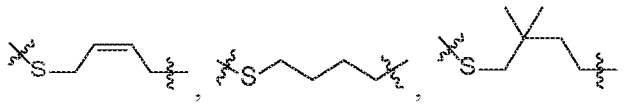
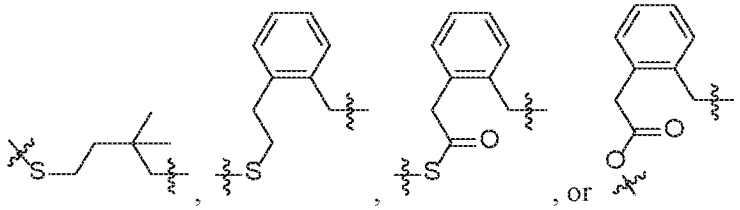
[00403] In some embodiments, L^3 is an optionally substituted C_5 alkylene or alkenylene, wherein one or more methylene units are optionally and independently replaced by –O–, –S–,–N(R')–, –C(O)–, –C(S)–, –C(NR')–, –S(O)–, –$S(O)_2$–, or 

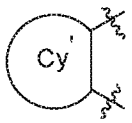
, and each of R' and Ring Cy' is independently as defined above and described herein. In some embodiments, L^3 is an optionally substituted C_5 alkylene. In some embodiments, $–L^3–G–$ is

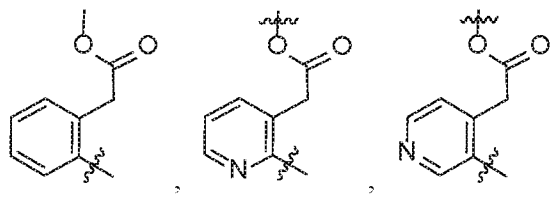
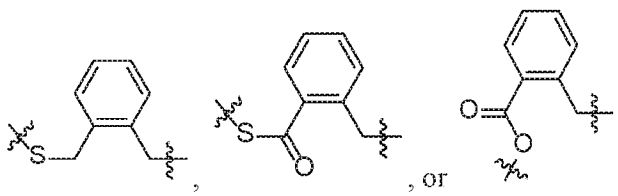
.

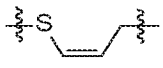
[00404] In some embodiments, L^3 is an optionally substituted C_4 alkylene or alkenylene, wherein one or more methylene units are optionally and independently replaced by –O–, –S–,–N(R')–, –C(O)–, –

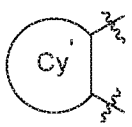
C(S)–, –C(NR')–, –S(O)–, –S(O)$_2$–, or  , and each of R' and Cy' is independently as defined above and described herein.

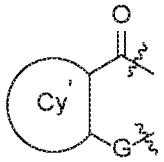
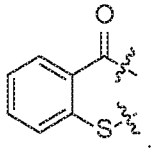
[00405] In some embodiments, –L^3–G– is  ,  , or .

[00406] In some embodiments, L^3 is an optionally substituted C_3 alkylene or alkenylene, wherein one or more methylene units are optionally and independently replaced by –O–, –S–,–N(R')–, –C(O)–, –C(S)–, –C(NR')–, –S(O)–, –S(O)$_2$–, or  , and each of R' and Cy' is independently as defined above and described herein.

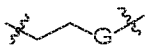
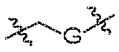
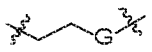
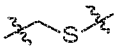
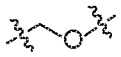
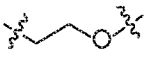
[00407] In some embodiments, –L^3–G– is  ,  , or .

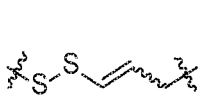
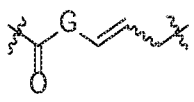
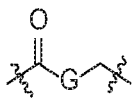
[00408] In some embodiments, L is . In some embodiments, L is or . In some embodiments, L is  or .

[00409] In some embodiments, L^3 is an optionally substituted C_2 alkylene or alkenylene, wherein one or more methylene units are optionally and independently replaced by –O–, –S–,–N(R')–, –C(O)–, –C(S)–, –C(NR')–, –S(O)–, –S(O)$_2$–, or  , and each of R' and Cy' is independently as defined above and described herein.

[00410] In some embodiments, –L^3–G– is  , wherein each of G and Cy' is independently as defined above and described herein. In some embodiments, L is  .

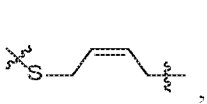
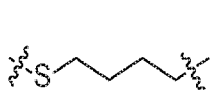
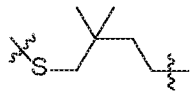
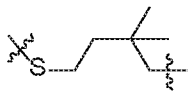
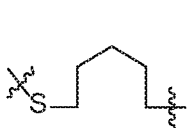
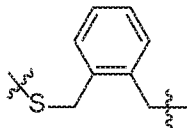
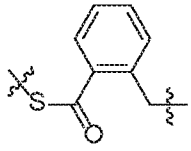
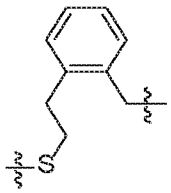
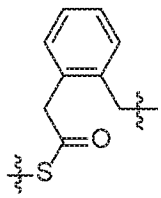
[00411] In some embodiments, L is –L^4–G–, wherein L^4 is an optionally substituted C_1–C_2 alkylene; and G is as defined above and described herein. In some embodiments, L is –L^4–G–, wherein L^4 is an optionally substituted C_1–C_2 alkylene; G is as defined above and described herein; and G is connected to R^1. In some embodiments, L is –L^4–G–, wherein L^4 is an optionally substituted methylene; G is as defined above and described herein; and G is connected to R^1. In some embodiments, L is –L^4–G–, wherein L^4 is methylene; G is as defined above and described herein; and G is connected to R^1. In some embodiments, L is –L^4–G–, wherein L^4 is an optionally substituted –$(CH_2)_2$–; G is as defined above and described herein; and G is connected to R^1. In some embodiments, L is –L^4–G–, wherein L^4 is –$(CH_2)_2$–; G is as defined above and described herein; and G is connected to R^1.

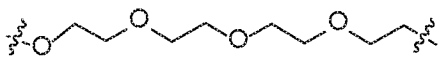
[00412] In some embodiments, L is , or  , wherein G is as defined above and described herein, and G is connected to R^1. In some embodiments, L is  , wherein G is as defined above and described herein, and G is connected to R^1. In some embodiments, L is  , wherein G is as defined above and described herein, and G is connected to R^1. In some embodiments, L is  , or , wherein the sulfur atom is connected to R^1. In some embodiments, L is  , or  , wherein the oxygen atom is connected to R^1.

[00413] In some embodiments, L is  ,  , or  , wherein G is as defined above and described herein.

[00414] In some embodiments, L is –S–R^{L3}– or –S–C(O)–R^{L3}–, wherein R^{L3} is an optionally substituted, linear or branched, C_1–C_9 alkylene, wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –$C(R')_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')-, –N(R')C(O)–, –N(R')C(O)O–, –OC(O)N(R')-, –S(O)–, –$S(O)_2$–, –$S(O)_2$N(R')–, –N(R')$S(O)_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–, wherein each of R' and –Cy– is independently as defined above and

described herein. In some embodiments, L is $-S-R^{L3}-$ or $-S-C(O)-R^{L3}-$, wherein R^{L3} is an optionally substituted C_1-C_6 alkylene. In some embodiments, L is $-S-R^{L3}-$ or $-S-C(O)-R^{L3}-$, wherein R^{L3} is an optionally substituted C_1-C_6 alkenylene. In some embodiments, L is $-S-R^{L3}-$ or $-S-C(O)-R^{L3}-$, wherein R^{L3} is an optionally substituted C_1-C_6 alkylene wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1-C_6 alkenylene, arylene, or heteroarylene. In some embodiments, In some embodiments, R^{L3} is an optionally substituted $-S-(C_1-C_6$ alkenylene$)-$, $-S-(C_1-C_6$ alkylene$)-$, $-S-(C_1-C_6$ alkylene$)-$arylene$-(C_1-C_6$ alkylene$)-$, $-S-CO-$arylene$-(C_1-C_6$ alkylene$)-$, or $-S-CO-(C_1-C_6$ alkylene$)-$arylene$-(C_1-C_6$ alkylene$)-$.

[00415] In some embodiments, L is  ,  ,  ,  ,  ,  ,  ,  , or  .

[00416] In some embodiments, L is . In some embodiments, L is . In some embodiments,  .

[00417] In some embodiments, the sulfur atom in the L embodiments described above and herein is connected to X. In some embodiments, the sulfur atom in the L embodiments described above and herein is connected to R^1.

[00418] In some embodiments, R^1 is halogen, R, or an optionally substituted C_1-C_{50} aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1-C_6 alkylene, C_1-C_6 alkenylene, $-C\equiv C-$, $-C(R')_2-$, $-Cy-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)-$, $-N(R')C(O)O-$, $-OC(O)N(R')-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-N(R')S(O)_2-$, $-SC(O)-$, $-C(O)S-$, $-OC(O)-$, or $-C(O)O-$, wherein each variable is independently as defined above and described herein. In some embodiments, R^1 is halogen, R, or an optionally substituted C_1-C_{10} aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1-C_6 alkylene, C_1-C_6 alkenylene, $-C\equiv C-$, $-C(R')_2-$, $-Cy-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)-$, $-N(R')C(O)O-$, $-OC(O)N(R')-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-N(R')S(O)_2-$, $-SC(O)-$, $-C(O)S-$, $-OC(O)-$, or $-C(O)O-$, wherein each variable is

independently as defined above and described herein.

[00419] In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is halogen. In some embodiments, R^1 is –F. In some embodiments, R^1 is –Cl. In some embodiments, R^1 is –Br. In some embodiments, R^1 is –I.

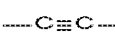
[00420] In some embodiments, R^1 is R wherein R is as defined above and described herein.

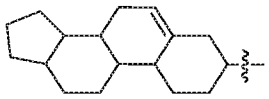
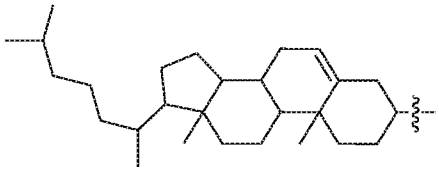
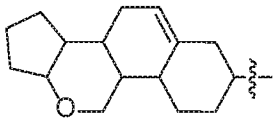
[00421] In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is an optionally substituted group selected from C_1–C_{50} aliphatic, phenyl, carbocyclyl, aryl, heteroaryl, or heterocyclyl.

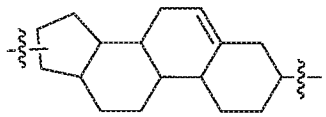
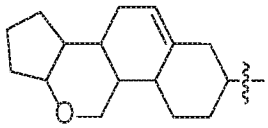
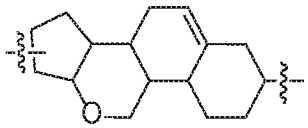
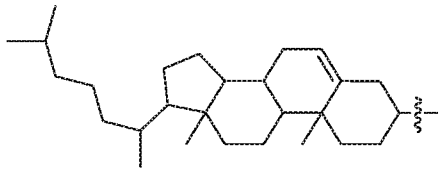
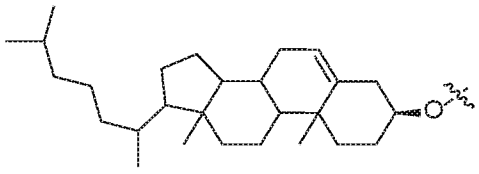
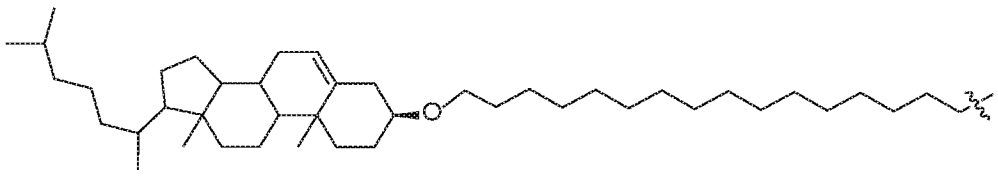
[00422] In some embodiments, R^1 is an optionally substituted C_1–C_{50} aliphatic. In some embodiments, R^1 is an optionally substituted C_1–C_{10} aliphatic. In some embodiments, R^1 is an optionally substituted C_1–C_6 aliphatic. In some embodiments, R^1 is an optionally substituted C_1–C_6 alkyl. In some embodiments, R^1 is optionally substituted, linear or branched hexyl. In some embodiments, R^1 is optionally substituted, linear or branched pentyl. In some embodiments, R^1 is optionally substituted, linear or branched butyl. In some embodiments, R^1 is optionally substituted, linear or branched propyl. In some embodiments, R^1 is optionally substituted ethyl. In some embodiments, R^1 is optionally substituted methyl.

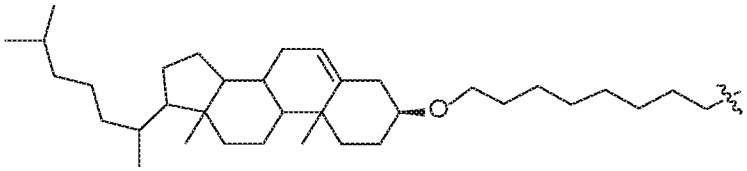
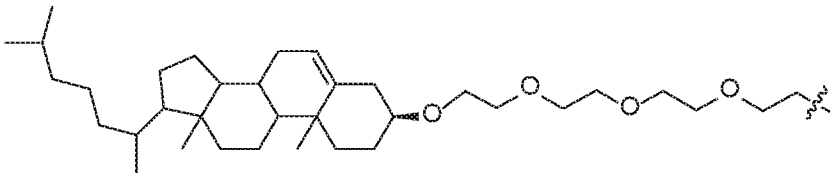
[00423] In some embodiments, R^1 is optionally substituted phenyl. In some embodiments, R^1 is substituted phenyl. In some embodiments, R^1 is phenyl.

[00424] In some embodiments, R^1 is optionally substituted carbocyclyl. In some embodiments, R^1 is optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^1 is optionally substituted monocyclic carbocyclyl. In some embodiments, R^1 is optionally substituted cycloheptyl. In some embodiments, R^1 is optionally substituted cyclohexyl. In some embodiments, R^1 is optionally substituted cyclopentyl. In some embodiments, R^1 is optionally substituted cyclobutyl. In some embodiments, R^1 is an optionally substituted cyclopropyl. In some embodiments, R^1 is optionally substituted bicyclic carbocyclyl.

[00425] In some embodiments, R^1 is an optionally substituted C_1–C_{50} polycyclic hydrocarbon. In some embodiments, R^1 is an optionally substituted C_1–C_{50} polycyclic hydrocarbon wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene,  , –$C(R')_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –$S(O)_2$–, –$S(O)_2$N(R′)–, –N(R′)$S(O)_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–, wherein each variable is independently as defined above and described herein. In some embodiments, R^1 is optionally substituted

 . In some embodiments, R^1 is  . In some embodiments, R^1 is optionally substituted  .

[00426] In some embodiments, R^1 is an optionally substituted C_1–C_{50} aliphatic comprising one or more optionally substituted polycyclic hydrocarbon moieties. In some embodiments, R^1 is an optionally substituted C_1–C_{50} aliphatic comprising one or more optionally substituted polycyclic hydrocarbon moieties, wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–, wherein each variable is independently as defined above and described herein. In some embodiments, R^1 is an optionally substituted C_1–C_{50} aliphatic comprising one or more optionally substituted ,  ,  , or  . In some embodiments, R^1 is  . In some embodiments, R^1 is  . In some embodiments, R^1 is  . In some

embodiments, R^1 is  . In some embodiments, R^1 is  .

[00427] In some embodiments, R^1 is an optionally substituted aryl. In some embodiments, R^1 is an optionally substituted bicyclic aryl ring.

[00428] In some embodiments, R^1 is an optionally substituted heteroaryl. In some embodiments, R^1 is an optionally substituted 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, sulfur, or oxygen. In some embodiments, R^1 is a substituted 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^1 is an unsubstituted 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, sulfur, or oxygen.

[00429] In some embodiments, R^1 is an optionally substituted 5 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur. In some embodiments, R^1 is an optionally substituted 6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00430] In some embodiments, R^1 is an optionally substituted 5-membered monocyclic heteroaryl ring having 1 heteroatom selected from nitrogen, oxygen, or sulfur. In some embodiments, R^1 is selected from pyrrolyl, furanyl, or thienyl.

[00431] In some embodiments, R^1 is an optionally substituted 5-membered heteroaryl ring having 2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, R^1 is an optionally substituted 5-membered heteroaryl ring having 1 nitrogen atom, and an additional heteroatom selected from sulfur or oxygen. Example R^1 groups include optionally substituted pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl or isoxazolyl.

[00432] In some embodiments, R^1 is a 6-membered heteroaryl ring having 1–3 nitrogen atoms. In other embodiments, R^1 is an optionally substituted 6-membered heteroaryl ring having 1–2 nitrogen atoms. In some embodiments, R^1 is an optionally substituted 6-membered heteroaryl ring having 2 nitrogen atoms. In certain embodiments, R^1 is an optionally substituted 6-membered heteroaryl ring having 1 nitrogen. Example R^1 groups include optionally substituted pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, or tetrazinyl.

[00433] In certain embodiments, R^1 is an optionally substituted 8–10 membered bicyclic heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^1 is an optionally substituted 5,6–fused heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, R^1 is an optionally substituted 5,6–fused heteroaryl ring having 1–2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, R^1 is an optionally substituted 5,6–fused heteroaryl ring having 1 heteroatom independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^1 is an optionally substituted indolyl. In some embodiments, R^1 is an optionally substituted azabicyclo[3.2.1]octanyl. In certain embodiments, R^1 is an optionally substituted 5,6–fused heteroaryl ring having 2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^1 is an optionally substituted azaindolyl. In some embodiments, R^1 is an optionally substituted benzimidazolyl. In some embodiments, R^1 is an optionally substituted benzothiazolyl. In some embodiments, R^1 is an optionally substituted benzoxazolyl. In some embodiments, R^1 is an optionally substituted indazolyl. In certain embodiments, R^1 is an optionally substituted 5,6–fused heteroaryl ring having 3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00434] In certain embodiments, R^1 is an optionally substituted 6,6–fused heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^1 is an optionally substituted 6,6–fused heteroaryl ring having 1–2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, R^1 is an optionally substituted 6,6–fused heteroaryl ring having 1 heteroatom independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^1 is an optionally substituted quinolinyl. In some embodiments, R^1 is an optionally substituted isoquinolinyl. According to one aspect, R^1 is an optionally substituted 6,6–fused heteroaryl ring having 2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^1 is a quinazoline or a quinoxaline.

[00435] In some embodiments, R^1 is an optionally substituted heterocyclyl. In some embodiments, R^1 is an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^1 is a substituted 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^1 is an unsubstituted 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00436] In some embodiments, R^1 is an optionally substituted heterocyclyl. In some embodiments, R^1 is an optionally substituted 6 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some

embodiments, R^1 is an optionally substituted 6 membered partially unsaturated heterocyclic ring having 2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^1 is an optionally substituted 6 membered partially unsaturated heterocyclic ring having 2 oxygen atoms.

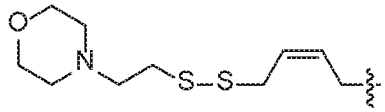
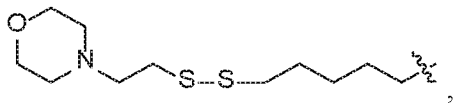
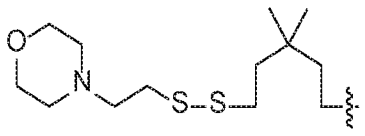
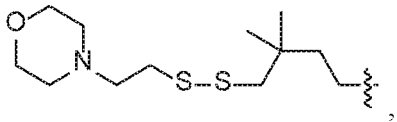
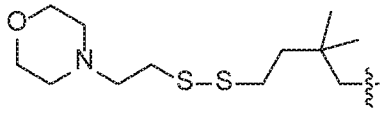
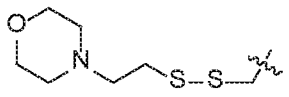
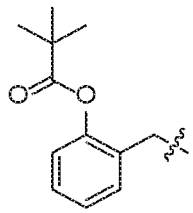
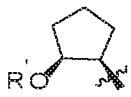
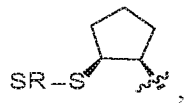
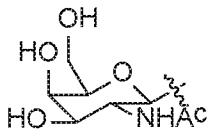
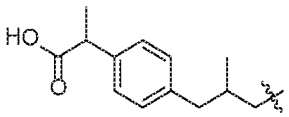
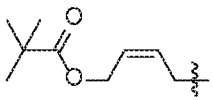
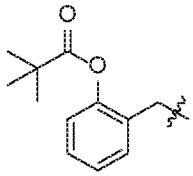
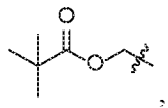
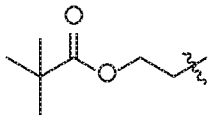
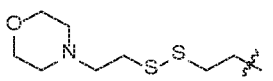
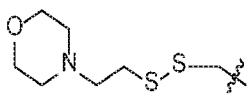
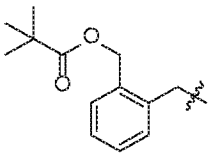
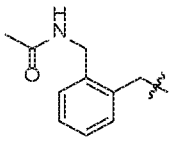
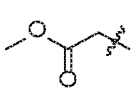
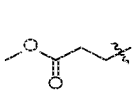
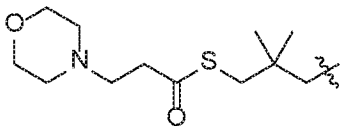
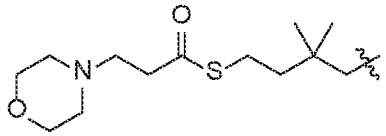
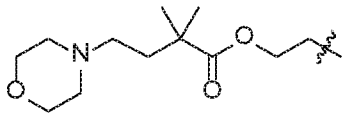
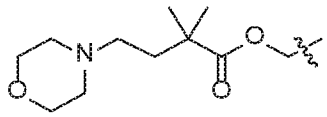
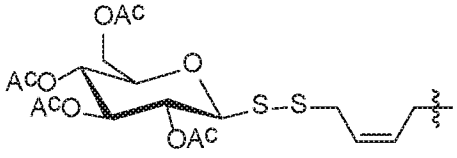
[00437] In certain embodiments, R^1 is a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, R^1 is oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepaneyl, aziridineyl, azetidineyl, pyrrolidinyl, piperidinyl, azepanyl, thiiranyl, thietanyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, thiepanyl, dioxolanyl, oxathiolanyl, oxazolidinyl, imidazolidinyl, thiazolidinyl, dithiolanyl, dioxanyl, morpholinyl, oxathianyl, piperazinyl, thiomorpholinyl, dithianyl, dioxepanyl, oxazepanyl, oxathiepanyl, dithiepanyl, diazepanyl, dihydrofuranonyl, tetrahydropyranonyl, oxepanonyl, pyrolidinonyl, piperidinonyl, azepanonyl, dihydrothiophenonyl, tetrahydrothiopyranonyl, thiepanonyl, oxazolidinonyl, oxazinanonyl, oxazepanonyl, dioxolanonyl, dioxanonyl, dioxepanonyl, oxathiolinonyl, oxathianonyl, oxathiepanonyl, thiazolidinonyl, thiazinanonyl, thiazepanonyl, imidazolidinonyl, tetrahydropyrimidinonyl, diazepanonyl, imidazolidinedionyl, oxazolidinedionyl, thiazolidinedionyl, dioxolanedionyl, oxathiolanedionyl, piperazinedionyl, morpholinedionyl, thiomorpholinedionyl, tetrahydropyranyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrothiophenyl, or tetrahydrothiopyranyl. In some embodiments, R^1 is an optionally substituted 5 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

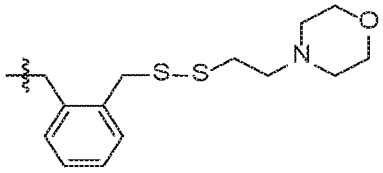
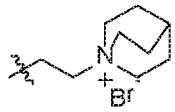
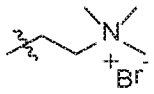
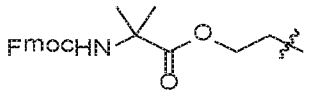
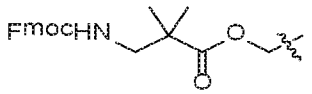
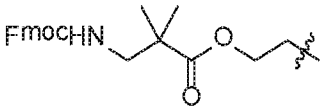
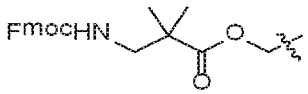
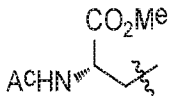
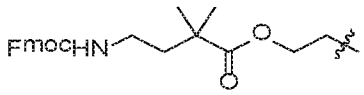
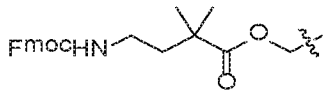
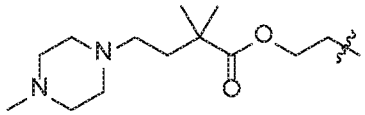
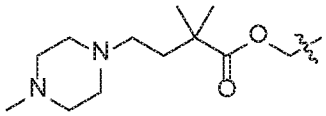
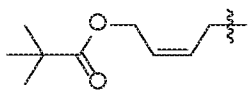
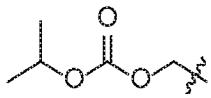
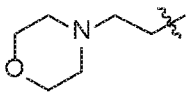
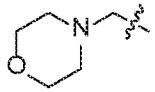
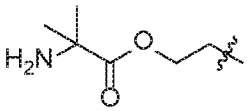
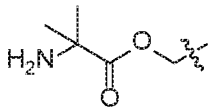
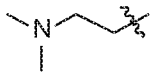
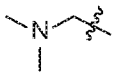
[00438] In certain embodiments, R^1 is an optionally substituted 5–6 membered partially unsaturated monocyclic ring having 1–2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, R^1 is an optionally substituted tetrahydropyridinyl, dihydrothiazolyl, dihydrooxazolyl, or oxazolinyl group.

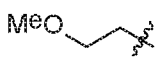
[00439] In some embodiments, R^1 is an optionally substituted 8-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^1 is an optionally substituted indolinyl. In some embodiments, R^1 is an optionally substituted isoindolinyl. In some embodiments, R^1 is an optionally substituted 1, 2, 3, 4-tetrahydroquinoline. In some embodiments, R^1 is an optionally substituted 1, 2, 3, 4-tetrahydroisoquinoline.

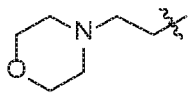
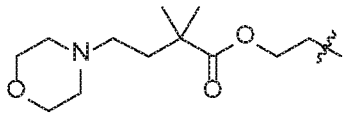
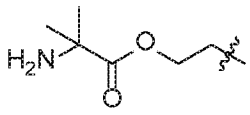
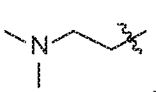
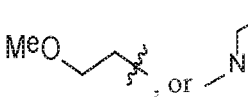
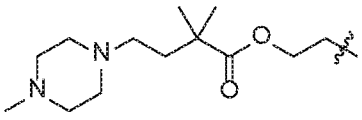
[00440] In some embodiments, R^1 is an optionally substituted C_1–C_{10} aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –$C(R')_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –$S(O)_2$–, –$S(O)_2$N(R′)–, –N(R′)$S(O)_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–, wherein each variable

is independently as defined above and described herein. In some embodiments, R^1 is an optionally substituted C_1–C_{10} aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally–Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –OC(O)–, or –C(O)O–, wherein each R' is independently as defined above and described herein. In some embodiments, R^1 is an optionally substituted C_1–C_{10} aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally–Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –OC(O)–, or –C(O)O–, wherein each R' is independently as defined above and described herein.

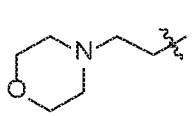
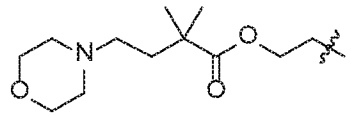
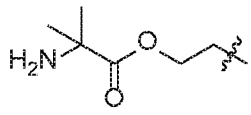
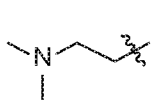
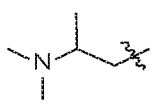
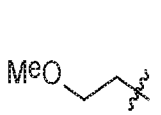
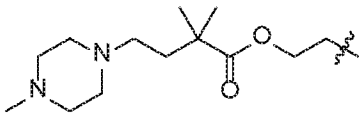
[00441] In some embodiments, R^1 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , (GalNAc),  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , 

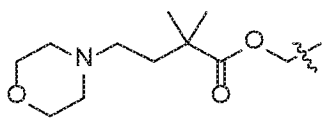
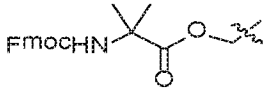
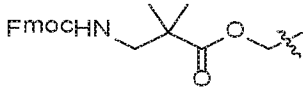


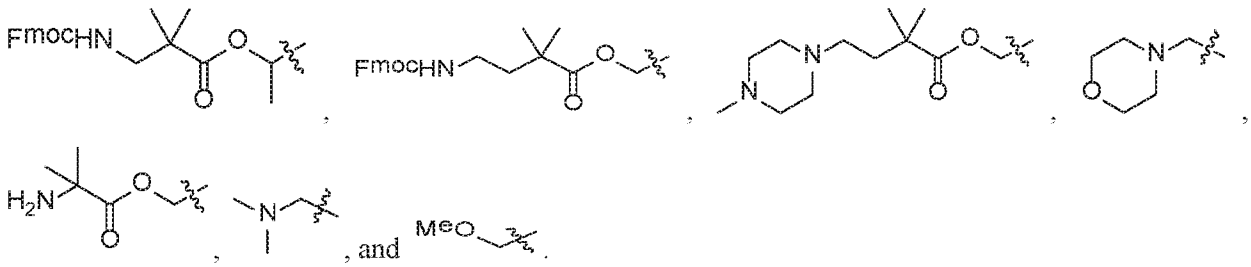
[00442] In some embodiments, R^1 is CH_3–,  ,  ,  ,  ,  , or  .

[00443] In some embodiments, R^1 comprises a terminal optionally substituted $-(CH_2)_2-$ moiety which is connected to L. Examples of such R^1 groups are depicted below:

 ,  ,  ,  ,  ,  , and  .

[00444] In some embodiments, R^1 comprises a terminal optionally substituted $-(CH_2)-$ moiety which is connected to L. Example such R^1 groups are depicted below:

 ,  ,  .

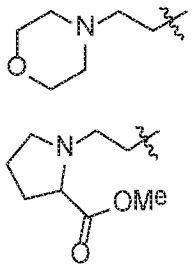
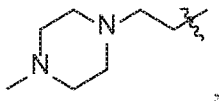
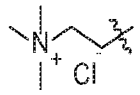
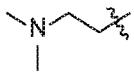


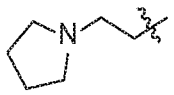
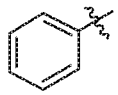
[00445] In some embodiments, R^1 is –S–R^{L2}, wherein R^{L2} is an optionally substituted C_1–C_9 aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')-, –N(R')C(O)–, –N(R')C(O)O–, –OC(O)N(R')-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –N(R')S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–, and each of R' and –Cy– is independently as defined above and described herein. In some embodiments, R^1 is –S–R^{L2}, wherein the sulfur atom is connected with the sulfur atom in L group.

[00446] In some embodiments, R^1 is –C(O)–R^{L2}, wherein R^{L2} is an optionally substituted C_1–C_9 aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')-, –N(R')C(O)–, –N(R')C(O)O–, –OC(O)N(R')-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –N(R')S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–, and each of R' and –Cy– is independently as defined above and described herein. In some embodiments, R^1 is –C(O)–R^{L2}, wherein the carbonyl group is connected with G in L group. In some embodiments, R^1 is –C(O)–R^{L2}, wherein the carbonyl group is connected with the sulfur atom in L group.

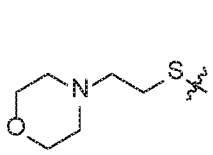
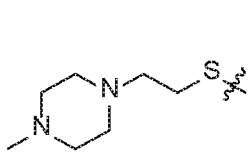
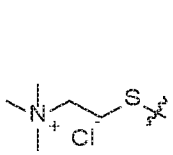
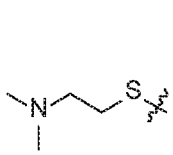
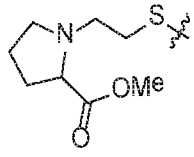
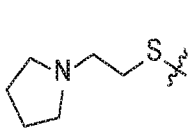
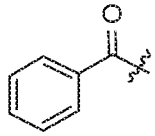
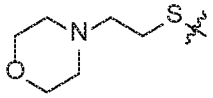
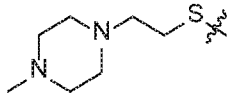
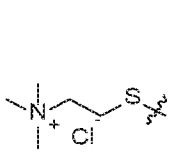
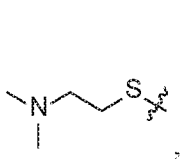
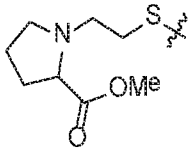
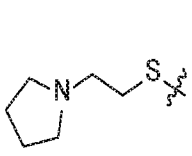
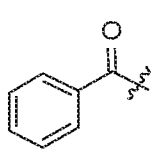
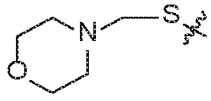
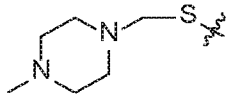
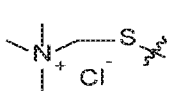
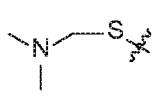
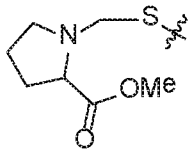
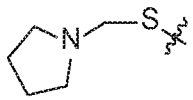
[00447] In some embodiments, R^{L2} is optionally substituted C_1–C_9 aliphatic. In some embodiments, R^{L2} is optionally substituted C_1–C_9 alkyl. In some embodiments, R^{L2} is optionally substituted C_1–C_9 alkenyl. In some embodiments, R^{L2} is optionally substituted C_1–C_9 alkynyl. In some embodiments, R^{L2} is an optionally substituted C_1–C_9 aliphatic wherein one or more methylene units are optionally and independently replaced by –Cy– or –C(O)–. In some embodiments, R^{L2} is an optionally substituted C_1–C_9 aliphatic wherein one or more methylene units are optionally and independently replaced by –Cy–. In some embodiments, R^{L2} is an optionally substituted C_1–C_9 aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted heterocycylene. In some embodiments, R^{L2} is an optionally substituted C_1–C_9 aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted arylene. In some embodiments, R^{L2} is an optionally substituted C_1–C_9 aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted heteroarylene. In some embodiments, R^{L2} is an optionally substituted C_1–C_9 aliphatic wherein one or more methylene units are

optionally and independently replaced by an optionally substituted C_3-C_{10} carbocyclylene. In some embodiments, R^{L2} is an optionally substituted C_1–C_9 aliphatic wherein two methylene units are optionally and independently replaced by –Cy– or –C(O)–. In some embodiments, R^{L2} is an optionally substituted C_1–C_9 aliphatic wherein two methylene units are optionally and independently replaced by –Cy– or –C(O)–. Example R^{L2} groups are depicted below:

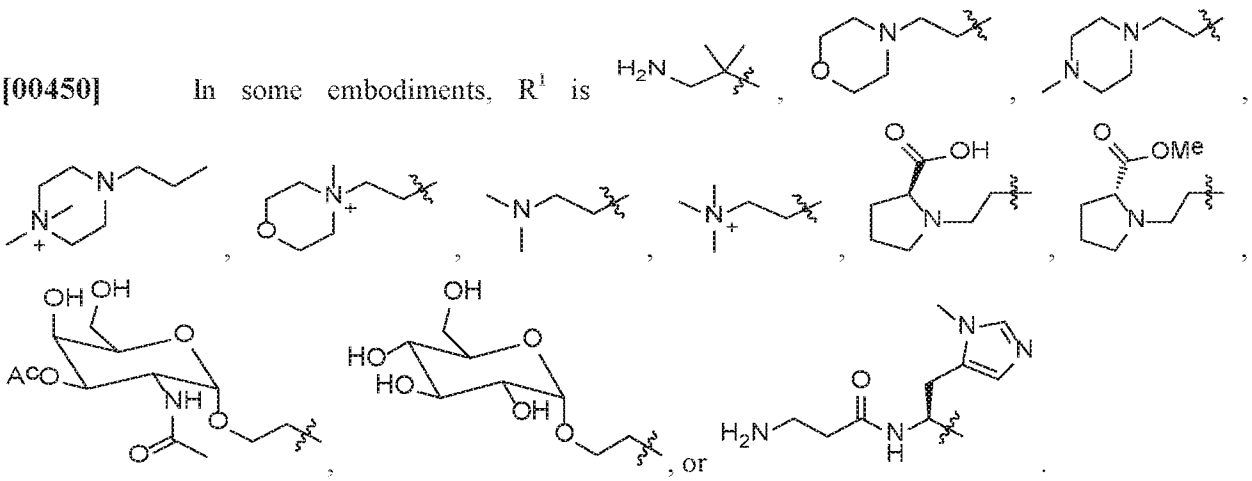






and 

[00448] In some embodiments, R^1 is hydrogen, or an optionally substituted group selected from








, –S–(C_1–C_{10} aliphatic), C_1–C_{10} aliphatic, aryl, C_1–C_6 heteroalkyl, heteroaryl and heterocyclyl. In some embodiments, R^1 is 






, or –S–(C_1–C_{10} aliphatic). In some embodiments, R^1 is 




, or 
.

[00449] In some embodiments, R^1 is an optionally substituted group selected from –S–(C_1-C_6 aliphatic), C_1-C_{10} aliphatic, C_1-C_6 heteroaliphatic, aryl, heterocyclyl and heteroaryl.

[00450] In some embodiments, R^1 is  , or

[00451] In some embodiments, the sulfur atom in the R^1 embodiments described above and herein is connected with the sulfur atom, G, E, or –C(O)– moiety in the L embodiments described above and herein. In some embodiments, the –C(O)– moiety in the R^1 embodiments described above and herein is connected with the sulfur atom, G, E, or –C(O)– moiety in the L embodiments described above and herein.

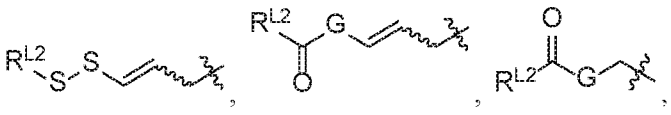
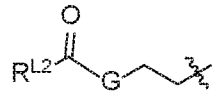
[00452] In some embodiments, –L–R^1 is any combination of the L embodiments and R^1 embodiments described above and herein.

[00453] In some embodiments, –L–R^1 is –L^3–G–R^1 wherein each variable is independently as defined above and described herein.

[00454] In some embodiments, –L–R^1 is –L^4–G–R^1 wherein each variable is independently as defined above and described herein.

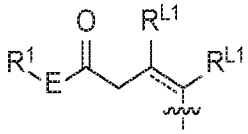
[00455] In some embodiments, –L–R^1 is –L^3–G–S–R^{L2}, wherein each variable is independently as defined above and described herein.

[00456] In some embodiments, –L–R^1 is –L^3–G–C(O)–R^{L2}, wherein each variable is independently as defined above and described herein.

[00457] In some embodiments, –L–R^1 is  , or  , wherein R^{L2} is an optionally substituted C_1–C_9 aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, , –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')-, –N(R')C(O)–, –N(R')C(O)O–, –OC(O)N(R')-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –N(R')S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–, and each G is independently as defined above and described herein.

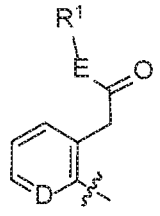
[00458] In some embodiments, –L–R^1 is –R^{L3}–S–S–R^{L2}, wherein each variable is independently as defined above and described herein. In some embodiments, –L–R^1 is –R^{L3}–C(O)–S–S–R^{L2}, wherein each variable is independently as defined above and described herein.

[00459] In some embodiments, –L–R^1 has the structure of:



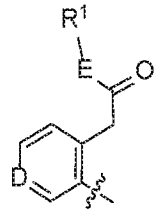
wherein each variable is independently as defined above and described herein.

[00460] In some embodiments, –L–R^1 has the structure of:



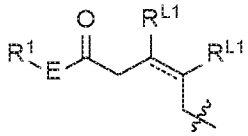
wherein each variable is independently as defined above and described herein.

[00461] In some embodiments, –L–R^1 has the structure of:



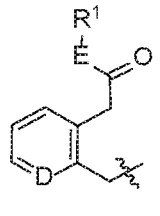
wherein each variable is independently as defined above and described herein.

[00462] In some embodiments, –L–R^1 has the structure of:



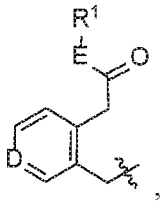
wherein each variable is independently as defined above and described herein.

[00463] In some embodiments, –L–R^1 has the structure of:



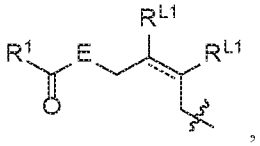
wherein each variable is independently as defined above and described herein.

[00464] In some embodiments, –L–R^1 has the structure of:



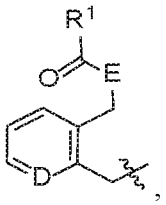
wherein each variable is independently as defined above and described herein.

[00465] In some embodiments, –L–R^1 has the structure of:



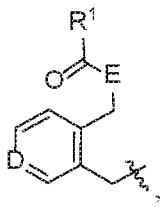
wherein each variable is independently as defined above and described herein.

[00466] In some embodiments, –L–R^1 has the structure of:



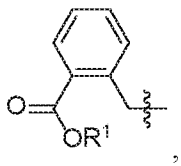
wherein each variable is independently as defined above and described herein.

[00467] In some embodiments, –L–R^1 has the structure of:



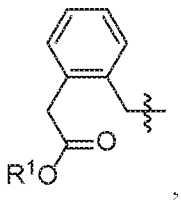
wherein each variable is independently as defined above and described herein.

[00468] In some embodiments, –L–R^1 has the structure of:



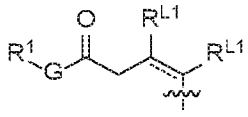
wherein each variable is independently as defined above and described herein.

[00469] In some embodiments, –L–R^1 has the structure of:



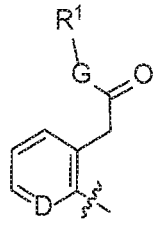
wherein each variable is independently as defined above and described herein.

[00470] In some embodiments, –L–R^1 has the structure of:



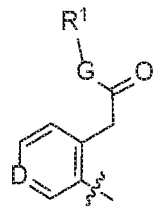
wherein each variable is independently as defined above and described herein.

[00471] In some embodiments, –L–R^1 has the structure of:



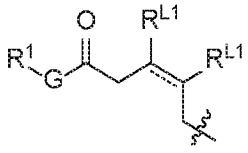
wherein each variable is independently as defined above and described herein.

[00472] In some embodiments, –L–R^1 has the structure of:



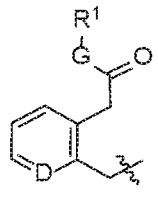
wherein each variable is independently as defined above and described herein.

[00473] In some embodiments, –L–R^1 has the structure of:



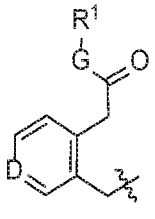
wherein each variable is independently as defined above and described herein.

[00474] In some embodiments, –L–R^1 has the structure of:



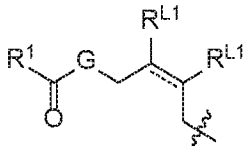
wherein each variable is independently as defined above and described herein.

[00475] In some embodiments, –L–R^1 has the structure of:



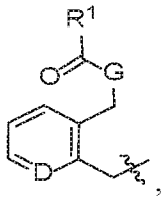
wherein each variable is independently as defined above and described herein.

[00476] In some embodiments, –L–R^1 has the structure of:



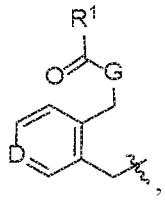
wherein each variable is independently as defined above and described herein.

[00477] In some embodiments, –L–R^1 has the structure of:



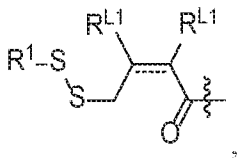
wherein each variable is independently as defined above and described herein.

[00478] In some embodiments, –L–R^1 has the structure of:



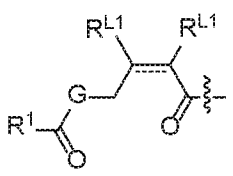
wherein each variable is independently as defined above and described herein.

[00479] In some embodiments, –L–R^1 has the structure of:



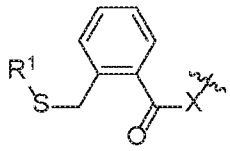
wherein each variable is independently as defined above and described herein.

[00480] In some embodiments, L has the structure of:



wherein each variable is independently as defined above and described herein.

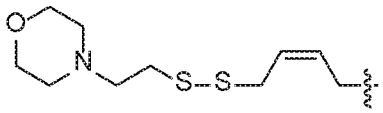
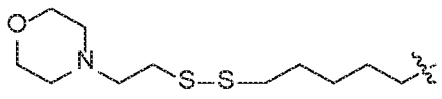
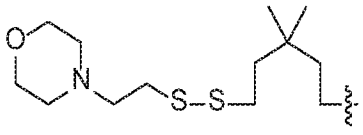
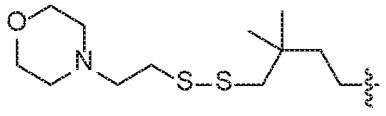
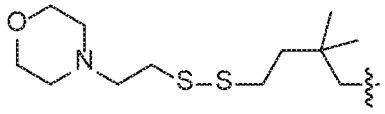
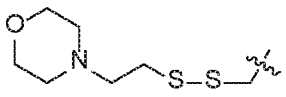
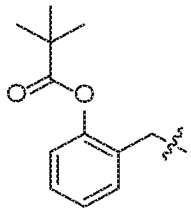
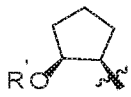
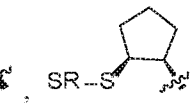
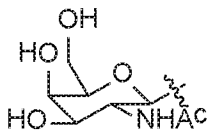
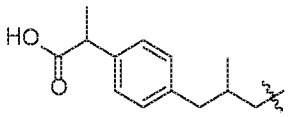
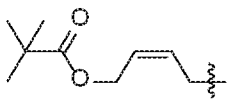
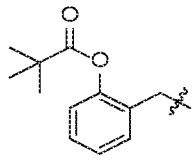
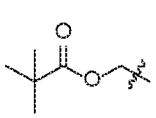
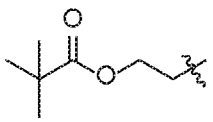
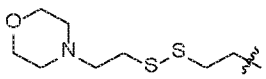
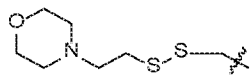
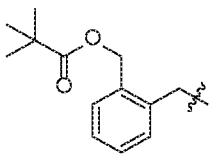
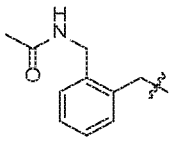
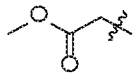
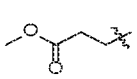
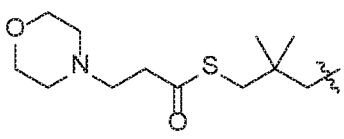
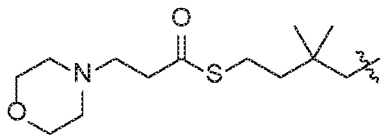
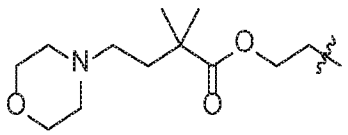
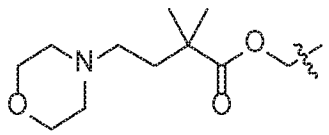
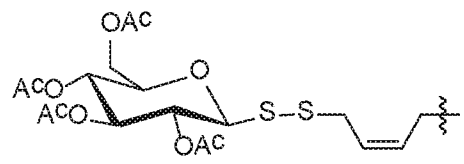
[00481] In some embodiments, –X–L–R^1 has the structure of:

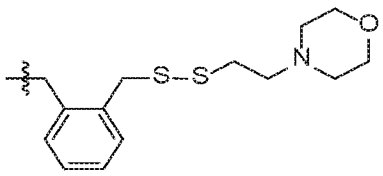
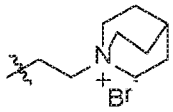
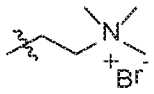
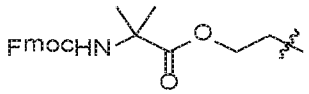
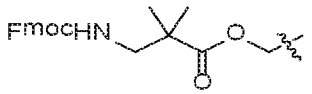
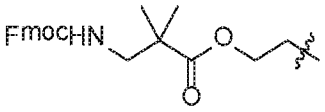
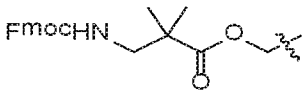
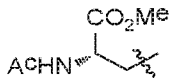
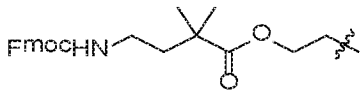
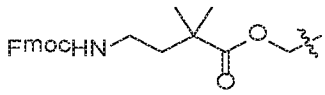
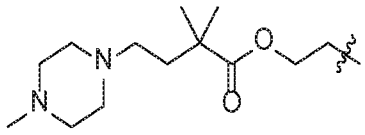
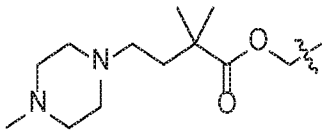
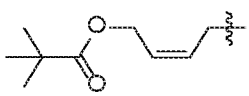
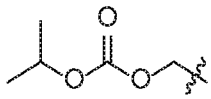


wherein:

the phenyl ring is optionally substituted, and

each of R^1 and X is independently as defined above and described herein.

[00482] In some embodiments, –L–R^1 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  (GalNAc),  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , 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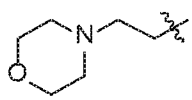
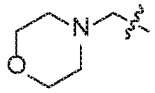
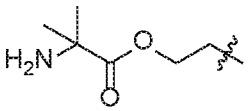
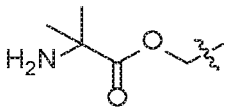
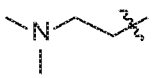
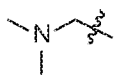
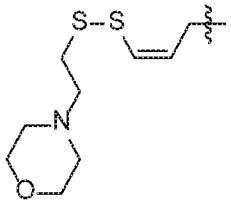
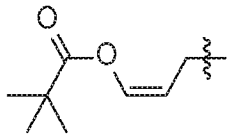







, or

.

[00483] In some embodiments, –L–R^1 is: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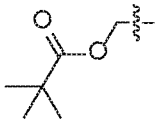
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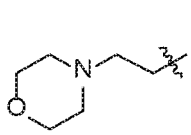
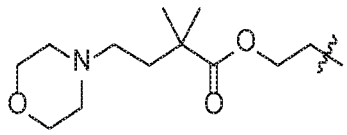
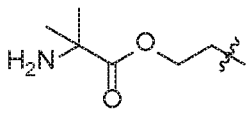
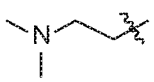
[00484] In some embodiments, –L–R^1 is CH_3–,





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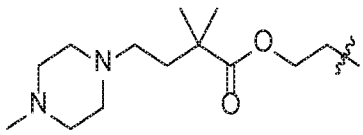
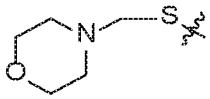
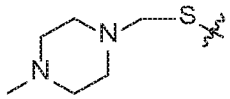
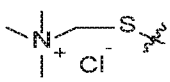
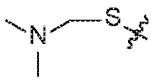

. In some embodiments, –L–R^1 is




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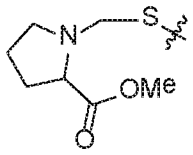
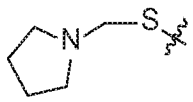
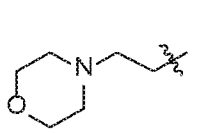
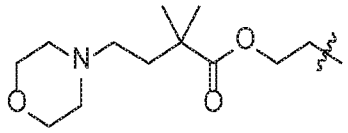
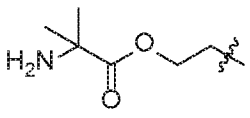
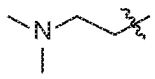
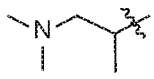
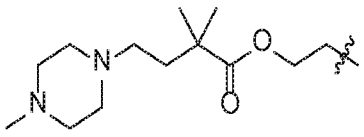
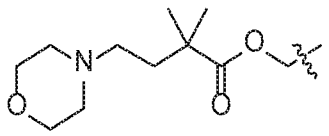
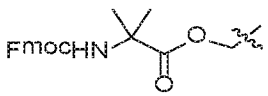
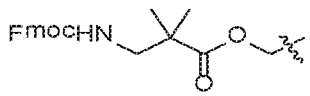
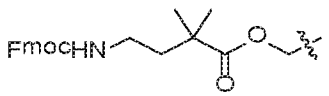
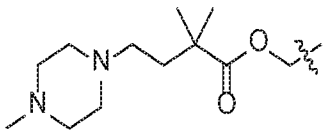
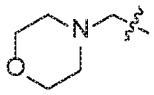
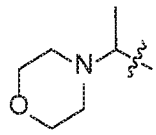
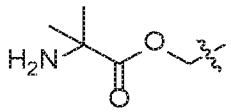
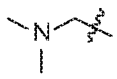



[00485] In some embodiments, –L–R^1 comprises a terminal optionally substituted –$(CH_2)_2$– moiety which is connected to X. In some embodiments, –L–R^1 comprises a terminal –$(CH_2)_2$– moiety which is connected to X. Examples of such –L–R^1 moieties are depicted below:

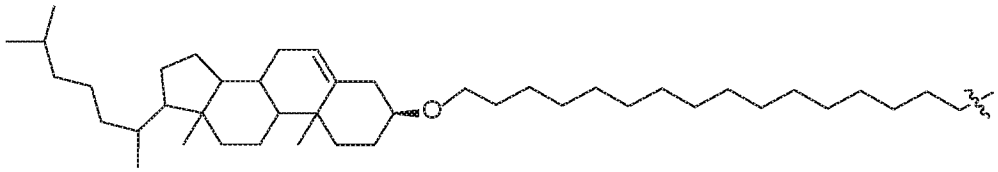
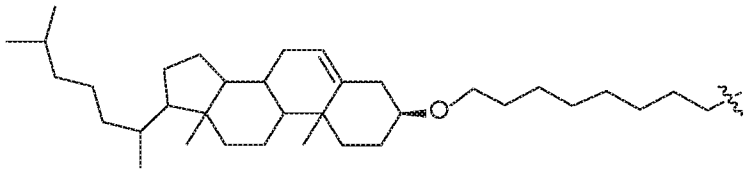








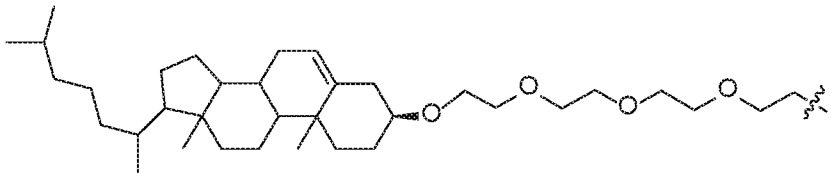
[00486] In some embodiments, –L–R^1 comprises a terminal optionally substituted –(CH_2)– moiety which is connected to X. In some embodiments, –L–R^1 comprises a terminal –(CH_2)– moiety which is connected to X. Examples of such –L–R^1 moieties are depicted below:

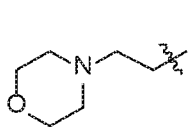
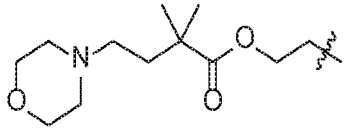
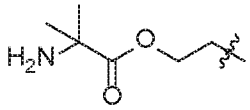
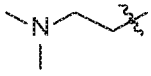
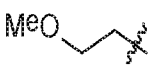
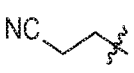
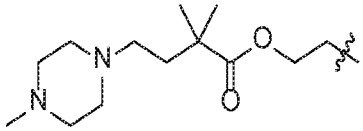










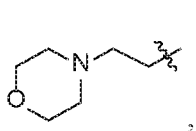
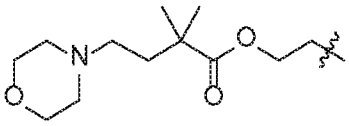
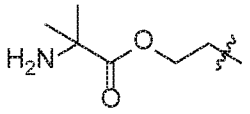
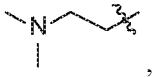
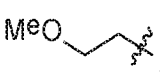
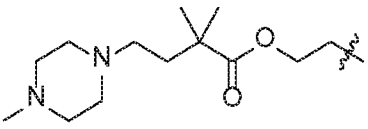
[00487] In some embodiments, –L–R^1 is

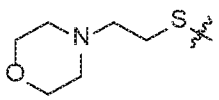
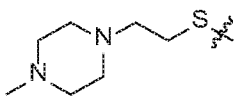
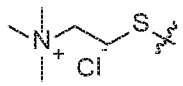
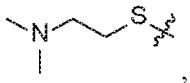
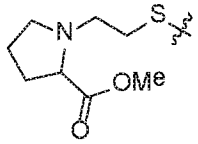
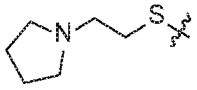
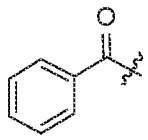



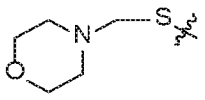
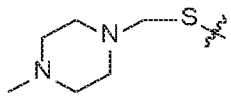
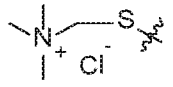
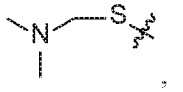
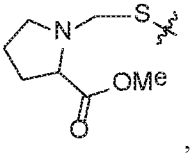
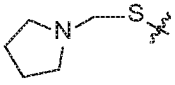
, or

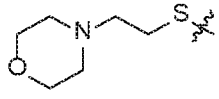


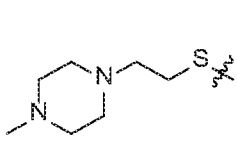
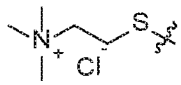
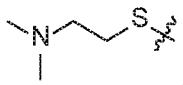
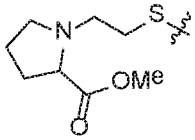
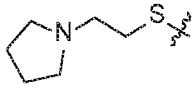
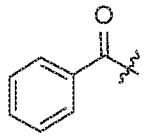
[00488] In some embodiments, –L–R^1 is CH_3–,  ,  ,  ,  ,  ,  ,or  ; and X is –S–.

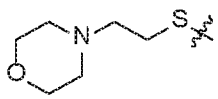
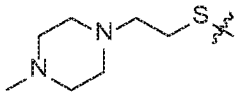
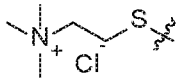
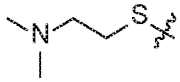
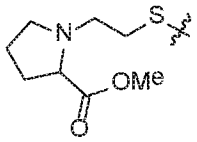
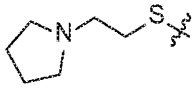
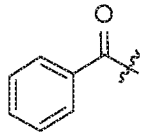
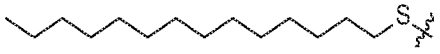
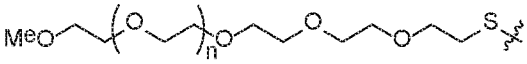
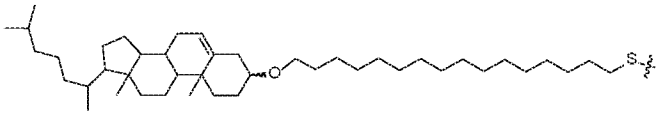
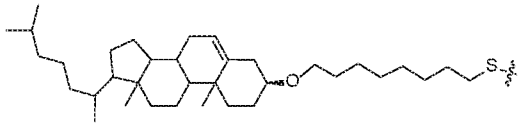
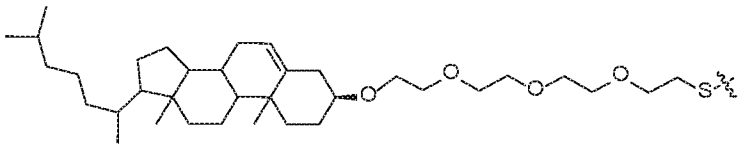
[00489] In some embodiments, –L–R^1 is CH_3–,  ,  ,  ,  ,  , or  , X is –S–, W is O, Y is –O–, and Z is –O–.

[00490] In some embodiments, R^1 is  ,  ,  ,  ,  ,  ,  , or –S–(C_1–C_{10} aliphatic).

[00491] In some embodiments, R^1 is  ,  ,  ,  ,  , or  .

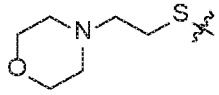
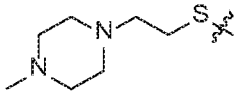
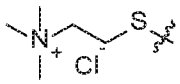
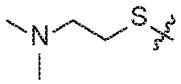
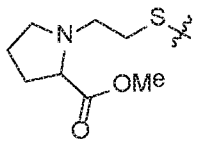
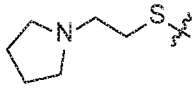
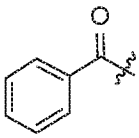
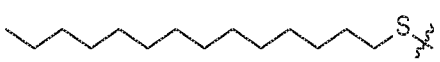
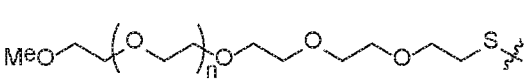
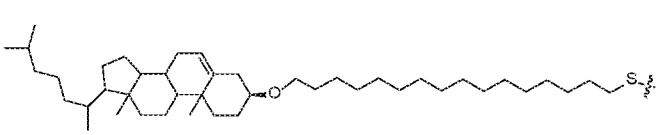
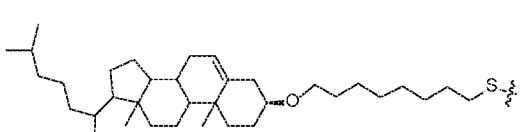
[00492] In some embodiments, X is –O– or –S–, and R^1 is  ,

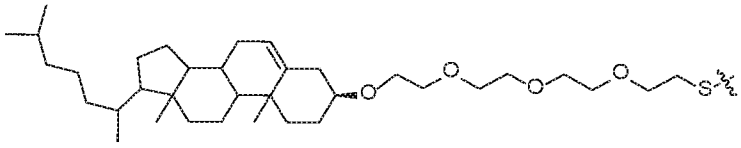






, or –S–(C_1–C_{10} aliphatic).

[00493] In some embodiments, X is –O– or –S–, and R^1 is  ,











, –S–(C_1–C_{10} aliphatic) or –S–(C_1–C_{50} aliphatic).

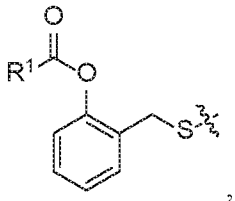
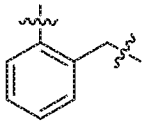
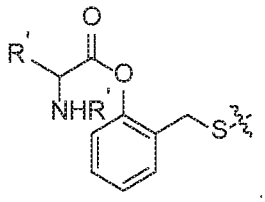
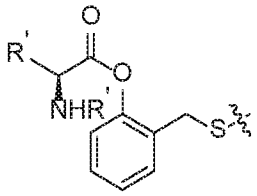
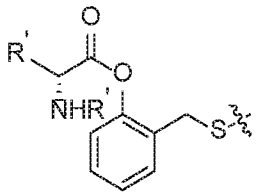
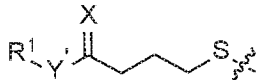
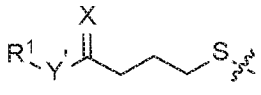
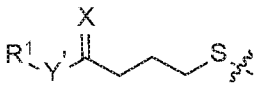
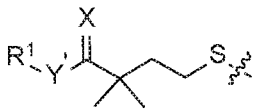
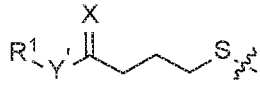
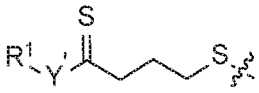
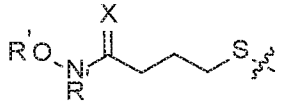
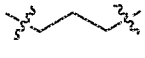
[00494] In some embodiments, L is a covalent bond and –L–R^1 is R^1.

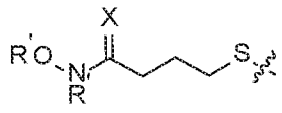
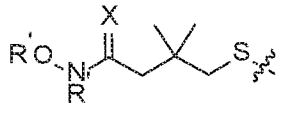
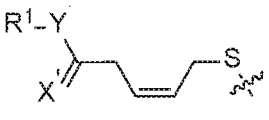
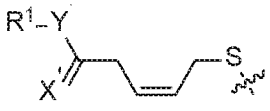
[00495] In some embodiments, –L–R^1 is not hydrogen.

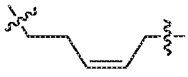
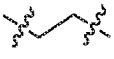
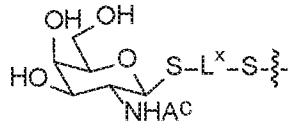
[00496] In some embodiments, –X–L–R^1 is R^1 is  ,










,



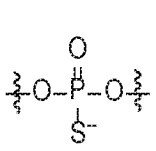
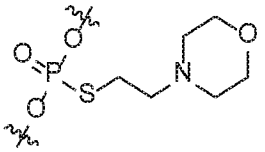
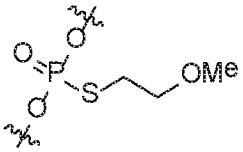
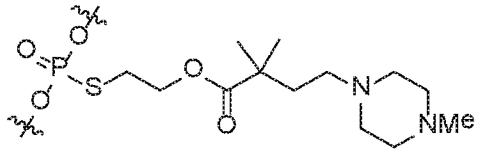
, –S–(C_1–C_{10} aliphatic) or –S–(C_1–C_{50} aliphatic).

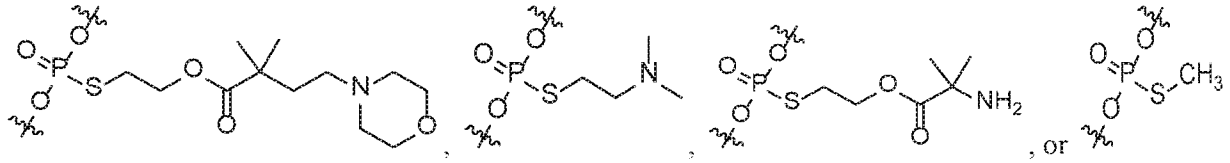
[00497] In some embodiments, –X–L–R^1 has the structure of  , wherein the  moiety is optionally substituted. In some embodiments, –X–L–R^1 is  . In some embodiments, –X–L–R^1 is  . In some embodiments, –X–L–R^1 is  . In some embodiments, –X–L–R^1 has the structure of  , wherein X' is O or S, Y' is –O–, –S– or –NR'–, and the moiety is optionally substituted. In some embodiments, Y' is –O–, –S– or –NH–. In some embodiments,  is . In some embodiments,  is  . In some embodiments,  is  . In some embodiments, –X–L–R^1 has the structure of  , wherein X' is O or S, and the  moiety is optionally

substituted. In some embodiments,  is  . In some embodiments, –X–L–R^1 is  , wherein the is optionally substituted. In some embodiments, –X–L–R^1 is , wherein the is substituted. In some embodiments, –X–L–R^1 is  , wherein the is unsubstituted.

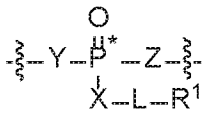
[00498] In some embodiments, –X–L–R^1 is R^1–C(O)–S–L^x–S–, wherein L^x is an optionally substituted group selected from , , , , and  . In some embodiments, L^x is ,  , , , and . In some embodiments, –X–L–R^1 is $(CH_3)_3$C–S–S–L^x–S–. In some embodiments, –X–L–R^1 is R^1–C(=X')–Y'–C(R)$_2$–S–L^x–S–. In some embodiments, –X–L–R^1 is R–C(=X')–Y'–CH_2–S–L^x–S–. In some embodiments, –X–L–R^1 is  .

[00499] As will be appreciated by a person skilled in the art, many of the –X–L–R^1 groups described herein are cleavable and can be converted to –X^- after administration to a subject. In some embodiments, –X–L–R^1 is cleavable. In some embodiments, –X–L–R^1 is –S–L–R^1, and is converted to –S^- after administration to a subject. In some embodiments, the conversion is promoted by an enzyme of a subject. As appreciated by a person skilled in the art, methods of determining whether the –S–L–R^1 group is converted to –S^- after administration is widely known and practiced in the art, including those used for studying drug metabolism and pharmacokinetics.

[00500] In some embodiments, the internucleotidic linkage having the structure of formula **I** is  ,  ,  ,  ,



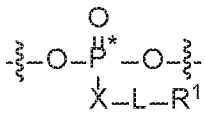
[00501] In some embodiments, the internucleotidic linkage of formula I has the structure of formula I-a:



(I-a)

wherein each variable is independently as defined above and described herein.

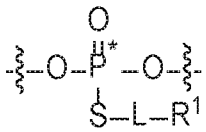
[00502] In some embodiments, the internucleotidic linkage of formula I has the structure of formula I-b:



(I-b)

wherein each variable is independently as defined above and described herein.

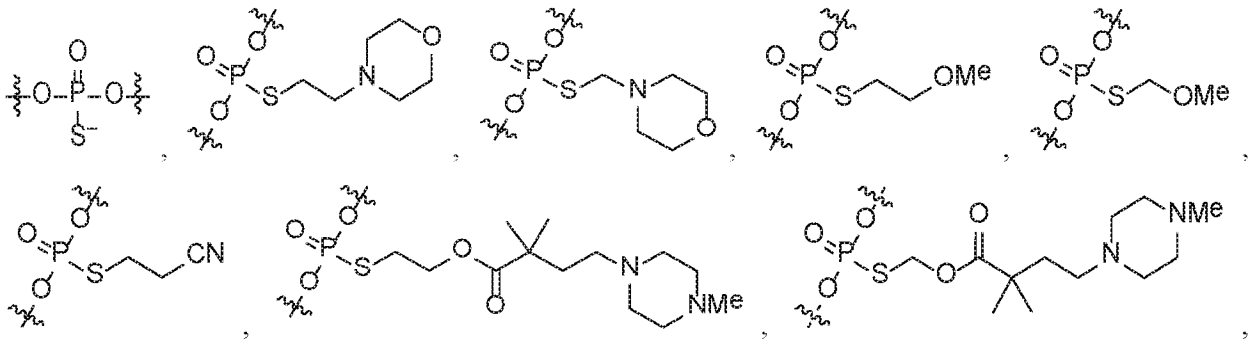
[00503] In some embodiments, the internucleotidic linkage of formula I is an phosphorothioate triester linkage having the structure of formula I-c:

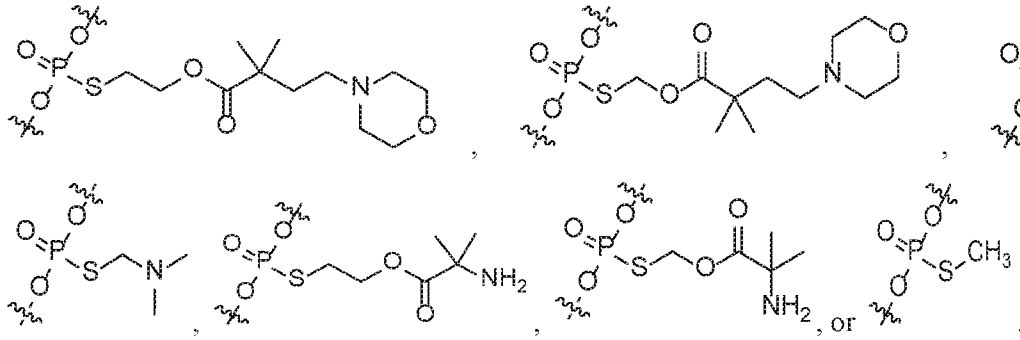


(I-c)

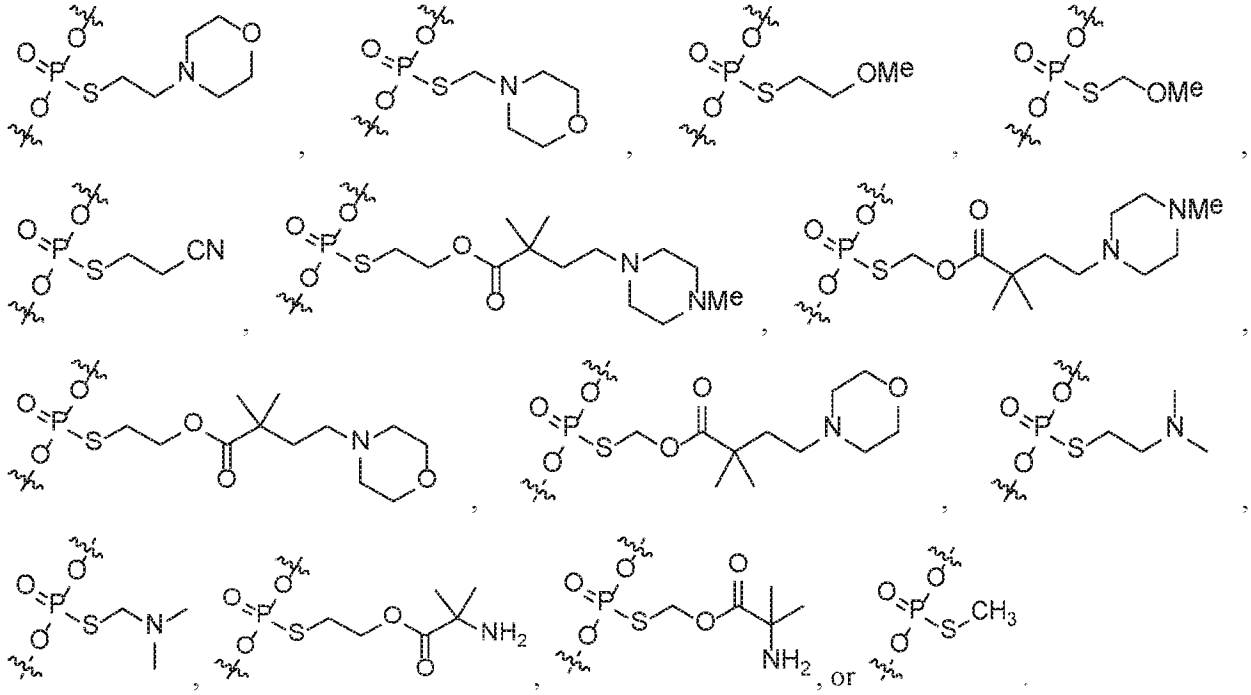
wherein R^1 is not –H when L is a covalent bond.

[00504] In some embodiments, the internucleotidic linkage having the structure of formula I is





[00505] In some embodiments, the internucleotidic linkage having the structure of formula **I-c** is



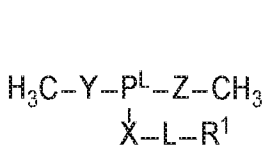
[00506] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising one or more natural phosphate linkages, and one or more modified internucleotidic linkages having the formula of **I-a**, **I-b**, or **I-c**.

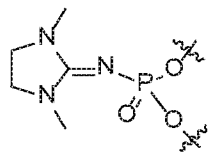
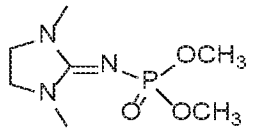
[00507] In some embodiments, a modified internucleotidic linkage has the structure of **I**. In some embodiments, a modified internucleotidic linkage has the structure of **I-a**. In some embodiments, a modified internucleotidic linkage has the structure of **I-b**. In some embodiments, a modified internucleotidic linkage has the structure of **I-c**.

[00508] In some embodiments, a modified internucleotidic linkage is phosphorothioate internucleotidic linkage. Examples of internucleotidic linkages having the structure of formula **I** that can be utilized in accordance with the present disclosure include those described in US 9394333, US 9744183, US 9605019, US 20130178612, US 20150211006, US 9598458, US 20170037399, WO 2017/015555, WO 2017/062862, the internucleotidic linkages of each of which is incorporated herein by reference.

[00509] Non-limiting examples of internucleotidic linkages that can be utilized in accordance with the present disclosure also include those described in the art, including, but not limited to, those described in any of: Gryaznov, S.; Chen, J.-K. J. Am. Chem. Soc. 1994, 116, 3143, Jones et al. J. Org. Chem. 1993, 58, 2983, Koshkin et al. 1998 Tetrahedron 54: 3607-3630, Lauritsen et al. 2002 Chem. Comm. 5: 530-531, Lauritsen et al. 2003 Bioo. Med. Chem. Lett. 13: 253-256, Mesmaeker et al. Angew. Chem., Int. Ed. Engl. 1994, 33, 226, Petersen et al. 2003 TRENDS Biotech. 21: 74-81, Schultz et al. 1996 Nucleic Acids Res. 24: 2966, Ts'o et al. Ann. N. Y. Acad. Sci. 1988, 507, 220, and Vasseur et al. J. Am. Chem. Soc. 1992, 114, 4006.

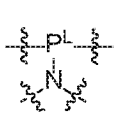
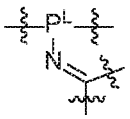
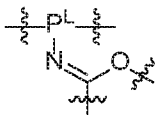
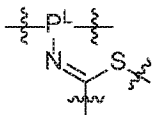
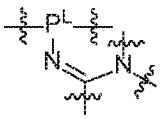
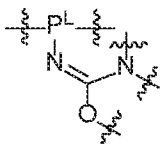
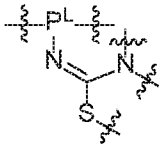
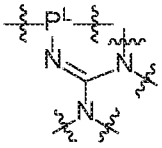
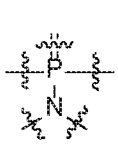
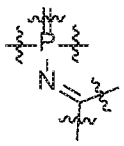
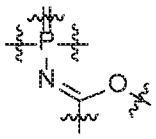
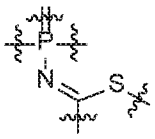
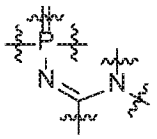
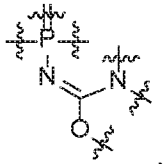
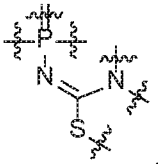
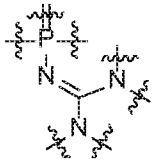
[00510] In some embodiments, oligonucleotides comprise one or more, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more non-negatively charged internucleotidic linkages. In some embodiments, a non-negatively charged internucleotidic linkage is not negatively charged in that at a given pH in an aqueous solution less than 50%, 40%, 40%, 30%, 20%, 10%, 5%, or 1% of the internucleotidic linkage exists in a negatively charged salt form. In some embodiments, a pH is about pH 7.4. In some embodiments, a pH is about 4-9. In some embodiments, the percentage is less than 10%. In some embodiments, the percentage is less than 5%. In some embodiments, the percentage is less than 1%. In some embodiments, an internucleotidic linkage is a non-negatively charged internucleotidic linkage in that the neutral form of the internucleotidic linkage has no pKa that is no more than about 1, 2, 3, 4, 5, 6, or 7 in water. In some embodiments, no pKa is 7 or less. In some embodiments, no pKa is 6 or less. In some embodiments, no pKa is 5 or less. In some embodiments, no pKa is 4 or less. In some embodiments, no pKa is 3 or less. In some embodiments, no pKa is 2 or less. In some embodiments, no pKa is 1 or less. In some embodiments, pKa of the neutral form of an internucleotidic linkage can be represented by pKa of the neutral form of a compound having the structure of CH_3–the internucleotidic linkage–CH_3. For example, pKa of the neutral form of an internucleotidic linkage having the structure of formula I may be represented by the pKa of the neutral form of a compound having the structure of



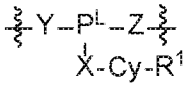
, pKa of  can be represented by pKa  . In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a positively-charged internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage comprises a guanidine moiety. In some embodiments, a non-negatively charged internucleotidic linkage comprises a heteroaryl base moiety. In some embodiments, a non-negatively charged internucleotidic linkage comprises a triazole moiety. In some embodiments, a non-negatively charged internucleotidic

linkage comprises an alkynyl moiety.

[00511] In some embodiments, a non-negatively charged internucleotidic linkage, e.g., a neutral internucleotidic linkage, comprises $-P^L(-N=)-$, wherein P^L is as described in the present disclosure. In some embodiments, a non-negatively charged internucleotidic linkage, e.g., a neutral internucleotidic linkage, comprises $-P(-N=)-$. In some embodiments, a non-negatively charged internucleotidic linkage, e.g., a neutral internucleotidic linkage, comprises $-P(=)(-N=)-$. In some embodiments, a non-negatively charged internucleotidic linkage, e.g., a neutral internucleotidic linkage, comprises $-P(=O)(-N=)-$. In some embodiments, a non-negatively charged internucleotidic linkage, e.g., a neutral internucleotidic linkage, comprises $-P(=S)(-N=)-$.

[00512] In some embodiments, a non-negatively charged internucleotidic linkage, e.g., a neutral internucleotidic linkage, comprises  ,  ,  ,  ,  ,  ,  , or  , wherein P^L is as described in the present disclosure. For example, in some embodiments, P^L is P; in some embodiments, P^L is P(O); in some embodiments, P^L is P(S); etc. In some embodiments, a non-negatively charged internucleotidic linkage, e.g., a neutral internucleotidic linkage, comprises  ,  ,  ,  ,  ,  ,  , or  .

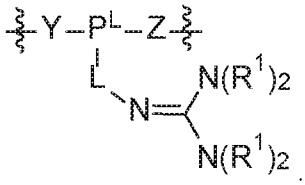
[00513] In some embodiments, a non-negatively charged internucleotidic linkage has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof (not negatively charged). In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, has the structure of formula **I-n-1** or a salt form thereof:



I-n-1

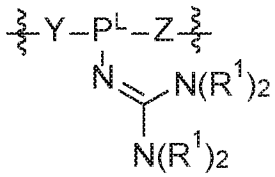
[00514] In some embodiments, X is a covalent bond and $-X-Cy-R^1$ is $-Cy-R^1$. In some embodiments, $-Cy-$ is an optionally substituted bivalent group selected from a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms. In some embodiments, $-Cy-$ is an optionally substituted bivalent 5-20 membered heteroaryl ring having 1-10 heteroatoms. In some embodiments, $-Cy-R^1$ is optionally substituted 5-20 membered heteroaryl ring having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, $-Cy-R^1$ is optionally substituted 5-membered heteroaryl ring having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, $-Cy-R^1$ is optionally substituted 6-membered heteroaryl ring having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, $-Cy-R^1$ is optionally substituted triazolyl.

[00515] In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, has the structure of formula **I-n-2** or a salt form thereof:



I-n-2

[00516] In some embodiments, R^1 is R'. In some embodiments, L is a covalent bond. In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, has the structure of formula **I-n-3** or a salt form thereof:

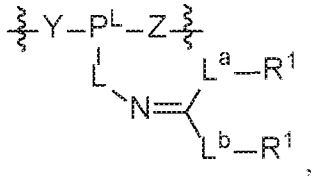


I-n-3

[00517] In some embodiments, two R' on different nitrogen atoms are taken together to form a ring as described. In some embodiments, a formed ring is 5-membered. In some embodiments, a formed ring is 6-membered. In some embodiments, a formed ring is substituted. In some embodiments, the two R' group that are not taken together to form a ring are each independently R. In some embodiments, the two R' group that are not taken together to form a ring are each independently hydrogen or an optionally substituted C_{1-6} aliphatic. In some embodiments, the two R' group that are not taken together to form a ring are each independently hydrogen or an optionally substituted C_{1-6} alkyl. In some embodiments, the two R' group that are not taken together to form a ring are the same. In some embodiments, the two R' group that are not taken together to form a ring are different. In some embodiments, both of them are

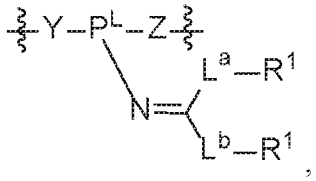
$-CH_3$.

[00518] In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, has the structure of formula **I-n-4** or a salt form thereof:



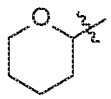
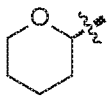
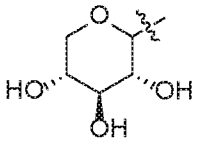
I-n-4

wherein each of L^a and L^b is independently L or $-N(R^1)-$, and each other variable is independently as described in the present disclosure. In some embodiments, L is a covalent bond, and an internucleotidic linkage of formula **I-n-4** has the structure of:

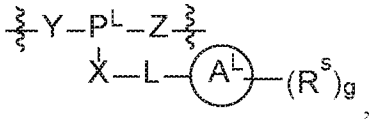


or a salt form thereof, wherein each variable is independently as described in the present disclosure.

[00519] In some embodiments, L^a is $-N(R^1)-$. In some embodiments, L^a is L as described in the present disclosure. In some embodiments, L^a is a covalent bond. In some embodiments, L^a is $-N(R')-$. In some embodiments, L^a is $-N(R)-$. In some embodiments, L^a is $-O-$. In some embodiments, L^a is $-S-$. In some embodiments, L^a is $-S(O)-$. In some embodiments, L^a is $-S(O)_2-$. In some embodiments, L^a is $-S(O)_2N(R')-$. In some embodiments, L^b is $-N(R^1)-$. In some embodiments, L^b is L as described in the present disclosure. In some embodiments, L^b is a covalent bond. In some embodiments, L^b is $-N(R')-$. In some embodiments, L^b is $-N(R)-$. In some embodiments, L^b is $-O-$. In some embodiments, L^b is $-S-$. In some embodiments, L^b is $-S(O)-$. In some embodiments, L^b is $-S(O)_2-$. In some embodiments, L^b is $-S(O)_2N(R')-$. In some embodiments, L^a and L^b are the same. In some embodiments, L^a and L^b are different. In some embodiments, at least one of L^a and L^b is $-N(R^1)-$. In some embodiments, at least one of L^a and L^b is $-O-$. In some embodiments, at least one of L^a and L^b is $-S-$. In some embodiments, at least one of L^a and L^b is a covalent bond. In some embodiments, as described herein, R^1 is R. In some embodiments, R^1 is $-H$. In some embodiments, R^1 is optionally substituted C_{1-10} aliphatic. In some embodiments, R^1 is optionally substituted C_{1-10} alkyl. In some embodiments, a structure of formula **I-n-4** is a structure of formula **I-n-2**. In some embodiments, a structure of formula **I-n-4** is a structure of formula **I-n-3**. In some embodiments, a non-negatively charged internucleotidic linkage, e.g., a neutral internucleotidic linkage, has the structure of formula I. In some embodiments, X, e.g., in formula I, II, etc., is $-N(-L-R^5)-$, wherein R^5 is R as described herein. In

some embodiments, X is –NH–. In some embodiments, L, e.g., in –X–L– of formula I, II, etc., comprises $-SO_2-$. In some embodiments, L is $-SO_2-$. In some embodiments, L is a covalent bond. In some embodiments, L is $-C(O)O-(C_{1-4}$ alkylene)– wherein the alkylene is optionally substituted. In some embodiments, L is $-C(O)OCH_2-$. In some embodiments, R^1, e.g., in formula I, III, etc., comprise an optionally substituted ring. In some embodiments, R^1 is R as described herein. In some embodiments, R^1 is optionally substituted phenyl. In some embodiments, R^1 is 4-methylphenyl. In some embodiments, R^1 is 4-methoxyphenyl. In some embodiments, R^1 is 4-aminophenyl. In some embodiments, R^1 is an optionally substituted heteroaliphatic ring. In some embodiments, R^1 is an optionally substituted 3-10 (e.g., 3, 4, 5, 6, 7, or 8) membered heteroaliphatic ring. In some embodiments, R^1 is an optionally substituted 5- or 6-membered saturated monocyclic heteroaliphatic ring having 1-3 heteroatoms. In some embodiments, the ring is 5-membered. In some embodiments, the ring is 6-membered. In some embodiments, the number of ring heteroatom(s) is 1. In some embodiments, the number of ring heteroatoms is 2. In some embodiments, a heteroatom is oxygen. In some embodiments, R^1 is optionally substituted  . In some embodiments, R^1 is optionally substituted  . In some embodiments, R^1 is  . In some embodiments, R^1 is optionally substituted C_{1-30} aliphatic. In some embodiments, R^1 is optionally substituted C_{1-10} alkyl.

[00520] In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, has the structure of formula **II** or a salt form thereof:



II

or a salt form thereof, wherein:

P^L is P(=W), P, or P→B(R')$_3$;

W is O, N(–L–R^5), S or Se;

each of X, Y and Z is independently –O–, –S–, –N(–L–R^5)–, or L;

R^5 is –H, –L–R', halogen, –CN, $-NO_2$, –L–Si(R')$_3$, –OR', –SR', or –N(R')$_2$;

Ring A^L is an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms;

each R^s is independently –H, halogen, –CN, $-N_3$, –NO, $-NO_2$, –L–R', –L–Si(R)$_3$, –L–OR',

–L–SR', –L–N(R')$_2$, –O–L–R', –O–L–Si(R)$_3$, –O–L–OR', –O–L–SR', or –O–L–N(R')$_2$;

g is 0-20;

each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L;

each –Cy– is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Cy^L is independently an optionally substituted trivalent or tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each R' is independently –R, –C(O)R, –C(O)OR, or –S(O)$_2$R;

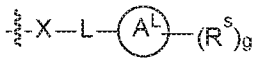
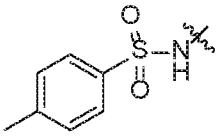
each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

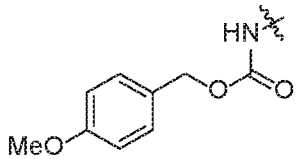
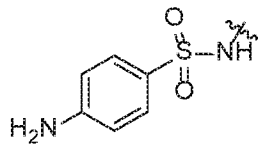
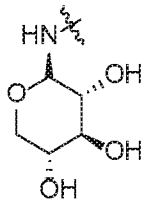
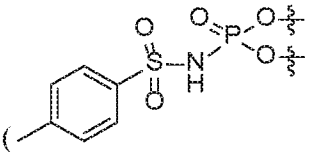
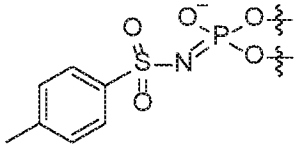
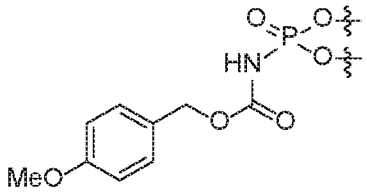
two R groups are optionally and independently taken together to form a covalent bond, or,

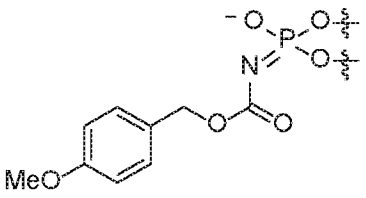
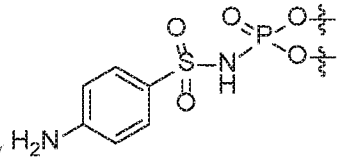
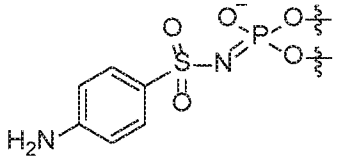
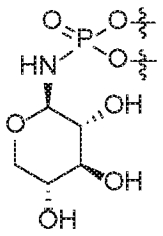
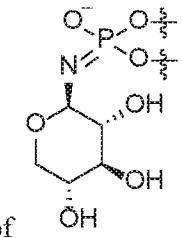
two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms, or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

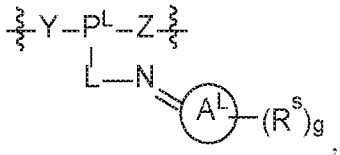
[00521] In some embodiments, Ring A^L in various structures of the present disclosure is an optionally substituted aryl ring. In some embodiments, Ring A^L is an optionally substituted phenyl ring. In some embodiments, Ring A^L is an optionally substituted 3-10 (e.g., 3, 4, 5, 6, 7, or 8) membered heteroaliphatic ring. In some embodiments, Ring A^L is an optionally substituted 5- or 6-membered

saturated monocyclic heteroaliphatic ring having 1-3 heteroatoms. In some embodiments, the ring is 5-membered. In some embodiments, the ring is 6-membered. In some embodiments, the number of ring heteroatom(s) is 1. In some embodiments, the number of ring heteroatoms is 2. In some embodiments, a heteroatom is oxygen. In some embodiments, R^s is optionally substituted C_1-C_6 alkyl group. In some embodiments, R^s is Me. In some embodiments, R^s is OR, wherein R is hydrogen or C_1-C_6 alkyl group. In some embodiments, R^s is OH. In some embodiments, R^s is OMe. In some embodiments, R^s is $-N(R')_2$. In some embodiments, R^s is $-NH_2$. In some embodiments,  is  .

In some embodiments, is  . In some embodiments, is  . In some embodiments, is  . In some embodiments, an internucleotidic linkage, e.g. a neutral internucleotidic linkage of formula I or II, is n002 ( , which, as one skilled in the art will appreciate, can exist under certain conditions in the form of ). In some embodiments, an internucleotidic linkage, e.g. a neutral internucleotidic linkage of formula I or II, is n005 ( , which, as one skilled in the art will appreciate, can exist under certain

conditions in the form of ). In some embodiments, an internucleotidic linkage, e.g. a neutral internucleotidic linkage of formula I or II, is n006 ( , which, as one skilled in the art will appreciate, can exist under certain conditions in the form of ). In some embodiments, an internucleotidic linkage, e.g. a neutral internucleotidic linkage of formula I or II, is n007 ( , which, as one skilled in the art will appreciate, can exist under certain conditions in a form of ).

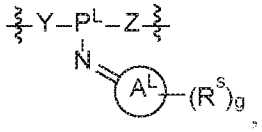
[00522] In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II**, has the structure of formula **II-a-1** or a salt form thereof:



II-a-1

or a salt form thereof.

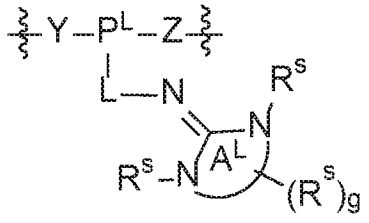
[00523] In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II**, has the structure of formula **II-a-2** or a salt form thereof:



II-a-2

or a salt form thereof.

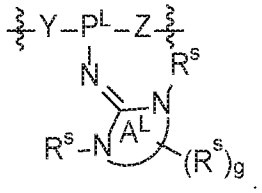
[00524] In some embodiments, A^L is bonded to –N= or L through a carbon atom. In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II** or **II-a-1**, **II-a-2**, has the structure of formula **II-b-1** or a salt form thereof:



II-b-1

[00525] In some embodiments, a structure of formula **II-a-1** or **II-a-2** may be referred to a structure of formula **II-a**. In some embodiments, a structure of formula **II-b-1** or **II-b-2** may be referred to a structure of formula **II-b**. In some embodiments, a structure of formula **II-c-1** or **II-c-2** may be referred to a structure of formula **II-c**. In some embodiments, a structure of formula **II-d-1** or **II-d-2** may be referred to a structure of formula **II-d**.

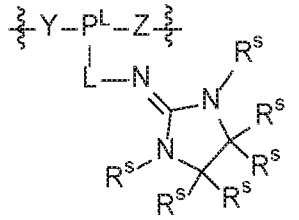
[00526] In some embodiments, A^L is bonded to –N= or L through a carbon atom. In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II** or **II-a-1**, **II-a-2**, has the structure of formula **II-b-2** or a salt form thereof:



II-b-2

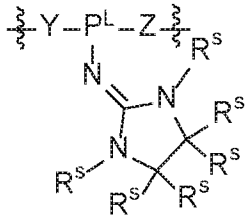
[00527] In some embodiments, Ring A^L is an optionally substituted 3-20 membered monocyclic ring having 0-10 heteroatoms (in addition to the two nitrogen atoms for formula **II-b**). In some embodiments, Ring A^L is an optionally substituted 5- membered monocyclic saturated ring.

[00528] In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II**, **II-a**, or **II-b**, has the structure of formula **II-c-1** or a salt form thereof:



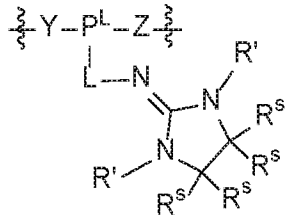
II-c-1

[00529] In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II**, **II-a**, or **II-b**, has the structure of formula **II-c-2** or a salt form thereof:



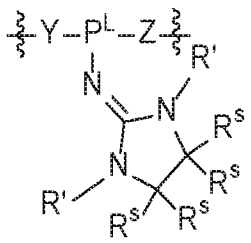
II-c-2

[00530] In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II**, **II-a**, **II-b**, or **II-c** has the structure of formula **II-d-1** or a salt form thereof:



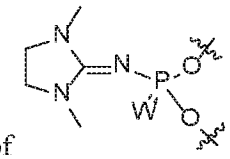
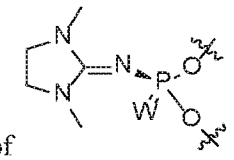
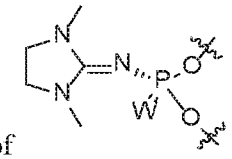
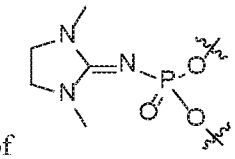
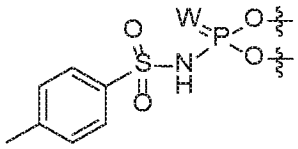
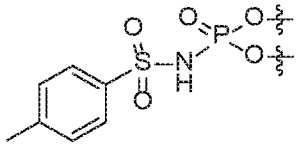
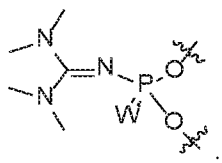
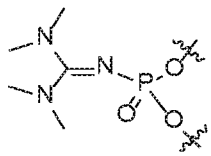
II-d-1

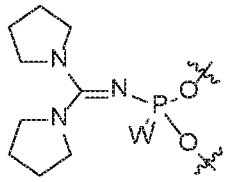
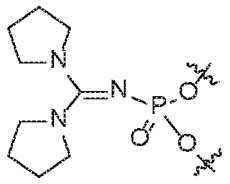
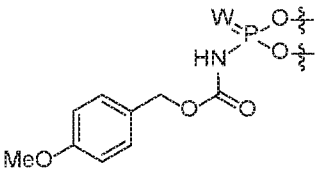
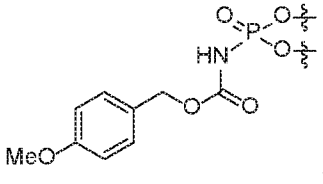
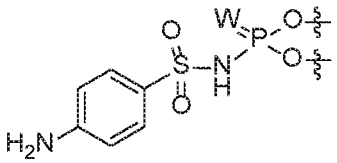
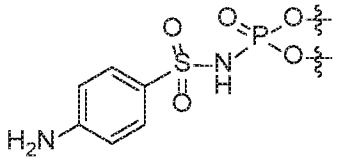
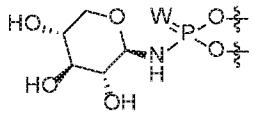
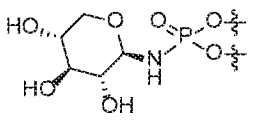
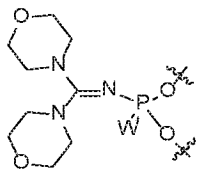
[00531] In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II**, **II-a**, **II-b**, or **II-c** has the structure of formula **II-d-2** or a salt form thereof:

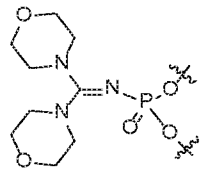
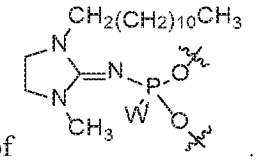


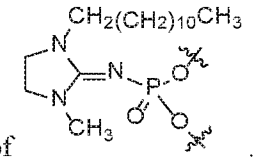
II-d-2

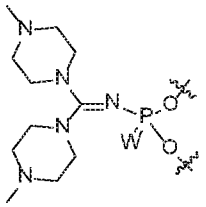
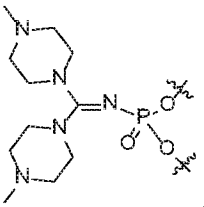
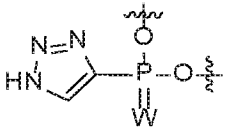
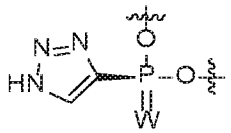
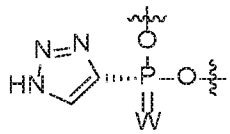
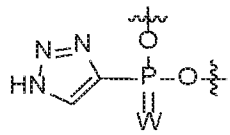
[00532] In some embodiments, each R' is independently optionally substituted C_{1-6} aliphatic. In some embodiments, each R' is independently optionally substituted C_{1-6} alkyl. In some embodiments, each R' is independently $-CH_3$. In some embodiments, each R^s is $-H$.

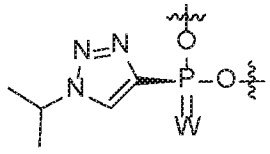
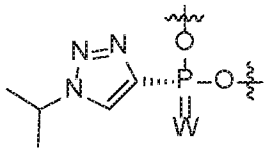
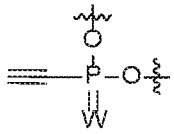
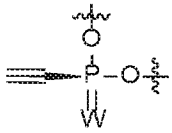
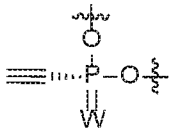
[00533] In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the

structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments,

a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  .

embodiments, a non-negatively charged internucleotidic linkage has the structure of  .

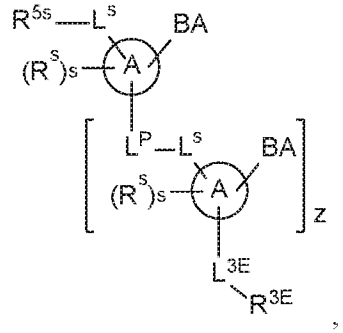
In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-

negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of . In some embodiments, W is O. In some embodiments, W is S. In some embodiments, a non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, the linkage phosphorus is *Rp*. In some embodiments, the linkage phosphorus is *Sp*.

[00534] In some embodiments, each non-negatively charged internucleotidic linkage or neutral internucleotidic linkage (e.g., those of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, or **II-d-2**) is independently *Rp* at its linkage phosphorus. In some embodiments, each negatively charged chiral internucleotidic linkage is *Sp* at its linkage phosphorus. In some embodiments, each phosphorothioate internucleotidic linkages is *Sp* at its linkage phosphorus. In some embodiments, each natural phosphate linkage is independently bonded to a sugar comprising a 2'-OR modification, wherein R is not –H. In some embodiments, each natural phosphate linkage is independently bonded to a sugar comprising a 2'-OR modification, wherein R is not –H, at a 3'-position. In some embodiments, each sugar that contains no 2'-OR modification wherein R is not –H is independently bonded to at least one non-natural phosphate linkages, in many cases, two non-natural natural phosphate linkages. In some embodiments, each 2'-F modified sugar is independently bonded to at least one non-natural phosphate linkages, in many cases, two non-natural natural phosphate linkages. In some embodiments, each non-natural phosphate linkage is a phosphorothioate internucleotidic linkage. In some embodiments, each non-natural phosphate linkage is a *Sp* phosphorothioate internucleotidic

linkage. In some embodiments, each sugar bonded to non-negatively charged internucleotidic linkage or neutral internucleotidic linkage (e.g., those of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, or **II-d-2**) independently contains no 2'-OR. In some embodiments, each sugar bonded to non-negatively charged internucleotidic linkage or neutral internucleotidic linkage (e.g., those of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, or **II-d-2**) is a 2'-F modified sugar.

[00535] In some embodiments, the present disclosure provides a compound, e.g., an oligonucleotide, a chirally controlled oligonucleotide, an oligonucleotide of a provided composition (e.g., of a plurality of oligonucleotides), having the structure of formula **O-I**:



O-I

or a salt thereof, wherein:

R^{5s} is independently R' or –OR';

each BA is independently an optionally substituted group selected from C_{3-30} cycloaliphatic, C_{6-30} aryl, C_{5-30} heteroaryl having 1-10 heteroatoms, C_{3-30} heterocyclyl having 1-10 heteroatoms, a natural nucleobase moiety, and a modified nucleobase moiety;

each R^s is independently –H, halogen, –CN, $-N_3$, –NO, $-NO_2$, –L–R', –L–Si(R)$_3$, –L–OR', –L–SR', –L–N(R')$_2$, –O–L–R', –O–L–Si(R)$_3$, –O–L–OR', –O–L–SR', or –O–L–N(R')$_2$;

each s is independently 0-20;

each L^s is independently $-C(R^{5s})_2-$, or L;

each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–,

–OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L;

each –Cy– is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Cy^L is independently an optionally substituted trivalent or tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Ring A is independently an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon;

each L^P is independently an internucleotidic linkage;

z is 1-1000;

L^{3E} is L or –L–L–;

R^{3E} is –R', –L–R', –OR', or a solid support;

each R' is independently –R, –C(O)R, –C(O)OR, or –S(O)$_2$R;

each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

two R groups are optionally and independently taken together to form a covalent bond, or

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms, or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

[00536] In some embodiments, each L^P independently has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, **III**, or a salt form thereof. In some embodiments, each L^P independently has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof. In some embodiments, each L^P independently has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**,

I-n-4, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1, II-d-2, III, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of formula I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, I-n-4, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1, II-d-2, or a salt form thereof. In some embodiments, each internucleotidic linkage independently has the structure of formula I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, I-n-4, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1, II-d-2, III, or a salt form thereof. In some embodiments, each internucleotidic linkage independently has the structure of formula I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, I-n-4, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1, II-d-2, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of formula I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1, II-d-2, or a salt form thereof. In some embodiments, each internucleotidic linkage independently has the structure of formula I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1, II-d-2, or a salt form thereof.

[00537] In some embodiments, each BA is independently an optionally substituted group selected from C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and C_{3-30} heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus, boron and silicon;

each Ring A is independently an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon; and

each L^P independently has the structure of formula I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, I-n-4, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1, II-d-2, III, or a salt form thereof. In some embodiments, each L^P independently has the structure of formula I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, I-n-4, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1, II-d-2, or a salt form thereof.

[00538] In some embodiments, each BA is independently an optionally substituted C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein the heteroaryl comprises one or more heteroatoms selected from oxygen and nitrogen;

each Ring A is independently an optionally substituted 5-10 membered monocyclic or bicyclic saturated ring having 0-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein the ring comprises at least one oxygen atom; and

each L^P independently has the structure of formula I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, I-n-4, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1, II-d-2, III, or a salt form thereof. In some embodiments, each L^P independently has the structure of formula I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, I-n-4, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1, II-d-2, or a salt form thereof.

[00539] In some embodiments, each BA is independently an optionally substituted A, T, C, G, or

U, or an optionally substituted tautomer of A, T, C, G, or U;

each Ring A is independently an optionally substituted 5-7 membered monocyclic or bicyclic saturated ring having one or more oxygen atoms; and

each L^P independently has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, **III**, or a salt form thereof. In some embodiments, each L^P independently has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof.

[00540] In some embodiments, each BA is independently an optionally substituted or protected nucleobase selected from adenine, cytosine, guanosine, thymine, and uracil and tautomers thereof;

each Ring A is independently an optionally substituted 5-7 membered monocyclic or bicyclic saturated ring having one or more oxygen atoms; and

each L^P independently has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, **III**, or a salt form thereof. In some embodiments, each L^P independently has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof.

[00541] In some embodiments, BA is an optionally substituted group selected from C_{3-30} cycloaliphatic, C_{6-30} aryl, C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{3-30} heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, a natural nucleobase moiety, and a modified nucleobase moiety. In some embodiments, BA is an optionally substituted group selected from C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{3-30} heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, a natural nucleobase moiety, and a modified nucleobase moiety. In some embodiments, BA is an optionally substituted group selected from C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, a natural nucleobase moiety, and a modified nucleobase moiety. In some embodiments, BA is optionally substituted C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, BA is optionally substituted natural nucleobases and tautomers thereof. In some embodiments, BA is protected natural nucleobases and tautomers thereof. Various nucleobase protecting groups for oligonucleotide synthesis are known and can be utilized in accordance with the present disclosure. In some embodiments, BA is an optionally substituted nucleobase selected from adenine, cytosine, guanosine, thymine, and uracil, and tautomers thereof. In some embodiments, BA is an optionally protected nucleobase selected from adenine, cytosine, guanosine, thymine, and uracil, and tautomers thereof.

[00542] In some embodiments, BA is optionally substituted C_{3-30} cycloaliphatic. In some embodiments, BA is optionally substituted C_{6-30} aryl. In some embodiments, BA is optionally substituted C_{3-30} heterocyclyl. In some embodiments, BA is optionally substituted C_{5-30} heteroaryl. In some embodiments, BA is an optionally substituted natural base moiety. In some embodiments, BA is an optionally substituted modified base moiety. BA is an optionally substituted group selected from C_{3-30} cycloaliphatic, C_{6-30} aryl, C_{3-30} heterocyclyl, and C_{5-30} heteroaryl. In some embodiments, BA is an optionally substituted group selected from C_{3-30} cycloaliphatic, C_{6-30} aryl, C_{3-30} heterocyclyl, C_{5-30} heteroaryl, and a natural nucleobase moiety.

[00543] In some embodiments, BA is connected through an aromatic ring. In some embodiments, BA is connected through a heteroatom. In some embodiments, BA is connected through a ring heteroatom of an aromatic ring. In some embodiments, BA is connected through a ring nitrogen atom of an aromatic ring.

[00544] In some embodiments, BA is a natural nucleobase moiety. In some embodiments, BA is an optionally substituted natural nucleobase moiety. In some embodiments, BA is a substituted natural nucleobase moiety. In some embodiments, BA is optionally substituted, or an optionally substituted tautomer of, A, T, C, U, or G. In some embodiments, BA is natural nucleobase A, T, C, U, or G. In some embodiments, BA is an optionally substituted group selected from natural nucleobases A, T, C, U, and G.

[00545] In some embodiments, BA is an optionally substituted purine base residue. In some embodiments, BA is a protected purine base residue. In some embodiments, BA is an optionally substituted adenine residue. In some embodiments, BA is a protected adenine residue. In some embodiments, BA is an optionally substituted guanine residue. In some embodiments, BA is a protected guanine residue. In some embodiments, BA is an optionally substituted cytosine residue. In some embodiments, BA is a protected cytosine residue. In some embodiments, BA is an optionally substituted thymine residue. In some embodiments, BA is a protected thymine residue. In some embodiments, BA is an optionally substituted uracil residue. In some embodiments, BA is a protected uracil residue. In some embodiments, BA is an optionally substituted 5-methylcytosine residue. In some embodiments, BA is a protected 5-methylcytosine residue.

[00546] In some embodiments, BA is a protected base residue as used in oligonucleotide preparation. In some embodiments, BA is a base residue illustrated in US 2011/0294124, US 2015/0211006, US 2015/0197540, and WO 2015/107425, each of which is incorporated herein by reference.

[00547] In some embodiments, R^{5s}–L^s– is $-CH_2OH$. In some embodiments, R^{5s}–L^s– is $-CH(R^{5s})-OH$, wherein R^{5s} is as described in the present disclosure. In some embodiments, L^s is $-CH_2-$. In some embodiments, L^s is $-CH(R^{5s})-$ wherein R^{5s} is not –H. In some embodiments, L^s is $-CH(R^{5s})-$

wherein R^{5s} is not –H and is otherwise R. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is methyl. In some embodiments, $-CH(R^{5s})-$ wherein R^{5s} is not –H has is *R*. In some embodiments, $-CH(R^{5s})-$ wherein R^{5s} is not –H has is *S*.

[00548] Example embodiments for variables, e.g., variables of each of the formulae, are additionally described in the present disclosure, and may be independently and optionally combined.

[00549] In some embodiments, the present disclosure provides oligonucleotides and oligonucleotide compositions that are chirally controlled. For instance, in some embodiments, a provided composition contains controlled levels of one or more individual oligonucleotide types, wherein an oligonucleotide type is defined by: 1) base sequence; 2) pattern of backbone linkages; 3) pattern of backbone chiral centers; and 4) pattern of backbone P-modifications. In some embodiments, oligonucleotides of the same oligonucleotide type are identical.

[00550] In some embodiments, a provided oligonucleotide is an altmer. In some embodiments, a provided oligonucleotide is a P-modification altmer. In some embodiments, a provided oligonucleotide is a stereoaltmer.

[00551] In some embodiments, a provided oligonucleotide is a blockmer. In some embodiments, a provided oligonucleotide is a P-modification blockmer. In some embodiments, a provided oligonucleotide is a stereoblockmer.

[00552] In some embodiments, a provided oligonucleotide is a gapmer.

[00553] In some embodiments, a provided oligonucleotide is a skipmer.

[00554] In some embodiments, a provided oligonucleotide is a hemimer. In some embodiments, a hemimer is an oligonucleotide wherein the 5'-end or the 3'-end has a sequence that possesses a structure feature that the rest of the oligonucleotide does not have. In some embodiments, the 5'-end or the 3'-end has or comprises 2 to 20 nucleotides. In some embodiments, a structural feature is a base modification. In some embodiments, a structural feature is a sugar modification. In some embodiments, a structural feature is a P-modification. In some embodiments, a structural feature is stereochemistry of the chiral internucleotidic linkage. In some embodiments, a structural feature is or comprises a base modification, a sugar modification, a P-modification, or stereochemistry of the chiral internucleotidic linkage, or combinations thereof. In some embodiments, a hemimer is an oligonucleotide in which each sugar moiety of the 5'-end sequence shares a common modification. In some embodiments, a hemimer is an oligonucleotide in which each sugar moiety of the 3'-end sequence shares a common modification. In some embodiments, a common sugar modification of the 5' or 3' end sequence is not shared by any other sugar moieties in the oligonucleotide. In some embodiments, an example hemimer is an oligonucleotide comprising a sequence of substituted or unsubstituted 2'-O-alkyl sugar modified nucleosides, bicyclic

sugar modified nucleosides, β-D-ribonucleosides or β-D- deoxyribonucleosides (for example 2'-MOE modified nucleosides, and LNA™ or ENA™ bicyclic sugar modified nucleosides) at one terminus and a sequence of nucleosides with a different sugar moiety (such as a substituted or unsubstituted 2'-O-alkyl sugar modified nucleosides, bicyclic sugar modified nucleosides or natural ones) at the other terminus. In some embodiments, a provided oligonucleotide is a combination of one or more of unimer, altmer, blockmer, gapmer, hemimer and skipmer. In some embodiments, a provided oligonucleotide is a combination of one or more of unimer, altmer, blockmer, gapmer, and skipmer. For instance, in some embodiments, a provided oligonucleotide is both an altmer and a gapmer. In some embodiments, a provided nucleotide is both a gapmer and a skipmer. One of skill in the chemical and synthetic arts will recognize that numerous other combinations of patterns are available and are limited only by the commercial availability and / or synthetic accessibility of constituent parts required to synthesize a provided oligonucleotide in accordance with methods of the present disclosure. In some embodiments, a hemimer structure provides advantageous benefits. In some embodiments, provided oligonucleotides are 5'-hemimers that comprises modified sugar moieties in a 5'-end sequence. In some embodiments, provided oligonucleotides are 5'-hemimers that comprises modified 2'-sugar moieties in a 5'-end sequence.

[00555] In some embodiments, a provided oligonucleotide comprises one or more optionally substituted nucleotides. In some embodiments, a provided oligonucleotide comprises one or more modified nucleotides. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted nucleosides. In some embodiments, a provided oligonucleotide comprises one or more modified nucleosides. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted nucleosides or sugars of LNAs.

[00556] In some embodiments, a provided oligonucleotide comprises one or more optionally substituted nucleobases. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted natural nucleobases. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted modified nucleobases. In some embodiments, a provided oligonucleotide comprises one or more 5-methylcytidine; 5-hydroxymethylcytidine, 5-formylcytosine, or 5-carboxylcytosine. In some embodiments, a provided oligonucleotide comprises one or more 5-methylcytidine.

[00557] In some embodiments, a provided oligonucleotide comprises one or more optionally substituted sugars. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted sugars found in naturally occurring DNA and RNA. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted ribose or deoxyribose. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted ribose or

deoxyribose, wherein one or more hydroxyl groups of the ribose or deoxyribose moiety is optionally and independently replaced by halogen, R', $-N(R')_2$, –OR', or –SR', wherein each R' is independently as defined above and described herein. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with R^{2s}, halogen, R', $-N(R')_2$, –OR', or –SR', wherein each R' is independently as defined above and described herein. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with halogen. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with one or more –F. halogen. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with –OR', wherein each R' is independently as defined above and described herein. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with –OR', wherein each R' is independently an optionally substituted C_1–C_6 aliphatic. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with –OR', wherein each R' is independently an optionally substituted C_1–C_6 alkyl. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with –OMe. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with –O–methoxyethyl.

[00558] In some embodiments, a provided oligonucleotide is single-stranded oligonucleotide. In some embodiments, a provided oligonucleotide is a hybridized oligonucleotide strand. In certain embodiments, a provided oligonucleotide is a partially hybridized oligonucleotide strand. In certain embodiments, a provided oligonucleotide is a completely hybridized oligonucleotide strand. In certain embodiments, a provided oligonucleotide is a double-stranded oligonucleotide. In certain embodiments, a provided oligonucleotide is a triple-stranded oligonucleotide (*e.g.*, a triplex).

[00559] In some embodiments, a provided oligonucleotide is chimeric. For example, in some embodiments, a provided oligonucleotide is DNA-RNA chimera, DNA-LNA chimera, *etc*.

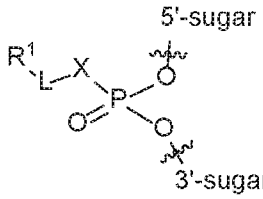
[00560] In some embodiments, an oligonucleotide is a chirally controlled oligonucleotide variant of an oligonucleotide described in WO2012/030683. For example, in some embodiments, a chirally controlled oligonucleotide variant comprises a chirally controlled version of a chiral internucleotidic

linkage which is not chirally controlled in WO2012/030683. In some embodiments, a chirally controlled oligonucleotide variant comprises one or more chirally controlled internucleotidic linkages which independently replace one or more natural phosphate linkages or non-chirally controlled modified internucleotidic linkages in WO2012/030683.

[00561] In some embodiments, a provided oligonucleotide is or comprises a portion of GNA, LNA, PNA, TNA or Morpholino.

[00562] In some embodiments, a provided oligonucleotide is from about 15 to about 25 nucleotide units in length. In some embodiments, a provided oligonucleotide is from about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotide units in length.

[00563] In some embodiments, the present disclosure provides oligonucleotides comprising one or more modified internucleotidic linkage, which can be chiral at linkage phosphorus and chirally controlled. In some embodiments, an oligonucleotide comprises one or more linkages L^{PO}, L^{PA} or L^{PB}, wherein:



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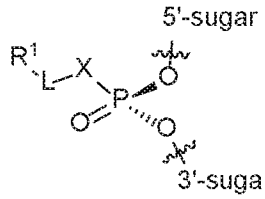

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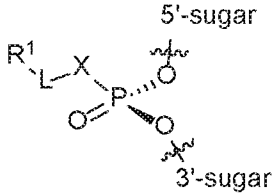
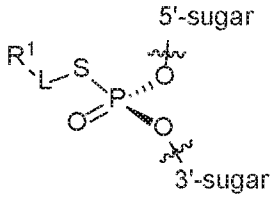
each L^{PO} is independently



or a salt form thereof;

each L^{PA} is independently an internucleotidic linkage having the structure of



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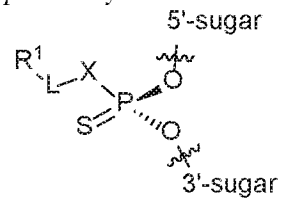

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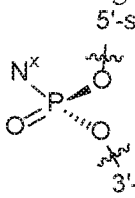

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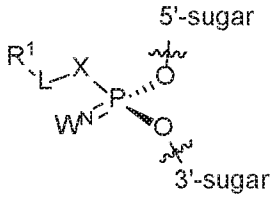
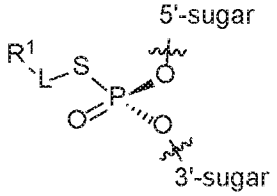


, or a salt form thereof;

each L^{PB} is independently an internucleotidic linkage having the structure of



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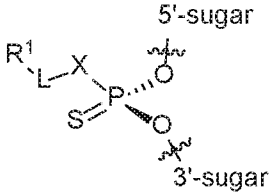

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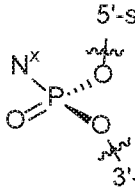

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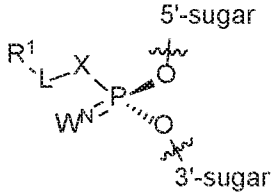
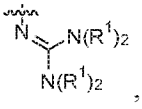
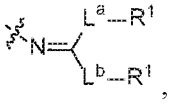
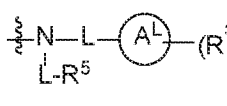
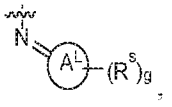
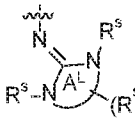
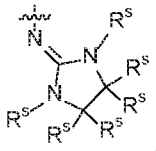
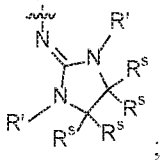
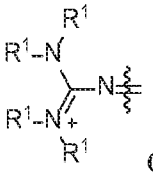
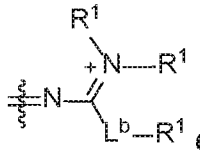
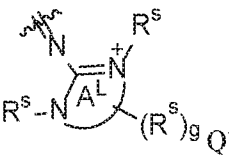
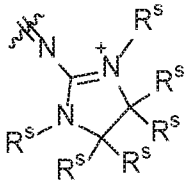
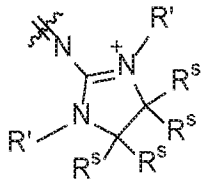
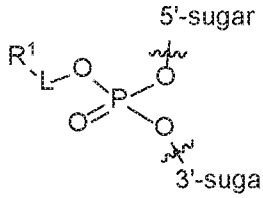


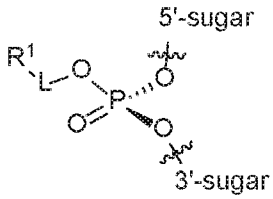
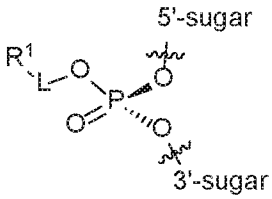
, or a salt form thereof;

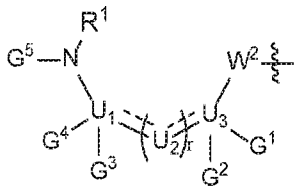
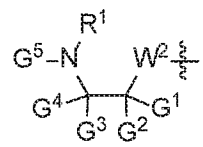
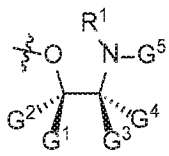
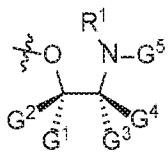
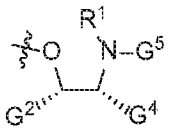
N^X is $-N(-L-R^5)-L-R^1$,  ,  ,  ,  ,  ,  ,  ; and

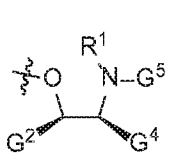
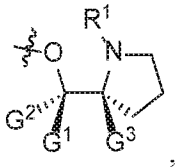
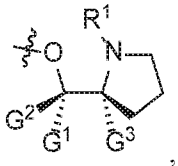
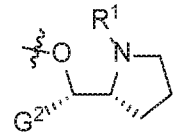
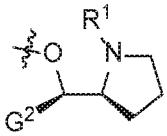
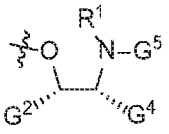
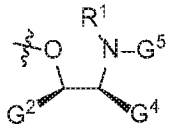
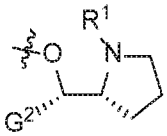
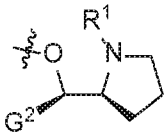
W^N is $=N-L-R^5$,  ,  ,  ,  ,  ;

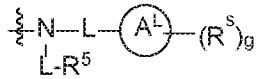
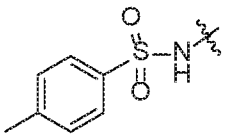
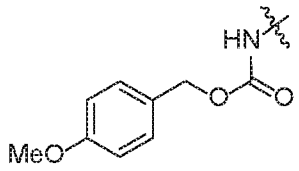
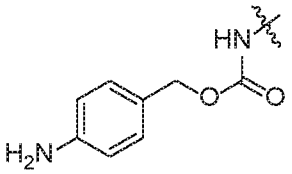
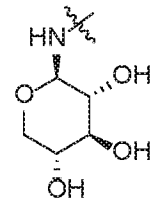
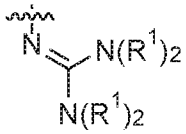
wherein each other variable is independently as described herein.

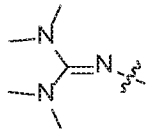
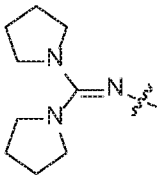
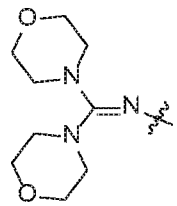
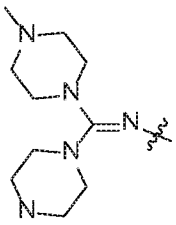
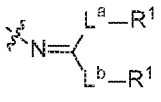
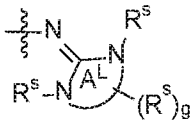


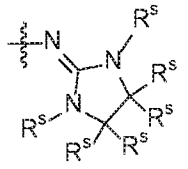
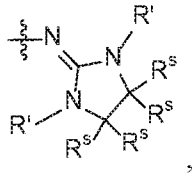
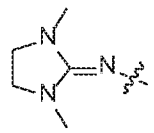
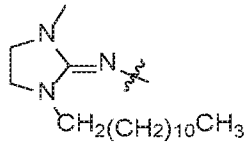
[00564] In some embodiments, each L^{PO} is independently  ,  , or a salt form thereof.

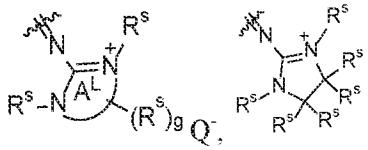
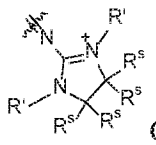
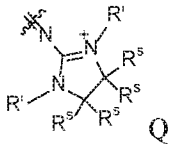
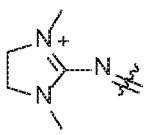
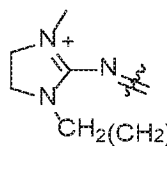
[00565] In some embodiments, $-O-L-R^1$ is $-OH$. In some embodiments, $-X-L-R^1$, *e.g.*, in L^{PO} is $-OCH_2CH_2CN$. In some embodiments, $-S-L-R^1$ is $-SH$. In some embodiments, L^{PA} is a phosphorothioate internucleotidic linkage with the specified stereochemistry. In some embodiments, L^{PB} is a phosphorothioate internucleotidic linkage with the specified stereochemistry. In some embodiments, X is –O–, and $-X-L-R^1$ is as described in the present disclosure, *e.g.*, $-X-L-R^1$ is  ,  ,  ,  ,  ,

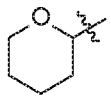
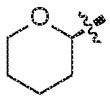
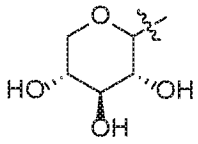
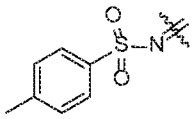
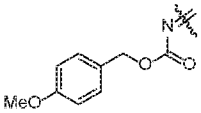
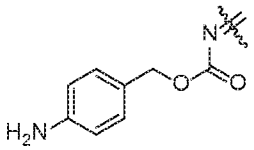
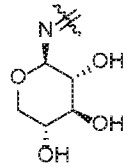
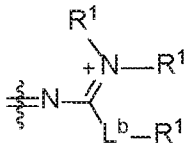
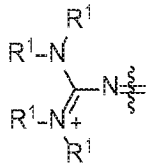
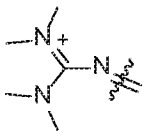
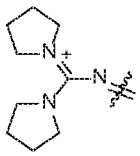
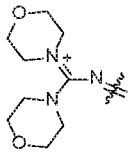
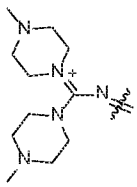





, wherein each variable is independently in accordance with the present disclosure, or H–X–L–R^1 is a chiral auxiliary as described herein. In some embodiments, –X–L–R^1 is  , or  , wherein G^4 and G^5 are taken together to form an optionally substituted ring as described herein. In some embodiments, –X–L–R^1 is  , or  . In some embodiments, G^2 is $-CH_2Si(R)_3$ as described herein. In some embodiments, G^2 is $-CH_2Si(Ph)_2Me$. In some embodiments, G^2 comprises an electron-withdrawing group as described herein, for example, in some embodiments, G^2 is $-CH_2SO_2R$ as described herein. In some embodiments, G^2 is $-CH_2SO_2Ph$.

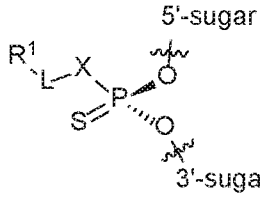
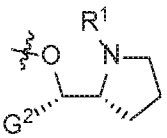
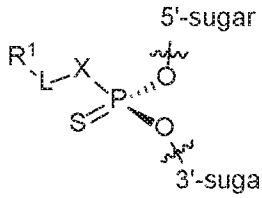
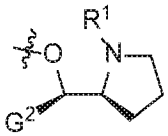
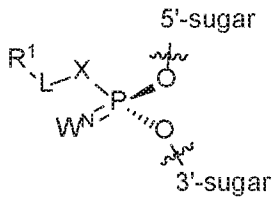
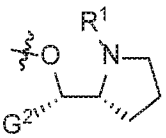
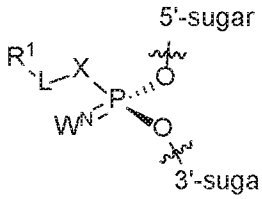
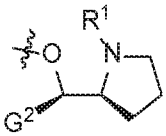
[00566] In some embodiments, N^x is $-N(-L-R^5)-L-R^1$, and an internucleotidic linkage having such a N^x group is an internucleotidic linkage having the structure of formula I wherein P^L is P=O, Y and Z are –O–, and X is $-N(-L-R^5)-$, wherein the linkage phosphorus stereochemistry is as specified. In some embodiments, N^x is  , and an internucleotidic linkage having such a N^x group is an internucleotidic linkage having the structure of formula II, wherein P^L is P=O, Y and Z are –O–, and X is $-N(-L-R^5)-$, wherein the linkage phosphorus stereochemistry is as specified. In some embodiments, N^x is  . In some embodiments, N^x is  . In some embodiments, N^x is  . In some embodiments, N^x is.  . In some embodiments, N^x is  , and an internucleotidic linkage having such a N^x group is an

internucleotidic linkage having the structure of formula I-n-3, wherein P^L is P=O, and Y and Z are –O–, wherein the linkage phosphorus stereochemistry is as specified. In some embodiments, R^1 is optionally substituted alkyl. In some embodiments, R^1 is methyl. In some embodiments, N^x is  . In some embodiments, two R^1 on the same nitrogen independently are taken together to form an optionally substituted ring as described herein, *e.g.*, an optionally substituted 5- or 6-membered ring which in addition to the nitrogen atom, has 1-3 heteroatoms. In some embodiments, the ring is saturated. In some embodiments, the ring is monocyclic. In some embodiments, N^x is  . In some embodiments, N^x is  . In some embodiments, N^x is  . Those skilled in the art will appreciate that two $-N(R^1)_2$ groups, in any, in a structure or formula can either be the same or different. In some embodiments, N^x is  , and an internucleotidic linkage having such a N^x group is an internucleotidic linkage having the structure of formula I-n-4, wherein P^L is P=O, L is a covalent bond, and Y and Z are –O–, wherein the linkage phosphorus stereochemistry is as specified. In some embodiments, N^x is , and an internucleotidic linkage having such a N^x group is an internucleotidic linkage having the structure of formula II-a-1, wherein P^L is P=O, L is a covalent bond, and Y and Z are –O–, wherein the linkage phosphorus stereochemistry is as specified. In some embodiments, N^x is  , and an internucleotidic linkage having such a N^x group is an internucleotidic linkage having the structure of formula II-b-1, wherein P^L is P=O, L is a covalent bond, and Y and Z are –O–, wherein the linkage phosphorus stereochemistry is as specified. In some

embodiments, N^X is  , and an internucleotidic linkage having such a N^X group is an internucleotidic linkage having the structure of formula II-c-1, wherein P^L is P=O, L is a covalent bond, and Y and Z are −O−, wherein the linkage phosphorus stereochemistry is as specified. In some embodiments, N^X is  , and an internucleotidic linkage having such a N^X group is an internucleotidic linkage having the structure of formula II-d-1, wherein P^L is P=O, L is a covalent bond, and Y and Z are −O−, wherein the linkage phosphorus stereochemistry is as specified. In some embodiments, R' or R^s is optionally substituted alkyl. In some embodiments, R' or R^s is $-CH_3$. In some embodiments, R' or R^s is $-CH_2(CH_2)_{10}CH_3$. In some embodiments, R^s is −H. In some embodiments, N^X is  . In some embodiments, N^X is  .

[00567] In some embodiments, P=W^N is a P^N group as described herein. In some embodiments, W^N is  , , or  , wherein each variable is as described herein (for example, in N^X). In some embodiments, W^N is  . In some embodiments, as described herein R' or R^s is optionally substituted alkyl or −H. In some embodiments, R' is $-CH_3$. In some embodiments, R' is $-CH_2(CH_2)_{10}CH_3$. In some embodiments, R^s is −H. In some embodiments, W^N is  . In some embodiments, W^N is  . In some embodiments, W^N is =N−L−R^5 wherein each variable is as described herein. For example, in some embodiments, L is $-SO_2-$. In some embodiments, L is $-C(O)OCH_2-$. In some embodiments, as described herein, R^5 is or comprise an optionally substituted ring. In some embodiments, R^5 is R as described herein. In some embodiments, R^5 is optionally substituted phenyl. In some embodiments, R^5 is 4-methylphenyl. In some embodiments,

R^5 is 4-methoxyphenyl. In some embodiments, R^5 is 4-aminophenyl. In some embodiments, R^5 is an optionally substituted heteroaliphatic ring. In some embodiments, R^5 is an optionally substituted 3-10 (e.g., 3, 4, 5, 6, 7, or 8) membered heteroaliphatic ring. In some embodiments, R^5 is an optionally substituted 5- or 6-membered saturated monocyclic heteroaliphatic ring having 1-3 heteroatoms. In some embodiments, the ring is 5-membered. In some embodiments, the ring is 6-membered. In some embodiments, the number of ring heteroatom(s) is 1. In some embodiments, the number of ring heteroatoms is 2. In some embodiments, a heteroatom is oxygen. In some embodiments, R^5 is optionally substituted  . In some embodiments, R^5 is optionally substituted  . In some embodiments, R^5 is  . In some embodiments, R^5 is optionally substituted C_{1-30} aliphatic. In some embodiments, R^5 is optionally substituted C_{1-10} alkyl. In some embodiments, W^N is  . In some embodiments, W^N is  . In some embodiments, W^N is  . In some embodiments, W^N is  . In some embodiments, W^N is  Q^-. In some embodiments, W^N is  Q^-. In In some embodiments, W^N is  Q^-. In some embodiments, W^N is  Q^-. In some embodiments, W^N is  Q^-. In some embodiments, W^N is  Q^-. In some embodiments, Q^- is PF_6^-.

[00568] In some embodiments, $-X-L-R^1$ in  is  . In some embodiments, $-X-L-R^1$ in  is  . In some embodiments, G^2 is $-CH_2Si(R)_3$ as described herein. In some embodiments, G^2 is $-CH_2Si(Ph)_2Me$. In some embodiments, $-X-L-R^1$ in  is  . In some embodiments, $-X-L-R^1$ in  is  . In some embodiments, G^2 comprises an electron-withdrawing group as described herein. In some embodiments, G^2 is $-CH_2SO_2R$, wherein R is not $-H$. In some embodiments, R is optionally substituted phenyl. In some embodiments, G^2 is $-CH_2SO_2Ph$. In some embodiments, R is optionally substituted C_{1-6} aliphatic, e.g., t-butyl. In some embodiments, as described herein, R^1 is $-C(O)R'$. In some embodiments, R^1 is $-C(O)CH_3$. In some embodiments, R^1 is $-H$.

[00569] In some embodiments, L^{PO} is a natural phosphate linkage. In some embodiments, L^{PA} is a Rp phosphorothioate internucleotidic linkage. In some embodiments, L^{PA} is a Rp non-negatively charged internucleotidic linkage, *e.g.*, n001. In some embodiments, L^{PB} is a Sp phosphorothioate internucleotidic linkage. In some embodiments, L^{PB} is a Sp non-negatively charged internucleotidic linkage, *e.g.*, n001. In some embodiments, an oligonucleotide comprises one or more linkages L^{PO}. In some embodiments, an oligonucleotide comprises one or more linkages L^{PA}. In some embodiments, an oligonucleotide comprises one or more linkages L^{PB}. In some embodiments, an oligonucleotide comprises one or more internucleotidic linkages independently selected from L^{PO}, L^{PA} and L^{PB}. In some embodiments, each internucleotidic linkage is independently selected from L^{PO}, L^{PA} and L^{PB}. In some embodiments, each internucleotidic linkage is independently selected from L^{PA} and L^{PB}. In some embodiments, at least one internucleotidic linkage is L^{PA} or L^{PB}. In some embodiments, each chirally

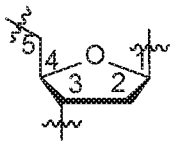
controlled internucleotidic linkage is independently selected from L^{PA} and L^{PB}.

[00570] In some embodiments, the present disclosure provides oligonucleotides (*e.g.*, chirally controlled oligonucleotides) and compositions thereof (*e.g.*, chirally controlled oligonucleotide compositions), wherein the internucleotidic linkages of the oligonucleotides or regions thereof are or comprise the following consecutive internucleotidic linkages (from 5' to 3'):

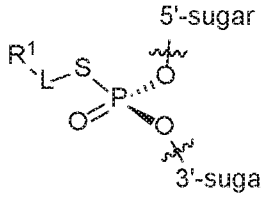
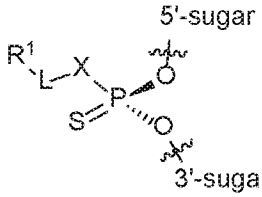
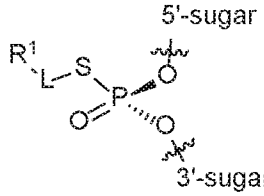
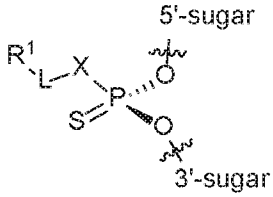
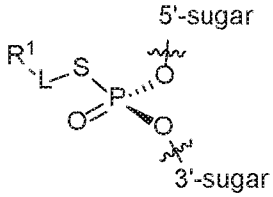
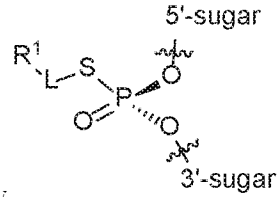
$(L^{PX}/L^{PO})t[(L^{PA})n(L^{PB})m]y$, $(L^{PX}/L^{PO})t[(L^{PO})n(L^{PB})m]y$, $(L^{PX}/L^{PO})t[(L^{PO}/L^{PA})n(L^{PB})m]y$, $[(L^{PA})n(L^{PB})m]y$, $[(L^{PO})n(L^{PB})m]y$, $((L^{PB})t[(L^{PA})n(L^{PB})m]y$, $(L^{PB})t[(L^{PO})n(L^{PB})m]y$, $(L^{PB})t[(L^{PO}/L^{PA})n(L^{PB})m]y$, $[(L^{PA})n(L^{PB})m]y$, $[(L^{PO})n(L^{PB})m]y$, $[(L^{PO}/L^{PA})n(L^{PB})m]y$, $(L^{PA})t(L^{PX})n(L^{PA})m$, $(L^{PA})t(L^{PB})n(L^{PA})m$, $(L^{PA})t[(L^{PX}/L^{PO})n]y(L^{PA})m$, $(L^{PA})t[(L^{PB}/L^{PX})n]y(L^{PA})m$, $(L^{PA})t[(L^{PB}/L^{PO})n]y(L^{PA})m$, $(L^{PX}/L^{PO})t(L^{PX})n(L^{PX}/L^{PO})m$, $(L^{PX}/L^{PO})t(L^{PB})n(L^{PX}/L^{PO})m$, $(L^{PX}/L^{PO})t[(L^{PX}/L^{PO})n]y(L^{PX}/L^{PO})m$, $(L^{PX}/L^{PO})t[(L^{PB}/L^{PO})n]y(L^{PX}/L^{PO})m$, $(L^{PX}/L^{PO})t[(L^{PB}/L^{PO})n]y(L^{PX}/L^{PO})m$, $(L^{PA}/L^{PO})t(L^{PX})n(L^{PA}/L^{PO})m$, $(L^{PA}/L^{PO})t(L^{PB})n(L^{PA}/L^{PO})m$, $(L^{PA}/L^{PO})t[(L^{PX}/L^{PO})n]y(L^{PA}/L^{PO})m$, $(L^{PA}/L^{PO})t[(L^{PB}/L^{PO})n]y(L^{PA}/L^{PO})m$, or $(L^{PA}/L^{PO})t[(L^{PB}/L^{PO})n]y(L^{PA}/L^{PO})m$, or a combination thereof, wherein:

each L^{PX} is independently L^{PA} or L^{PB}; and

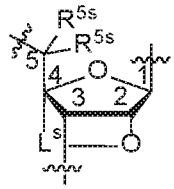
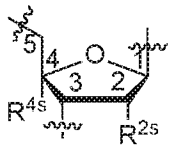
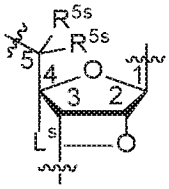
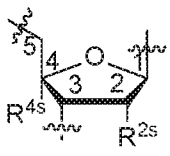
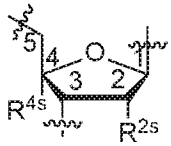
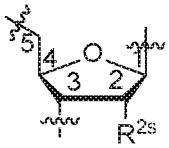
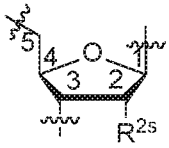
each other variable is independently as described herein.

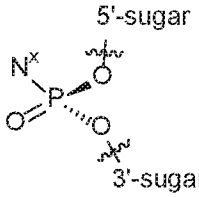
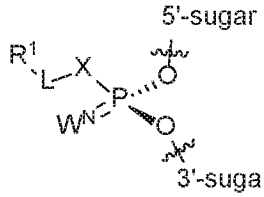
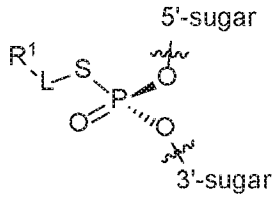
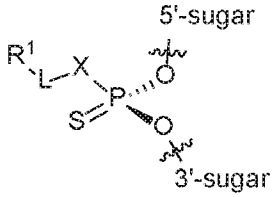
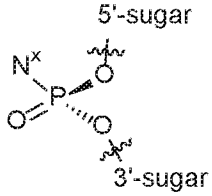
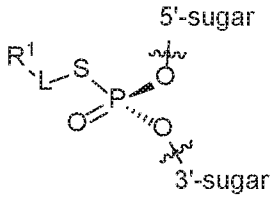
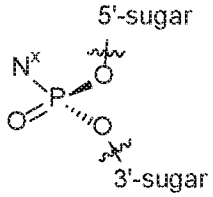
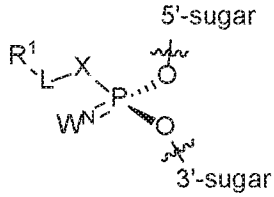
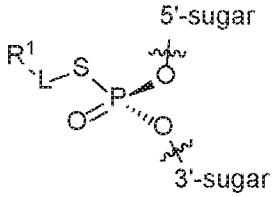
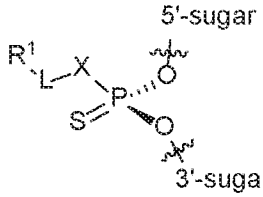
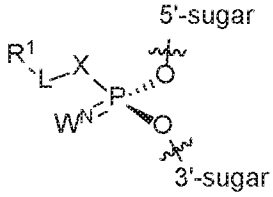
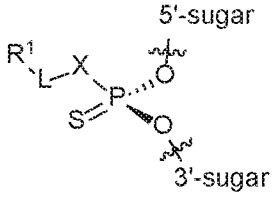
[00571] In some embodiments, internucleotidic linkages of an provided oligonucleotides or regions thereof comprise or are consecutive internucleotidic linkages $[(L^{PA})n(L^{PB})m]y$, $[(L^{PO})n(L^{PB})m]y$, $(L^{PB})t[(L^{PA})n(L^{PB})m]y$, or $(L^{PB})t[(L^{PO})n(L^{PB})m]y$. In some embodiments, internucleotidic linkages of an provided oligonucleotides or regions thereof comprise or are consecutive internucleotidic linkages $(L^{PA})(L^{PB})m$. In some embodiments, internucleotidic linkages of an provided oligonucleotides or regions thereof comprise or are consecutive internucleotidic linkages $[(L^{PA})(L^{PB})m]y$. In some embodiments, internucleotidic linkages of an provided oligonucleotides or regions thereof comprise or are consecutive internucleotidic linkages $(L^{PB})t(L^{PA})(L^{PB})m$. In some embodiments, each sugar between two of the consecutive internucleotidic linkages independently contains no 2'-modification. In some embodiments, each sugar between two of the consecutive internucleotidic linkages is independently 

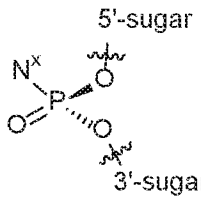
. In some embodiments, n is 1. In some embodiments, y is 1. In some embodiments, y is 2-10. In some embodiments, t is 1. In some embodiments, t is 2-10. In some embodiments, t is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, n is 1, and m is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, t is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, n is 1, and m is 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, t is 2-10, n is 1 and m is 2-10. In

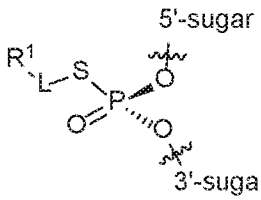
some embodiments, each L^{PA} is independently  or  , or a salt form thereof. In some embodiments, each L^{PB} is independently  or  , or a salt form thereof. In some embodiments, each L^{PA} is independently  or a salt form thereof, and each each L^{PB} is independently  or a salt form thereof.

[00572] In some embodiments, internucleotidic linkages of an provided oligonucleotides or regions thereof comprise or are consecutive internucleotidic linkages (from 5' to 3') $(L^{PO})m(L^{PA}/L^{PB})n$, $L^{PO}(L^{PA}/L^{PB})n$, $(L^{PO})m(L^{PB})n$, $L^{PO}(L^{PB})n$, $[(L^{PO})m(L^{PA}/L^{PB})n]y$, $[L^{PO}(L^{PA}/L^{PB})n]y$, $[(L^{PO})m(L^{PB})n]y$, $[L^{PO}(L^{PB})n]y$, $(L^{PA}/L^{PB})t(L^{PO})m(L^{PA}/L^{PB})n$, $(L^{PA}/L^{PB})tL^{PO}(L^{PA}/L^{PB})n$, $(L^{PA}/L^{PB})t(L^{PO})m(L^{PB})n$, $(L^{PA}/L^{PB})tL^{PO}(L^{PB})n$, $(L^{PA}/L^{PB})t[(L^{PO})m(L^{PA}/L^{PB})n]y$, $(L^{PA}/L^{PB})t[L^{PO}(L^{PA}/L^{PB})n]y$, $(L^{PA}/L^{PB})t[(L^{PO})m(L^{PB})n]y$, $(L^{PA}/L^{PB})t[L^{PO}(L^{PB})n]y$, $(L^{PO})m(L^{PA}/L^{PB})n(L^{PA}/L^{PB})t$, $L^{PO}(L^{PA}/L^{PB})n(L^{PA}/L^{PB})t$, $(L^{PO})m(L^{PB})n(L^{PA}/L^{PB})t$, $L^{PO}(L^{PB})n(L^{PA}/L^{PB})t$, $[(L^{PO})m(L^{PA}/L^{PB})n]y(L^{PA}/L^{PB})t$, $[L^{PO}(L^{PA}/L^{PB})n]y(L^{PA}/L^{PB})t$, $[(L^{PO})m(L^{PB})n]y(L^{PA}/L^{PB})t$, $[L^{PO}(L^{PB})n]y(L^{PA}/L^{PB})t$, $(L^{PA}/L^{PB})t[(L^{PO})m(L^{PA}/L^{PB})n]y(L^{PA}/L^{PB})t$, $L^{PB}(L^{PA}/L^{PB})t[(L^{PO})m(L^{PA}/L^{PB})n]y(L^{PA}/L^{PB})tL^{PB}$, $(L^{PA}/L^{PB})t[(L^{PO})m(L^{PB})n]y(L^{PA}/L^{PB})t$, $L^{PB}(L^{PA}/L^{PB})t[(L^{PO})m(L^{PB})n]y(L^{PA}/L^{PB})tL^{PB}$, $(L^{PA}/L^{PB})t[(L^{PO})(L^{PA}/L^{PB})]y(L^{PA}/L^{PB})t$, $L^{PB}(L^{PA}/L^{PB})t[(L^{PO})(L^{PA}/L^{PB})]y(L^{PA}/L^{PB})tL^{PB}$, $(L^{PA}/L^{PB})t[(L^{PO})(L^{PB})]y(L^{PA}/L^{PB})t$, $L^{PB}(L^{PA}/L^{PB})t[(L^{PO})(L^{PB})]y(L^{PA}/L^{PB})tL^{PB}$, or a combination thereof, wherein each variable is independently as described herein. In some embodiments, at least one L^{PA}/L^{PB} of $(L^{PA}/L^{PB})t$ is L^{PA}. In some embodiments, at least one L^{PA}/L^{PB} of $(L^{PA}/L^{PB})t$ is L^{PB}. In some embodiments, at least one L^{PA}/L^{PB} of $(L^{PA}/L^{PB})t$ is L^{PA}, and at least one L^{PA}/L^{PB} of $(L^{PA}/L^{PB})t$ is L^{PB}. In some embodiments, at least one

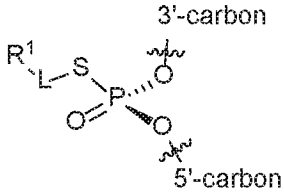
L^{PA}/L^{PB} of $(L^{PA}/L^{PB})m$ is L^{PA}. In some embodiments, at least one L^{PA}/L^{PB} of $(L^{PA}/L^{PB})m$ is L^{PB}. In some embodiments, at least one L^{PA}/L^{PB} of $(L^{PA}/L^{PB})m$ is L^{PA}, and at least one L^{PA}/L^{PB} of $(L^{PA}/L^{PB})m$ is L^{PB}. In some embodiments, each L^{PA}/L^{PB} of $(L^{PA}/L^{PB})m$ is L^{PB}. In some embodiments, a sugar bonded to a L^{PO} linkage at its 3'-carbon comprises a 2'-modification, wherein the 2'-modification is not 2'-F. In some embodiments, a sugar bonded to a L^{PO} linkage at its 3'-carbon is independently  or  , wherein R^{2s} is not −H or −OH. In some embodiments, each sugar bonded to a L^{PO} linkage at its 3'-carbon is independently  or  , wherein R^{2s} is not −H or −OH. In some embodiments, each sugar bonded to a L^{PO} linkage at its 3'-carbon is independently  , wherein R^{2s} is not −H or −OH. In some embodiments, R^{4s} is −H. In some embodiments, R^{2s} is not −H, −F or −OH. In some embodiments, each sugar bonded to a L^{PO} linkage at its 3'-carbon is independently  , wherein R^{2s} is not −H, −F or −OH. In some embodiments, R^{2s} is −OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R^{2s} is −OMe. In some embodiments, a 5'-end sugar, a 3'-end sugar, and/or a sugar between L^{PA}/L^{PB} and L^{PA}/L^{PB} comprises a 2'-F modification. In some embodiments, a 5'-end sugar, a 3'-end sugar, and/or a sugar between L^{PA}/L^{PB} and L^{PA}/L^{PB} is  , wherein R^{2s} is −F. In some embodiments, each sugar comprises a 2'-F is bonded to a modified internucleotidic linkage, e.g., at its 3'-carbon. In some embodiments, a modified internucleotidic linkage is L^{PA} or L^{PB}. In some

embodiments, each L^{PA} is independently  or  , or a salt form thereof. In some embodiments, each L^{PB} is independently  or  , or a salt form thereof. In some embodiments, t is 2-10. In some embodiments, each L^{PA} is independently  or a salt form thereof, and each L^{PB} is independently  or a salt form thereof. In some embodiments, each modified internucleotidic linkage in a provided oligonucleotide is independently L^{PO} (wherein $-X-L-R^1$ is not $-H$),  ,  ,  or  , or a salt form thereof. In some embodiments, each modified internucleotidic linkage is independently  or  , or a salt form thereof. In some embodiments, each



or


, or a salt form thereof. In some embodiments, m is 1. In some embodiments, each m is 1. In some embodiments, n is 2 or more. In some embodiments, each n is 2 or more. In some embodiments, t is 1. In some embodiments, t is 2 or more. In some embodiments, t is 3. In some embodiments, t is 4. In some embodiments, t is 5. In some embodiments, t is 6. In some embodiments, t is 7. In some embodiments, t is 8. In some embodiments, t is 9. In some embodiments, t is 10. In some embodiments, each t is independently 2 or more. In some embodiments, each t is independently 3 or more. In some embodiments, each t is independently 4 or more. In some embodiments, each t is independently 5 or more.

[00573] In some embodiments, each of L^{PO}, L^{PA} and L^{PB} independently bonds to a 5'-sugar through its 3'-carbon, and to a 3'-sugar through its 5'-carbon, *e.g.*, each L^{PA} is independently an internucleotidic linkage having the structure of


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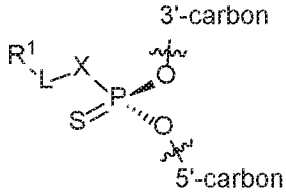

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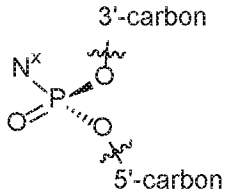
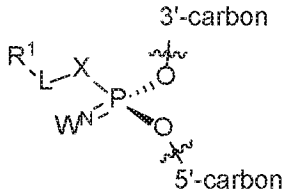
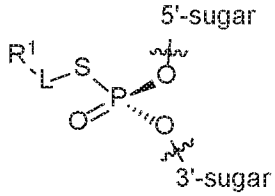


, or


, or a salt form thereof; each L^{PB} is independently an internucleotidic linkage having the structure of


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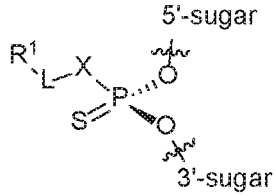

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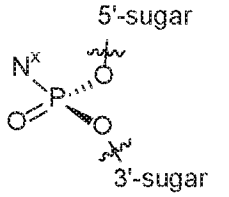

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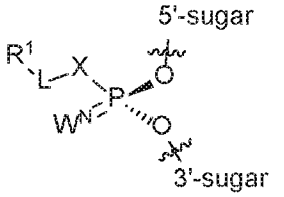
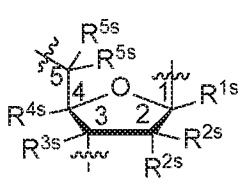
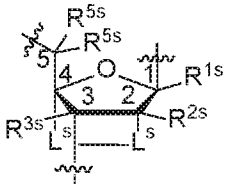
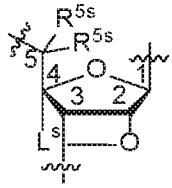
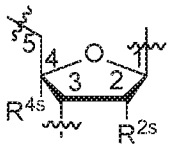
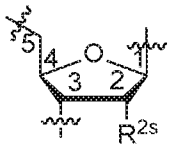


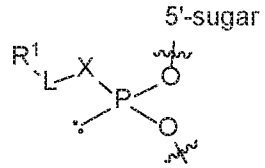
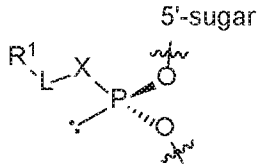
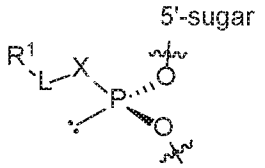
, or a salt form thereof. Example sugar structures are described herein, *e.g.*, in some embodiments, each sugar moiety independently has the structure of

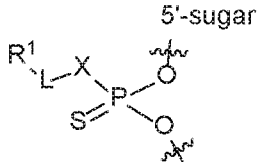
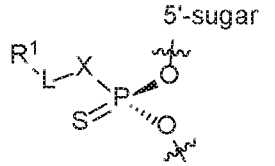
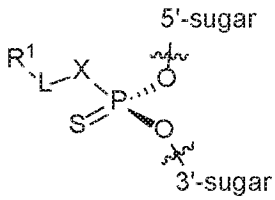
, , , , or , wherein each variable is independently as described in the present disclosure.

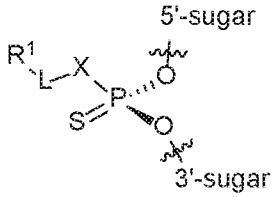
[00574] In some embodiments, L^{PO} has a pattern, location, number, percentage, *etc.* as described herein for a natural phosphate linkage. In some embodiments, L^{PA} has a pattern, location, number, percentage, *etc.* as described herein for a *Rp* internucleotidic linkage. In some embodiments, a *Rp* internucleotidic linkage is a *Rp* phosphorothioate internucleotidic linkage. In some embodiments, a *Rp* internucleotidic linkage is a *Rp* non-negatively charged internucleotidic linkage (e.g., n001). In some embodiments, L^{PB} has a pattern, location, number, percentage, *etc.* as described herein for a *Sp* internucleotidic linkage. In some embodiments, a *Sp* internucleotidic linkage is a *Sp* phosphorothioate internucleotidic linkage. In some embodiments, a *Sp* internucleotidic linkage is a *Sp* non-negatively charged internucleotidic linkage (e.g., n001).

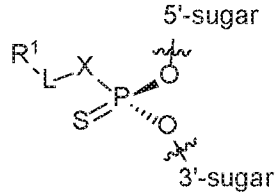
[00575] In some embodiments, the present disclosure provides an oligonucleotide, wherein the first internucleotidic linkage from the 5'-end is an internucleotidic linkage of O^{5P}, and each other internucleotidic linkage is independently selected from O^{P}, $*^{PD}$, $*^{PD}S$, $*^{PD}R$, $*^{N}$, $*^{N}S$ and $*^{N}R$, wherein:

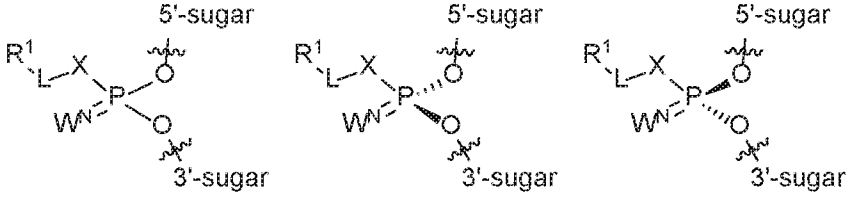
O^{5P} is  ,  ,  , L^{PO}, L^{PA}, L^{PB}, or a salt form thereof;

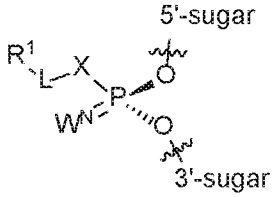
each O^{P} is independently L^{PO};

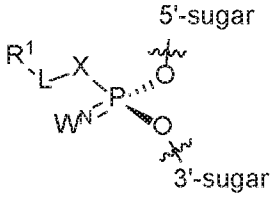
each $*^{PD}$ is independently  ,  ,  , or a salt form thereof;

each $^{*PD}S$ is independently  or a salt form thereof;

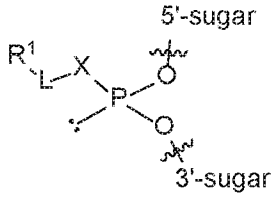
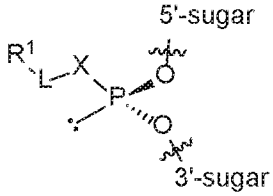
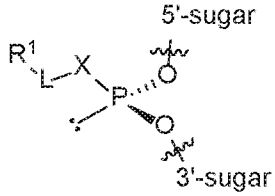
each $^{*PD}R$ is independently  or a salt form thereof;

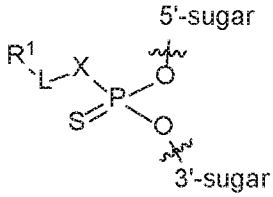
each ^{*N} is independently  , or a salt form thereof;

each $^{*N}S$ is independently  or a salt form thereof; and

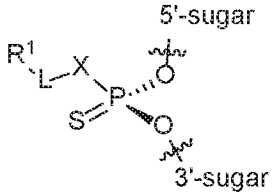
each $^{*N}R$ is independently  or a salt form thereof;

wherein each variable in independently as described herein, wherein $-X-L-R^1$ is not $-OH$.

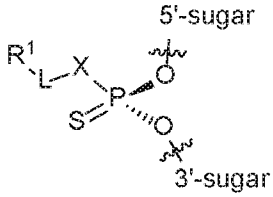
[00576] In some embodiments, O^{SP} is independently  ,  ,  , L^{PO}, L^{PA}, L^{PB}, or a salt form thereof. In some embodiments, each O^P is independently L^{PO}. In some embodiments, each ^{*PD} is independently



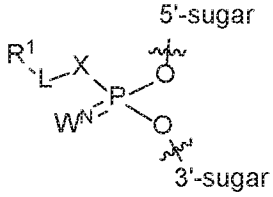
or a salt form thereof. In some embodiments, each ^{*PD}S is independently



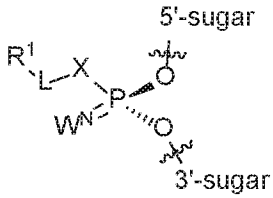
or a salt form thereof. In some embodiments, each ^{*PD}R is independently



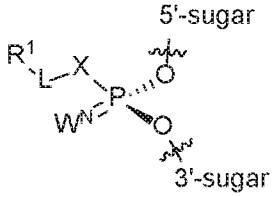
or a salt form thereof. In some embodiments, each ^{*N} is independently



or a salt form thereof. In some embodiments, each ^{*N}S is independently

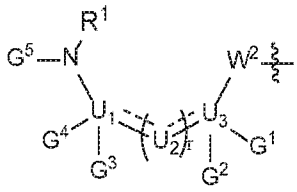
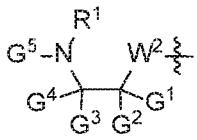
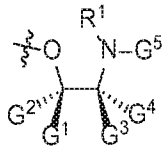
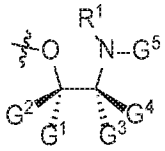
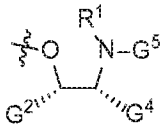
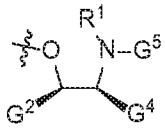
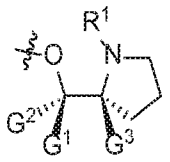
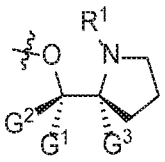
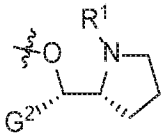
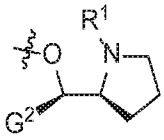
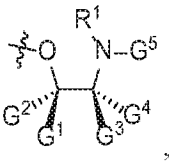
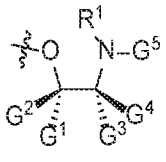
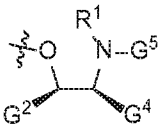
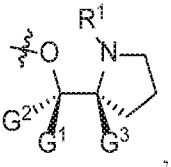
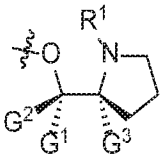
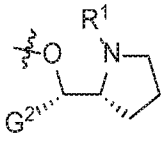
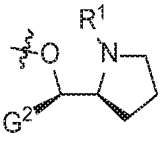


or a salt form thereof. In some embodiments, each ^{*N}R is independently



or a salt form thereof.

[00577] In some embodiments, X is −O−. In some embodiments, −L−R^1 contains an electron-withdrawing group. In some embodiments, −L−R^1 is $-CH_2G^2$, wherein the methylene unit is optionally substituted. In some embodiments, −L−R^1 is $-CH(R')G^2$. In some embodiments, G^2 does not comprise a chiral element, and G^2 comprises an electron-withdrawing group as described herein, *e.g.*, in some embodiments, G^2 is $-CH_2CN$ (*e.g.*, in O^{SP}, O^P, ^{*PD}, or ^{*N}, wherein linkage phosphorus is not chirally controlled). In some embodiments, G^2 comprises a chiral element, *e.g.*, wherein linkage phosphorus is chirally controlled. In some embodiments, −X−L−R^1 is of such a structure that H−X−L−R^1 is a chiral

reagent described herein, or a capped chiral reagent described herein wherein an amino group of the chiral reagent (typically of $-W^1-H$ or $-W^2-H$, which comprises an amino group $-NHG^5-$) is capped, e.g., with $-C(O)R'$ (replacing a $-H$, e.g., $-N[-C(O)R']G^5-$). In some embodiments, $-X-L-R^1$ is  ,  ,  ,  ,  ,  ,  ,  ,  , or  , wherein each variable is independently in accordance with the present disclosure. In some embodiments, $-X-L-R^1$ is  ,  ,  ,  ,  ,  , or  , wherein each variable is independently in accordance with the present disclosure. In some embodiments, R^1 is $-H$ or $-C(O)R'$. In some embodiments, wherein R^1 is $-H$, *e.g.*, in O^{5P}. In some embodiments, R^1 is $-C(O)R'$ (*e.g.*, in O^{5P}, O^P, $*^{PD}S$, $*^{PD}R$, $*^NS$, $*^NR$, *etc.*). In some embodiments, R^1 is $CH_3C(O)-$. In some embodiments, as described herein, G^2 is In some embodiments, G^2 is $-C(R)_2Si(R)_3$, wherein $-C(R)_2-$ is optionally substituted $-CH_2-$, and each R of $-Si(R)_3$ is independently an optionally substituted group selected from C_{1-10} aliphatic, heterocyclyl, heteroaryl and aryl. In some embodiments, G^2 is $-CH_2Si(Me)(Ph)_2$. In some embodiments, *e.g.*, in $*^{PD}S$, $*^{PD}R$, *etc.*, G^2 is $-CH_2Si(Me)(Ph)_2$. In some embodiments, G^2 comprises an electron-withdrawing group as described herein. In some embodiments, G^2 is $-C(R)_2SO_2R'$, wherein $-C(R)_2-$ is optionally substituted $-CH_2-$, and R' is an optionally substituted group selected from C_{1-10} aliphatic, heterocyclyl, heteroaryl and aryl. In some embodiments, R' is phenyl. In some embodiments, *e.g.*, in $*^NS$, $*^NR$, *etc.*, G^2 is $-CH_2SO_2Ph$.

[00578] In some embodiments, the present disclosure provides an oligonucleotide ("a first oligonucleotide"), which has an identical structure as an oligonucleotide described in a Table herein or an oligonucleotide described in *e.g.*, US 20150211006, US 20170037399, US 20180216107, US 20180216108, US 20190008986, WO 2017/015555, WO 2017/015575, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, WO 2017/210647, WO 2018/022473, WO

2018/067973, WO 2018/098264, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/032612, *etc.*, the oligonucleotide of each of which is incorporated herein by reference ("a second oligonucleotide"), which second oligonucleotide comprises modified internucleotidic linkages, except that compared to the second oligonucleotide, in the first oligonucleotide:

the first internucleotidic linkage from the 5'-end is an internucleotidic linkage of O^{5P}; and for the rest linkages:

at each location where there is a phosphate linkage in the second oligonucleotide, there is independently a linkage of O^{P} in the first oligonucleotide;

at each location where there is a stereorandom phosphorothioate linkages in the second oligonucleotide, there is independently a linkage of $*^{PD}$ in the first oligonucleotide;

at each location where there is a *Sp* phosphorothioate linkage in the second oligonucleotide, there is independently a linkage of $*^{PD}S$ in the first oligonucleotide;

at each location where there is a *Rp* phosphorothioate linkage in the second oligonucleotide, there is independently a linkage of $*^{PD}R$ in the first oligonucleotide;

at each location where there is a stereorandom non-negatively charged internucleotidic linkage in the second oligonucleotide, there is independently a linkage of $*^{N}$ in the first oligonucleotide;

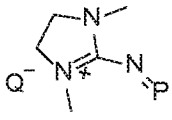
at each location where there is a *Sp* non-negatively charged internucleotidic linkage in the second oligonucleotide, there is independently a linkage of $*^{N}S$ in the first oligonucleotide;

at each location where there is a *Rp* non-negatively charged internucleotidic linkage in the second oligonucleotide, there is independently a linkage of $*^{N}R$ in the first oligonucleotide, and

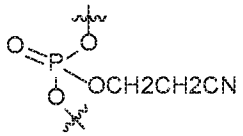
each nucleobase in the first oligonucleotide is optionally and independently protected (*e.g.*, as in oligonucleotide synthesis), and each additional chemical moiety, if any, in the first oligonucleotide is optionally and independently protected (*e.g.*, −OH in a carbohydrate moiety protected as −OAc).

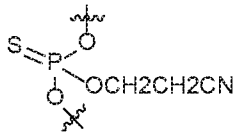
[00579] In some embodiments, at each location where there is a phosphate linkage in the second oligonucleotide, there is independently a linkage of O^{P} in the first oligonucleotide; at each location where there is a stereorandom phosphorothioate linkages in the second oligonucleotide, there is independently a linkage of $*^{PD}$ in the first oligonucleotide; at each location where there is a *Sp* phosphorothioate linkage in the second oligonucleotide, there is independently a linkage of $*^{PD}S$ in the first oligonucleotide; at each location there is a *Rp* phosphorothioate linkage in the second oligonucleotide, there is independently a linkage of $*^{PD}R$ in the first oligonucleotide; at each location there is a stereorandom non-negatively charged internucleotidic linkage in the second oligonucleotide, there is independently a linkage of $*^{N}$ in the first oligonucleotide; at each location there is a *Sp* non-negatively charged internucleotidic linkage in the second oligonucleotide, there is independently a linkage of $*^{N}S$ in the first oligonucleotide; at each

location there is a *Rp* non-negatively charged internucleotidic linkage in the second oligonucleotide, there is independently a linkage of $^{*N}R$ in the first oligonucleotide, and each nucleobase in the first oligonucleotide is optionally and independently protected (*e.g.*, as in oligonucleotide synthesis), and each additional chemical moiety, if any, in the first oligonucleotide is optionally and independently protected (*e.g.*, –OH in a carbohydrate moiety protected as –OAc); wherein each of O^{5P}, O^{P}, ^{*PD}, $^{*PD}S$, $^{*PD}R$, ^{*N}, $^{*N}S$ and $^{*N}R$ is independently as described herein. In some embodiments, such an oligonucleotide is linked to a support optionally through a linker, *e.g.*, a CNA linker to CPG. In some embodiments, as appreciated by those skilled in the art, after a removal process of $-X-L-R^1$, a linkage of O^{5P}, O^{P}, ^{*PD}, $^{*PD}S$, $^{*PD}R$, ^{*N}, $^{*N}S$ or $^{*N}R$ becomes a linkage it replaces. In some embodiments, such oligonucleotides (*e.g.*, first oligonucleotides) are useful intermediates for preparing their corresponding oligonucleotides (*e.g.*, second oligonucleotides). In some embodiments, the present disclosure provides chirally controlled oligonucleotide composition of a provided first oligonucleotide or a stereoisomer thereof.

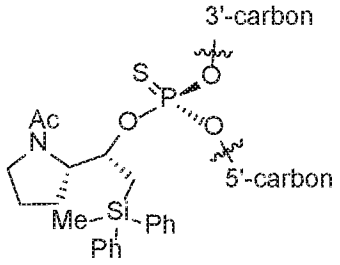
[00580] In some embodiments, as appreciated by those skilled in the art, W^N is of such a structure that its N-moiety has the same non-hydrogen atoms and connections of non-hydrogen atoms as the N-moiety of the non-negatively charged internucleotidic linkage it replaces (without considering single, double, or triple bond *etc.*). For example, in some embodiments, P^N in ^{*N} is  (such a ^{*N} is $n001^P$), and its corresponding non-negatively charged internucleotidic linkage is n001.

[00581] In some embodiments, a provided oligonucleotide has the same "Description" as an oligonucleotide listed in a Table herein (*e.g.*, Table A1), except that:

the oligonucleotide comprises at least one linkage of O^P, and/or at each location in the oligonucleotide where there is a phosphate linkage, there is independently a linkage of O^P, wherein O^P is  ;

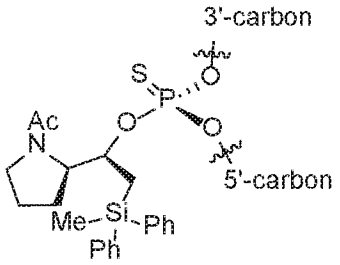
at each location where there is a stereorandom phosphorothioate linkages, there is independently a linkage of ^{*PD}, wherein ^{*PD} is  ;

at each location where there is a *Sp* phosphorothioate linkage, there is independently a linkage of



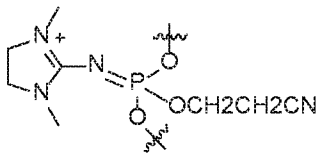
^{*PD}S, wherein ^{*PD}S is ;

at each location where there is a *Rp* phosphorothioate linkage, there is independently a linkage of



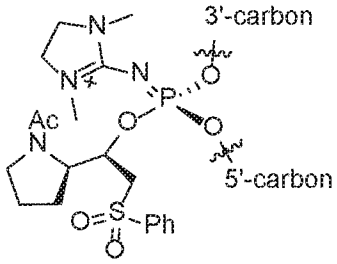
^{*PD}R, wherein ^{*PD}R is ;

at each location where there is a stereorandom n001, there is independently a linkage of ^{*N},



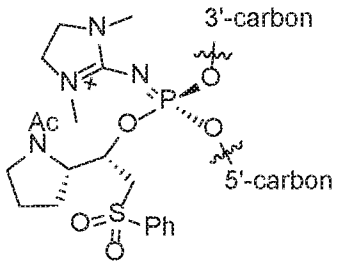
wherein ^{*N} is (as appreciated by those skilled in the art, it is associated with an anion (*e.g.*, Q^- such as PF_6^- (which can be an anion in a modification step)));

at each location where there is a *Sp* n001, there is independently a linkage of ^{*N}S, wherein ^{*N}S is



(as appreciated by those skilled in the art, it is associated with an anion (*e.g.*, Q^- such as PF_6^- (which can be an anion in a modification step))); and

at each location where there is a *Rp* n001, there is independently a linkage of ^{*N}R, wherein ^{*N}R is



(as appreciated by those skilled in the art, it is associated with an anion (*e.g.*, Q^- such as PF_6^- (which can be an anion in a modification step))); and

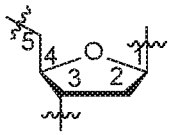
the oligonucleotide is optionally connected to a solid support, optionally through a linker. In some embodiments, the oligonucleotide is connected to a solid support, *e.g.*, CPG, polystyrene support, *etc.* In some embodiments, the oligonucleotide is connected to a solid support through a linker, *e.g.*, a CNA linker. In some embodiments, such an oligonucleotide is an oligonucleotide of formula O-I or a salt form thereof.

Certain Embodiments of Stereochemistry and Pattern of Backbone Chiral Centers

[00582] Among other things, the present disclosure provides oligonucleotides comprising one or more chirally controlled internucleotidic linkages. In some embodiments, the present disclosure provides chirally controlled oligonucleotide compositions. In some embodiments, each chiral linkage phosphorus of provided oligonucleotides is independently chirally controlled (stereocontrolled) (e.g., each independently having a stereopurity (diastereopurity) of at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% (e.g., as typically assessed using an appropriate dimer comprising an internucleotidic linkage containing the linkage phosphorus, and the two nucleoside units being linked by the internucleotidic linkage)). In some embodiments, a stereopurity is at least 90%. In some embodiments, a stereopurity is at least 95%. In some embodiments, a stereopurity is at least 96%. In some embodiments, a stereopurity is at least 97%. In some embodiments, a stereopurity is at least 98%. In some embodiments, a stereopurity is at least 99%. With the capability to fully control stereochemistry and other modifications (e.g., base modifications, sugar modifications, internucleotidic linkage modifications, etc.), the present disclosure provides technologies of improved properties and/or activities compared to corresponding non-chirally controlled technologies.

[00583] In some embodiments, pattern of backbone chiral centers of a region, particularly a core region or a middle region, or of an oligonucleotide (e.g., an oligonucleotide of a plurality of oligonucleotides) is or comprises (Np/Op)t[(Rp)n(Sp)m]y, (Np/Op)t[(Op)n(Sp)m]y, (Np/Op)t[(Op/Rp)n(Sp)m]y, (Sp)t[(Rp)n(Sp)m]y, (Sp)t[(Op)n(Sp)m]y, (Sp)t[(Op/Rp)n(Sp)m]y, [(Rp)n(Sp)m]y, [(Op)n(Sp)m]y, [(Op/Rp)n(Sp)m]y, (Rp)t(Np)n(Rp)m, (Rp)t(Sp)n(Rp)m, (Rp)t[(Np/Op)n]y(Rp)m, (Rp)t[(Sp/Np)n]y(Rp)m, (Rp)t[(Sp/Op)n]y(Rp)m, (Np/Op)t(Np)n(Np/Op)m, (Np/Op)t(Sp)n(Np/Op)m, (Np/Op)t[(Np/Op)n]y(Np/Op)m, (Np/Op)t[(Sp/Op)n]y(Np/Op)m, (Np/Op)t[(Sp/Op)n]y(Np/Op)m, (Rp/Op)t(Np)n(Rp/Op)m, (Rp/Op)t(Sp)n(Rp/Op)m, (Rp/Op)t[(Np/Op)n]y(Rp/Op)m, (Rp/Op)t[(Sp/Op)n]y(Rp/Op)m, or (Rp/Op)t[(Sp/Op)n]y(Rp/Op)m (unless otherwise specified, description of patterns of modifications and stereochemistry are from 5' to 3' as typically used in the art), wherein *S*p indicates *S* configuration of a chiral linkage phosphorus of a chiral modified internucleotidic linkage, *R*p indicates *R* configuration of a chiral linkage phosphorus of a chiral modified internucleotidic linkage, *O*p indicates an achiral linkage phosphorus of a natural phosphate linkage, each *N*p is independently *R*p, or *S*p, and each of m, n, t and y is independently 1-50 as

described in the present disclosure. In some embodiments, a pattern of backbone chiral centers is or comprises [(Rp/Op)n(Sp)m]y. In some embodiments, a pattern of backbone chiral centers is or comprises [(Rp)n(Sp)m]y. In some embodiments, a pattern of backbone chiral centers is or comprises [(Op)n(Sp)m]y. In some embodiments, a pattern of backbone chiral centers is or comprises (Np/Op)t[(Rp/Op)n(Sp)m]y. In some embodiments, a pattern of backbone chiral centers is or comprises (Np/Op)t[(Rp)n(Sp)m]y. In some embodiments, a pattern of backbone chiral centers is or comprises (Np/Op)t[(Op)n(Sp)m]y. In some embodiments, a pattern of backbone chiral centers is or comprises (Sp)t[(Rp/Op)n(Sp)m]y. In some embodiments, a pattern of backbone chiral centers is or comprises (Sp)t[(Rp)n(Sp)m]y. In some embodiments, a pattern of backbone chiral centers is or comprises (Sp)t[(Op)n(Sp)m]y. In some embodiments, a pattern of backbone chiral centers is or comprises (Rp)t(Np)n(Rp)m. In some embodiments, a pattern of backbone chiral centers is or comprises (Rp)t(Sp)n(Rp)m. In some embodiments, a pattern of backbone chiral centers is or comprises (Rp)t[(Np/Op)n]y(Rp)m. In some embodiments, a pattern of backbone chiral centers is or comprises (Rp)t[(Sp/Np)n]y(Rp)m. In some embodiments, a pattern of backbone chiral centers is or comprises (Rp)t[(Sp/Op)n]y(Rp)m. In some embodiments, a pattern of backbone chiral centers is or comprises (Np/Op)t(Np)n(Np/Op)m. In some embodiments, a pattern of backbone chiral centers is or comprises (Np/Op)t(Sp)n(Np/Op)m. In some embodiments, a pattern of backbone chiral centers is or comprises (Np/Op)t[(Np/Op)n]y(Np/Op)m. In some embodiments, a pattern of backbone chiral centers is or comprises (Np/Op)t[(Sp/Op)n]y(Np/Op)m. In some embodiments, a pattern of backbone chiral centers is or comprises (Np/Op)t[(Sp/Op)n]y(Np/Op)m. In some embodiments, a pattern of backbone chiral centers is or comprises (Rp/Op)t(Np)n(Rp/Op)m. In some embodiments, a pattern of backbone chiral centers is or comprises (Rp/Op)t(Sp)n(Rp/Op)m. In some embodiments, a pattern of backbone chiral centers is or comprises (Rp/Op)t[(Np/Op)n]y(Rp/Op)m. In some embodiments, a pattern of backbone chiral centers is or comprises (Rp/Op)t[(Sp/Op)n]y(Rp/Op)m. In some embodiments, a pattern of backbone chiral centers is or comprises (Rp)(Rp/Op)t[(Sp/Op)n]y(Rp/Op)m(Rp). In some embodiments, n is 1. For example, in some embodiments, a pattern of backbone chiral centers is or comprises (Sp)t[Op(Sp)m]y; in some embodiments, a pattern of backbone chiral centers is or comprises (Sp)t[Rp(Sp)m]y. In some embodiments, y is 1. In some embodiments, m is 2 or more. In some embodiments, t is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, n is 1, and m is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, t is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, n is 1, and m is 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, there are at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 internucleotidic linkages preceding, and there are at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 internucleotidic linkages after the Rp or Op. In some embodiments, there are at least 2 internucleotidic linkages preceding and/or following. In some embodiments, there are at least 3 internucleotidic linkages preceding and/or following. In some embodiments, there are at least 4 internucleotidic linkages preceding

and/or following. In some embodiments, there are at least 5 internucleotidic linkages preceding and/or following. In some embodiments, there are at least 6 internucleotidic linkages preceding and/or following. In some embodiments, there are at least 7 internucleotidic linkages preceding and/or following. In some embodiments, there are at least 8 internucleotidic linkages preceding and/or following. In some embodiments, there are at least 9 internucleotidic linkages preceding and/or following. In some embodiments, there are at least 10 internucleotidic linkages preceding and/or following. In some embodiments, y is 1. In some embodiments, y is 2 or more. In some embodiments, y is 2, 3, 4, or 5. In some embodiments, y is 2. In some embodiments, y is 3. In some embodiments, y is 4. In some embodiments, y is 5. In some embodiments, a region having such a pattern of backbone chiral centers contains no 2'-modifications on its sugar moieties, wherein the 2'-modification is 2'-OR^1 or 2'-O–L–, wherein R^1 is not hydrogen and L comprises a carbon atom and connects to another carbon atom of the sugar moiety. In some embodiments, each sugar moiety of a region having such a pattern of backbone chiral centers is independently a natural DNA sugar moiety (

. As appreciated by a person having ordinary skill in the art, for a natural DNA sugar moiety in natural DNA, C1 is connected to a base, C3 and C5 are each independently connected to internucleotidic linkages or –OH (when at the 5'- or 3'-end)). Certain benefits/advantages provided by such patterns of backbone chiral centers are described in US 20170037399, WO 2017/015555, and WO 2017/062862.

[00584] In some embodiments, y, t, n and m each are independently 1-20 as described in the present disclosure. In some embodiments, y is 1. In some embodiments, y is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, y is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, y is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, y is 1. In some embodiments, y is 2. In some embodiments, y is 3. In some embodiments, y is 4. In some embodiments, y is 5. In some embodiments, y is 6. In some embodiments, y is 7. In some embodiments, y is 8. In some embodiments, y is 9. In some embodiments, y is 10.

[00585] In some embodiments, n is 1. In some embodiments, n is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, n is 1-10. In some embodiments, n is 1, 2, 3, 4, 5, 6, 7 or 8. In some embodiments, n is 1. In some embodiments, n is 2, 3, 4, 5, 6, 7 or 8. In some embodiments, n is 3, 4, 5, 6, 7 or 8. In some embodiments, n is 4, 5, 6, 7 or 8. In some embodiments, n is 5, 6, 7 or 8. In some embodiments, n is 6, 7 or 8. In some embodiments, n is 7 or 8. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is 5. In some embodiments, n is 6. In some embodiments, n is 7. In some embodiments, n is 8. In some embodiments,

n is 9. In some embodiments, n is 10.

[00586] In some embodiments, m is 0-50. In some embodiments, m is 1-50. In some embodiments, m is 1. In some embodiments, m is 2-50. In some embodiments, m is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, m is 2, 3, 4, 5, 6, 7 or 8. In some embodiments, m is 3, 4, 5, 6, 7 or 8. In some embodiments, m is 4, 5, 6, 7 or 8. In some embodiments, m is 5, 6, 7 or 8. In some embodiments, m is 6, 7 or 8. In some embodiments, m is 7 or 8. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4. In some embodiments, m is 5. In some embodiments, m is 6. In some embodiments, m is 7. In some embodiments, m is 8. In some embodiments, m is 9. In some embodiments, m is 10. In some embodiments, m is 11. In some embodiments, m is 12. In some embodiments, m is 13. In some embodiments, m is 14. In some embodiments, m is 15. In some embodiments, m is 16. In some embodiments, m is 17. In some embodiments, m is 18. In some embodiments, m is 19. In some embodiments, m is 20. In some embodiments, m is 21. In some embodiments, m is 22. In some embodiments, m is 23. In some embodiments, m is 24. In some embodiments, m is 25. In some embodiments, m is at least 2. In some embodiments, m is at least 3. In some embodiments, m is at least 4. In some embodiments, m is at least 5. In some embodiments, m is at least 6. In some embodiments, m is at least 7. In some embodiments, m is at least 8. In some embodiments, m is at least 9. In some embodiments, m is at least 10. In some embodiments, m is at least 11. In some embodiments, m is at least 12. In some embodiments, m is at least 13. In some embodiments, m is at least 14. In some embodiments, m is at least 15. In some embodiments, m is at least 16. In some embodiments, m is at least 17. In some embodiments, m is at least 18. In some embodiments, m is at least 19. In some embodiments, m is at least 20. In some embodiments, m is at least 21. In some embodiments, m is at least 22. In some embodiments, m is at least 23. In some embodiments, m is at least 24. In some embodiments, m is at least 25. In some embodiments, m is at least greater than 25.

[00587] In some embodiments, t is 1-20. In some embodiments, t is 1. In some embodiments, t is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, t is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, t is 1-5. In some embodiments, t is 2. In some embodiments, t is 3. In some embodiments, t is 4. In some embodiments, t is 5. In some embodiments, t is 6. In some embodiments, t is 7. In some embodiments, t is 8. In some embodiments, t is 9. In some embodiments, t is 10. In some embodiments, t is 11. In some embodiments, t is 12. In some embodiments, t is 13. In some embodiments, t is 14. In some embodiments, t is 15. In some embodiments, t is 16. In some embodiments, t is 17. In some embodiments, t is 18. In some embodiments, t is 19. In some embodiments, t is 20.

[00588] In some embodiments, each of t and m is independently at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, each of t and m is independently at least 3. In some embodiments, each of t and m is independently at least 4. In some embodiments, each of t and m is independently at least 5. In some embodiments, each of t and m is independently at least 6. In some embodiments, each of t and m is independently at least 7. In some embodiments, each of t and m is independently at least 8. In some embodiments, each of t and m is independently at least 9. In some embodiments, each of t and m is independently at least 10.

[00589] In some embodiments, provided oligonucleotides comprises a block, e.g., a first block, a 5'-wing, etc., that has a pattern of backbone chiral centers of or comprising a t-section, e.g., (Sp)t, (Rp)t, (Np/Op)t, (Rp/Op)t, etc., a block, e.g., a second block, a core, etc., that has a pattern of backbone chiral centers of or comprising a y- or n-section, e.g., (Np)n, (Sp)n, [(Np/Op)n]y, [(Rp/Op)n]y, [(Sp/Op)n]y, etc., and a block, e.g., a third block, a 3'-wing, etc., that has a pattern of backbone chiral centers of or comprising a m-section, e.g., (Sp)m, (Rp)m, (Np/Op)m, (Rp/Op)m, etc.

[00590] In some embodiments, a t-, y-, n-, or m-section that comprises Np or Rp, e.g., (Rp)t, (Np/Op)t, (Rp/Op)t, (Np)n, [(Np/Op)n]y, [(Rp/Op)n]y, (Rp)m, (Np/Op)m, (Rp/Op)m, etc. independently comprises at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, or 95%, or 100% Rp. In some embodiments, a t- or m-section that comprises Np or Rp independently comprises at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, or 95%, or 100% Rp. In some embodiments, provided oligonucleotides comprise at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, or 95%, or 100% Rp. In some embodiments, a percentage is at least 10%. In some embodiments, a percentage is at least 20%. In some embodiments, a percentage is at least 30%. In some embodiments, a percentage is at least 40%. In some embodiments, a percentage is at least 50%. In some embodiments, a percentage is at least 60%. In some embodiments, a percentage is at least 70%. In some embodiments, a percentage is at least 75%. In some embodiments, a percentage is at least 80%. In some embodiments, a percentage is at least 85%. In some embodiments, a percentage is at least 90%. In some embodiments, a percentage is at least 95%. In some embodiments, a percentage is 100%.

[00591] In some embodiments, each sugar moiety bonded to a Rp or Op linkage phosphorus at 3' independently comprises a modification. In some embodiments, each sugar moiety bonded to a Rp or Op linkage phosphorus at 5' independently comprises a modification. In some embodiments, each sugar moiety bonded to a Rp linkage phosphorus at 3' independently comprises a modification. In some embodiments, each sugar moiety bonded to a Rp linkage phosphorus at 5' independently comprises a modification. In some embodiments, each sugar moiety bonded to an Op linkage phosphorus at 3' independently comprises a modification. In some embodiments, each sugar moiety bonded to an Op linkage phosphorus at 5' independently comprises a modification. In some embodiments, each sugar

moiety bonded to a Sp linkage phosphorus at 3' independently comprises a modification. In some embodiments, each sugar moiety bonded to a Sp linkage phosphorus at 5' independently comprises a modification. In some embodiments, each sugar moiety independently comprises a modification. In some embodiments, a modification is a 2'-modification. In some embodiments, a modification is 2'-OR, wherein R is not hydrogen. In some embodiments, a modification is 2'-OR, wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, a modification is 2'-OR, wherein R is substituted C_{1-6} alkyl. In some embodiments, a modification is 2'-OR, wherein R is optionally substituted C_{2-6} alkyl. In some embodiments, a modification is 2'-OR, wherein R is substituted C_{2-6} alkyl. In some embodiments, R is $-CH_2CH_2OMe$. In some embodiments, a modification is or comprises –L– connecting two sugar carbons, e.g., those found in LNA. In some embodiments, a modification is –L– connecting C2 and C4 of a sugar moiety. In some embodiments, L is $-CH_2-CH(R)-$, wherein R is as described in the present disclosure. In some embodiments, L is $-CH_2-CH(R)-$, wherein R is as described in the present disclosure and is not hydrogen. In some embodiments, L is $-CH_2-(R)-CH(R)-$, wherein R is as described in the present disclosure and is not hydrogen. In some embodiments, L is $-CH_2-(S)-CH(R)-$, wherein R is as described in the present disclosure and is not hydrogen. In some embodiments, a block, a wing, a core, or an oligonucleotide has sugar modifications as described in the present disclosure.

[00592] In some embodiments, a provided pattern of backbone chiral centers is or comprises (Rp/Sp)-(All Rp or All Sp)-(Rp/Sp), wherein each Rp/Sp is independently Rp or Sp. In some embodiments, a provided pattern of backbone chiral centers is or comprises (Rp)-(All Sp)-(Rp). In some embodiments, a provided pattern of backbone chiral centers is or comprises (Sp)-(All Sp)-(Sp). In some embodiments, a provided pattern of backbone chiral centers is or comprises (Sp)-(All Rp)-(Sp). In some embodiments, a provided pattern of backbone chiral centers is or comprises (Rp/Sp)-(repeating (Sp)m(Rp)n)-(Rp/Sp). In some embodiments, a provided pattern of backbone chiral centers is or comprises (Rp/Sp)-(repeating SpSpRp)-(Rp/Sp).

Blocks

[00593] In some embodiments, provided oligonucleotides comprise one or more blocks, characterized by base modifications, sugar modifications, types of internucleotidic linkages, stereochemistry of linkage phosphorus, etc. In some embodiments, provided oligonucleotides comprises or are of a 5'-first block-second block-third block-3' structure. In some embodiments, a first block is a 5'-wing. In some embodiments, a first block is 5'-end region. In some embodiments, a second block is a core. In some embodiments, a second block is a middle region between a 5'-end and a 3'-end region. In some embodiments, a third block a 3'-wing. In some embodiments, a third block is a 3'-end region. Each of a 5'-wing, 5'-end region, core, middle region, 3'-wing, and 3'-end region can independently be a

block.

[00594] In some embodiments, provided oligonucleotides comprises or are of a 5'-wing-core-wing-3', 5'-wing-core-3' or 5'-core-wing-3' structures. In some embodiments, a first block, a second block, a third block, a wing (e.g., a 5'-wing, a 3'-wing) and/or a core of provided oligonucleotides are each independently a block or comprise one or more blocks as described in the present disclosure.

[00595] Various blocks, 5'-wings, 3'-wings and cores can be utilized in accordance with the present disclosure, including those described in US 20150211006, US 20150211006, WO 2017015555, WO 2017015575, WO 2017062862, WO 2017160741, blocks, 5'-wings, 3'-wings and cores of each of which are incorporated herein by reference.

[00596] In some embodiments, a block is a linkage phosphorus stereochemistry block. For example, in some embodiments, a block comprises only Rp, Sp, or Op linkage phosphorus. In some embodiments, a block is a Rp block comprising only Rp linkage phosphorus. In some embodiments, a block is a Rp/Op block comprising only Rp/Op linkage phosphorus. In some embodiments, a block is a Sp/Op block comprising only Sp/Op linkage phosphorus. In some embodiments, a block is an Op block. In some embodiments, an oligonucleotide, or a region thereof (a first block, a second block, a third block, a wing, a core, etc.) comprises one or more of a Rp block, a Sp block and/or an Op block. In some embodiments, a block comprises one or more, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more, linkage phosphorus.

[00597] In some embodiments, a block is a sugar modification block. In some embodiments, a block is a 2'-modification block wherein each sugar moiety of the block independently comprises the 2'-modification. In some embodiments, a 2'-modification is 2'-OR wherein R is as described in the present disclosure. In some embodiments, a 2'-modification is a 2'-OR wherein R is not hydrogen. In some embodiments, a 2'-modification is 2'-OMe. In some embodiments, a 2'-modification is 2'-MOE. In some embodiments, a modification is a LNA modification. In some embodiments, an oligonucleotide, or a region thereof (a first block, a second block, a third block, a wing, a core, etc.) comprises one or more sugar modification blocks, each independently of its own sugar modification. In some embodiments, a block comprises one or more, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more, sugar moieties.

[00598] As illustrated herein, a block can be of various lengths. In some embodiments, a block is of 1-30, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleobases in length. In some embodiments, a 5'-first block-second-block-third block-3', or a 5'-wing-core-wing-3' is of 5-10-5, 3-10-4, 3-10-6, 4-12-4, etc.

[00599] In some embodiments, an oligonucleotide or a block or region thereof (e.g., a 5'-end region, a 5'-wing, a middle region, a core region, a 3'-end region, a 3'-ring, etc.) comprises one or more,

e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more, non-negatively charged internucleotidic linkages as described in the present disclosure. In some embodiments, a provided oligonucleotide comprises two or more, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more, consecutive non-negatively charged internucleotidic linkages. In some embodiments, a block or region comprises two or more, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more, consecutive non-negatively charged internucleotidic linkages. In some embodiments, the number is 1. In some embodiments, the number is 2. In some embodiments, the number is 3. In some embodiments, the number is 4. In some embodiments, the number is 5. In some embodiments, the number is 6. In some embodiments, the number is 7. In some embodiments, the number is 8. In some embodiments, the number is 9. In some embodiments, the number is 10 or more. In some embodiments, each internucleotidic linkage between nucleoside units in a block, e.g., a 5'-end region, a 5'-wing, is a non-negatively charged internucleotidic linkage except the first internucleotidic linkage between two nucleoside units of the block from the 5'-end of the block. In some embodiments, each internucleotidic linkage between nucleoside units in a block, e.g., a 3'-end region, a 3'-wing, is a non-negatively charged internucleotidic linkage except the first internucleotidic linkage between two nucleoside units of the block from the 3'-end of the block. In some embodiments, each internucleotidic linkage between nucleoside units in a region, e.g., a 5'-end region, a 5'-wing, is a non-negatively charged internucleotidic linkage except the first internucleotidic linkage between two nucleoside units of the region from the 5'-end of the region. In some embodiments, each internucleotidic linkage between nucleoside units in a region, e.g., a 3'-end region, a 3'-wing, is a non-negatively charged internucleotidic linkage except the first internucleotidic linkage between two nucleoside units of the region from the 3'-end of the region. In some embodiments, each internucleotidic linkage in a region or block, e.g., a 5'-end region, a 5'-wing, a middle region, a core region, a 3'-end region, a 3'-ring, etc., is independently a non-negatively charged internucleotidic linkage, a natural phosphate internucleotidic linkage or a *Rp* chiral internucleotidic linkage. In some embodiments, each internucleotidic linkage in a region or block is independently a non-negatively charged internucleotidic linkage, a natural phosphate internucleotidic linkage or a *Rp* phosphorothioate internucleotidic linkage. In some embodiments, about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more of internucleotidic linkages of an oligonucleotide or a region or block, e.g., a 5'-end region, a 5'-wing, a middle region, a core region, a 3'-end region, a 3'-ring, etc., is independently a non-negatively charged internucleotidic linkage, a natural phosphate internucleotidic linkage or a *Rp* chiral internucleotidic linkage. In some embodiments, about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more of internucleotidic linkages of an oligonucleotide or a region or block is independently a non-negatively charged internucleotidic linkage, a natural phosphate internucleotidic linkage or a *Rp* phosphorothioate internucleotidic linkage. In some

embodiments, about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more of internucleotidic linkages of an oligonucleotide or a region or block is independently a non-negatively charged internucleotidic linkage or a natural phosphate internucleotidic linkage. In some embodiments, about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more of internucleotidic linkages of an oligonucleotide or a region or block is independently a non-negatively charged internucleotidic linkage. In some embodiments, the percentage is 45% or more. In some embodiments, the percentage is 50% or more. In some embodiments, the percentage is 60% or more. In some embodiments, the percentage is 70% or more. In some embodiments, the percentage is 80% or more. In some embodiments, the percentage is 90% or more. In some embodiments, a region or block is a wing. In some embodiments, a region or block is a 5'-wing. In some embodiments, a region or block is a 3'-wing. In some embodiments, a region or block is a core. As described herein, a region or block, e.g., a wing, a core, etc., can have various lengths, e.g., comprising 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more nucleobases. In some embodiments, each nucleobase is independently optionally substituted A, T, C, G, U or an optionally substituted tautomer of A, T, C, G, or U.

Length

[00600] As described in the present disclosure, provided oligonucleotides can be of various lengths, e.g., 2-200, 10-15, 10-25, 15-20, 15-25, 15-40, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 50, 60, 70, 80, 90, 100, 150, nucleobases in length, wherein each nucleobase is independently optionally substituted A, T, C, G, or U, or an optionally substituted tautomer of A, T, C, G, or U. In some embodiments, provided oligonucleotides, e.g., oligonucleotide of a plurality in chirally controlled oligonucleotide compositions, are 15 nucleobases in length. In some embodiments, provided oligonucleotides are 16 nucleobases in length. In some embodiments, provided oligonucleotides are 17 nucleobases in length. In some embodiments, provided oligonucleotides are 18 nucleobases in length. In some embodiments, provided oligonucleotides are 19 nucleobases in length. In some embodiments, provided oligonucleotides are 20 nucleobases in length. In some embodiments, provided oligonucleotides are 21 nucleobases in length. In some embodiments, provided oligonucleotides are 22 nucleobases in length. In some embodiments, provided oligonucleotides are 23 nucleobases in length. In some embodiments, provided oligonucleotides are 24 nucleobases in length. In some embodiments, provided oligonucleotides are 25 nucleobases in length.

[00601] As described in the present disclosure, provided oligonucleotides, oligonucleotides of a plurality in chirally controlled oligonucleotide compositions, may comprise various modifications, e.g., base modifications, sugar modifications, internucleotidic linkage modifications, etc. In some

embodiments, the oligonucleotide composition comprises at least one modified nucleotide, at least one modified sugar moiety, at least one morpholino moiety, at least one 2'-deoxy ribonucleotide, at least one locked nucleotide, and/or at least one bicyclic nucleotide.

Nucleobases

[00602] In some embodiments, a nucleobase is a natural nucleobase. In some embodiments, a nucleobase is a modified nucleobase (non-natural nucleobase). In some embodiments, a nucleobase, e.g., BA, in provided oligonucleotides is a natural nucleobase (*e.g.*, adenine, cytosine, guanosine, thymine, or uracil) or a modified nucleobase derived from a natural nucleobase, *e.g.*, optionally substituted adenine, cytosine, guanosine, thymine, or uracil, or tautomeric forms thereof. Examples include, but are not limited to, uracil, thymine, adenine, cytosine, and guanine, and tautomeric forms thereof, having their respective amino groups protected by protecting groups, *e.g.*, one or more of −R, −C(O)R, *etc.* Example protecting groups, including those useful for oligonucleotide synthesis, are widely known in the art and can be utilized in accordance with the present disclosure. In some embodiments, a protected nucleobase and/or derivative is selected from nucleobases with one or more acyl protecting groups, 2-fluorouracil, 2-fluorocytosine, 5-bromouracil, 5-iodouracil, 2,6-diaminopurine, azacytosine, pyrimidine analogs such as pseudoisocytosine and pseudouracil and other modified nucleobases such as 8-substituted purines, xanthine, or hypoxanthine (the latter two being the natural degradation products). Example modified nucleobases are also disclosed in Chiu and Rana, *RNA*, **2003**, *9*, 1034-1048, Limbach *et al. Nucleic Acids Research*, **1994**, *22*, 2183-2196 and Revankar and Rao, *Comprehensive Natural Products Chemistry*, vol. 7, 313. In some embodiments, a modified nucleobase is substituted uracil, thymine, adenine, cytosine, or guanine. In some embodiments, a modified nucleobase is a functional replacement, *e.g.*, in terms of hydrogen bonding and/or base pairing, of uracil, thymine, adenine, cytosine, or guanine. In some embodiments, a nucleobase is optionally substituted uracil, thymine, adenine, cytosine, 5-methylcytosine, or guanine. In some embodiments, a nucleobase is uracil, thymine, adenine, cytosine, 5-methylcytosine, or guanine.

[00603] In some embodiments, a modified base is optionally substituted adenine, cytosine, guanine, thymine, or uracil. In some embodiments, a modified nucleobase is independently adenine, cytosine, guanine, thymine or uracil, modified by one or more modifications by which:

(1) a nucleobase is modified by one or more optionally substituted groups independently selected from acyl, halogen, amino, azide, alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, heteroaryl, carboxyl, hydroxyl, biotin, avidin, streptavidin, substituted silyl, and combinations thereof;

(2) one or more atoms of a nucleobase are independently replaced with a different atom selected

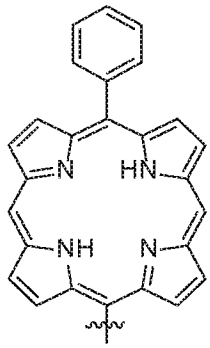
from carbon, nitrogen or sulfur;

(3) one or more double bonds in a nucleobase are independently hydrogenated; or

(4) one or more optionally substituted aryl or heteroaryl rings are independently inserted into a nucleobase.

[00604] Modified nucleobases also include expanded-size nucleobases in which one or more aryl rings, such as phenyl rings, have been added. Nucleic base replacements described in the Glen Research catalog (available at the Glen Research website); Krueger AT *et al*, *Acc. Chem. Res.*, 2007, *40*, 141-150; Kool, ET, *Acc. Chem. Res.*, 2002, *35*, 936-943; Benner S.A., *et al.*, *Nat. Rev. Genet.*, 2005, *6*, 553-543; Romesberg, F.E., *et al.*, *Curr. Opin. Chem. Biol.*, 2003, *7*, 723-733; Hirao, I., *Curr. Opin. Chem. Biol.*, 2006, *10*, 622-627, are contemplated as useful for oligonucleotides of the present disclosure.

[00605] In some embodiments, modified nucleobases include structures such as, but not limited to, corrin- or porphyrin-derived rings. Porphyrin-derived base replacements have been described in Morales-Rojas, H and Kool, ET, *Org. Lett.*, 2002, *4*, 4377-4380. Shown below is an example of a porphyrin-derived ring which can be used as a nucleobase replacement:



[00606] In some embodiments, a modified nucleobase is fluorescent. Examples of such fluorescent modified nucleobases include phenanthrene, pyrene, stillbene, isoxanthine, isozanthopterin, terphenyl, terthiophene, benzoterthiophene, coumarin, lumazine, tethered stillbene, benzo-uracil, and naphtho-uracil.

[00607] In some embodiments, a modified nucleobase is a universal base or a degenerate base, e.g., 3-nitropyrrole, 5'-nitroindole, P, K, etc.

[00608] In some embodiments, other nucleosides can also be used in technologies disclosed in the present disclosure and include nucleosides that incorporate modified nucleobases, or nucleobases covalently bound to modified sugars. Some examples of nucleosides that incorporate modified nucleobases include 4-acetylcytidine; 5-(carboxyhydroxylmethyl)uridine; 2′ -*O*-methylcytidine; 5-carboxymethylaminomethyl-2-thiouridine; 5-carboxymethylaminomethyluridine; dihydrouridine; 2′ -*O*-methylpseudouridine; beta,D-galactosylqueosine; 2′ -*O*-methylguanosine; N^6-isopentenyladenosine; 1-

methyladenosine; 1-methylpseudouridine; 1-methylguanosine; 1-methylinosine; 2,2-dimethylguanosine; 2-methyladenosine; 2-methylguanosine; N^7-methylguanosine; 3-methyl-cytidine; 5-methylcytidine; 5-hydroxymethylcytidine; 5-formylcytosine; 5-carboxylcytosine; N^6-methyladenosine; 7-methylguanosine; 5-methylaminoethyluridine; 5-methoxyaminomethyl-2-thiouridine; beta,D-mannosylqueosine; 5-methoxycarbonylmethyluridine; 5-methoxyuridine; 2-methylthio-N^6-isopentenyladenosine; *N*-((9-beta,D-ribofuranosyl-2-methylthiopurine-6-yl)carbamoyl)threonine; *N*-((9-beta,D-ribofuranosylpurine-6-yl)-*N*-methylcarbamoyl)threonine; uridine-5-oxyacetic acid methylester; uridine-5-oxyacetic acid (v); pseudouridine; queosine; 2-thiocytidine; 5-methyl-2-thiouridine; 2-thiouridine; 4-thiouridine; 5-methyluridine; 2′ -*O*-methyl-5-methyluridine; and 2′ -*O*-methyluridine.

[00609] In some embodiments, a nucleobase is optionally substituted A, T, C, G or U, wherein one or more $-NH_2$ are independently and optionally replaced with $-C(-L-R^1)_3$, one or more $-NH-$ are independently and optionally replaced with $-C(-L-R^1)_2-$, one or more $=N-$ are independently and optionally replaced with $-C(-L-R^1)-$, one or more $=CH-$ are independently and optionally replaced with $=N-$, and one or more $=O$ are independently and optionally replaced with $=S$, $=N(-L-R^1)$, or $=C(-L-R^1)_2$, wherein two or more $-L-R^1$ are optionally taken together with their intervening atoms to form a 3-30 membered bicyclic or polycyclic ring having 0-10 heteroatom ring atoms. In some embodiments, a modified nucleobase is optionally substituted A, T, C, G or U, wherein one or more $-NH_2$ are independently and optionally replaced with $-C(-L-R^1)_3$, one or more $-NH-$ are independently and optionally replaced with $-C(-L-R^1)_2-$, one or more $=N-$ are independently and optionally replaced with $-C(-L-R^1)-$, one or more $=CH-$ are independently and optionally replaced with $=N-$, and one or more $=O$ are independently and optionally replaced with $=S$, $=N(-L-R^1)$, or $=C(-L-R^1)_2$, wherein two or more $-L-R^1$ are optionally taken together with their intervening atoms to form a 3-30 membered bicyclic or polycyclic ring having 0-10 heteroatom ring atoms, wherein the modified base is different than the natural A, T, C, G and U. In some embodiments, a nucleobase is optionally substituted A, T, C, G or U. In some embodiments, a modified base is substituted A, T, C, G or U, wherein the modified base is different than the natural A, T, C, G and U.

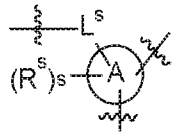
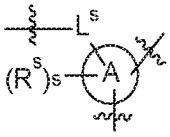
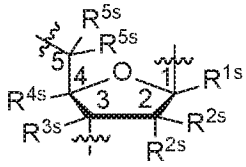
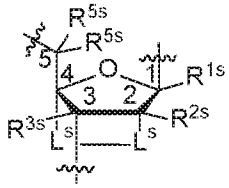
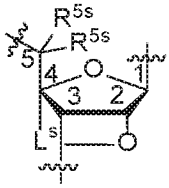
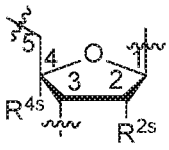
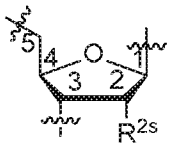
[00610] In some embodiments, a modified nucleobase may be optionally substituted. In some embodiments, a modified nucleobase contains one or more, *e.g.*, heteroatoms, alkyl groups, or linking moieties connected to fluorescent moieties, biotin or avidin moieties, or other proteins or peptides. In some embodiments, a nucleobase or modified nucleobase comprises or is conjugated with one or more biomolecule binding moieties such as *e.g.*, antibodies, antibody fragments, biotin, avidin, streptavidin, receptor ligands, or chelating moieties. In some embodiments, a modified nucleobase is modified by substitution with a fluorescent or biomolecule binding moiety. In some embodiments, a substituent on a nucleobase or modified nucleobase is a fluorescent moiety. In some embodiments, a substituent on a

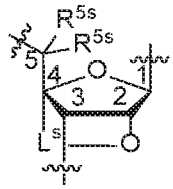
nucleobase or modified nucleobase is biotin or avidin.

[00611] Example nucleobases are also described in US 20110294124, US 20120316224, US 20140194610, US 20150211006, US 20150197540, WO 2015107425, WO/2017/015555, WO/2017/015575, and WO/2017/062862, the nucleobases of each of which is incorporated herein by reference.

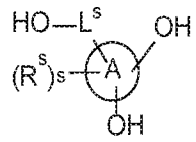
Sugars

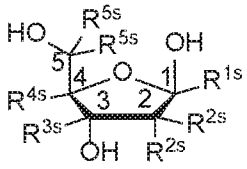
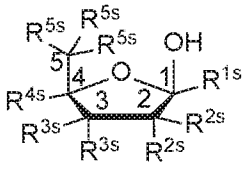
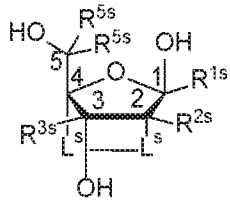
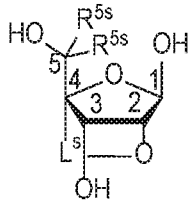
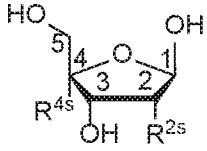
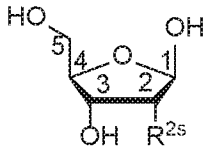
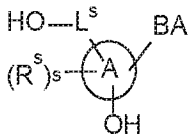
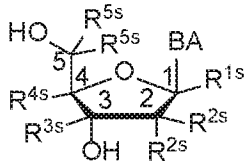
[00612] In some embodiments, oligonucleotides comprise one or more modified sugar moieties beside the natural sugar moieties. In some embodiments, a sugar is a natural sugar. In some embodiments, a sugar is a modified sugar (non-natural sugar). The most common naturally occurring nucleotides are comprised of ribose sugars linked to the nucleobases adenosine (A), cytosine (C), guanine (G), and thymine (T) or uracil (U). Also included in the present disclosure are modified nucleotides wherein an internucleotidic linkage is linked to various positions of a sugar or modified sugar. As non-limiting examples, an internucleotidic linkage can be linked to the 2′, 3′, 4′ or 5′ position of a sugar.

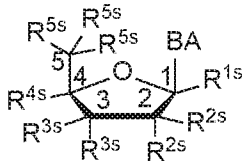
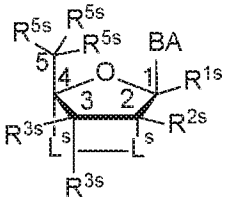
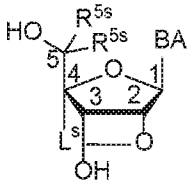
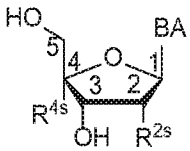
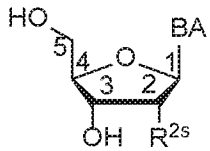
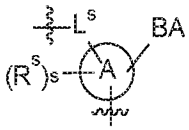
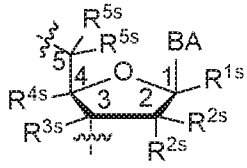
[00613] In some embodiments, a sugar moiety is  , wherein each variable is independently as described in the present disclosure. In some embodiments, a sugar moiety is  , wherein L^s is $-C(R^{5s})_2-$, wherein each R^{5s} is independently as described in the present disclosure. In some embodiments, a sugar moiety has the structure of  ,  ,  ,  , or  , wherein each variable is independently as described in the present disclosure. In some embodiments, a sugar moiety has the

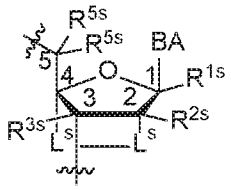
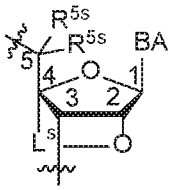
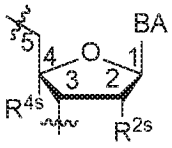
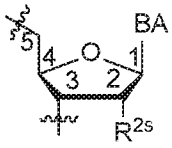


structure of , wherein each variable is independently as described in the present disclosure.

In some embodiments, a sugar has or is derived from the structure of  ,

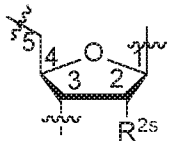
 ,  ,  ,  ,  , or  , wherein each variable is independently as described in the present disclosure. In some embodiments, a nucleoside has the structure of  ,  ,

 ,  ,  ,  , or  , wherein each variable is independently as described in the present disclosure. In some embodiments, a nucleoside moiety has or comprises the structure of  ,  ,

 ,  ,  , or  , wherein each variable is independently as described in the present disclosure. In some embodiments, L^s is −CH(R)−, wherein R is

as described in the present disclosure. In some embodiments, R is –H. In some embodiments, R is not –H, and L^s is –(R)–CH(R)–. In some embodiments, R is not –H, and L^s is –(S)–CH(R)–. In some embodiments, R, as described in the present disclosure, is optionally substituted C_{1-6} alkyl. In some embodiments, R is methyl.

[00614] Various types of sugar modifications are known and can be utilized in accordance with the present disclosure. In some embodiments, a sugar modification is a 2'-modification (e.g. R^{2s} (*e.g.*, in



)). In some embodiments, a 2'-modification is 2'-F. In some embodiments, a 2'-modification is 2'-OR, wherein R is not hydrogen. In some embodiments, a 2'-modification is 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a 2'-modification is 2'-OR, wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, a 2'-modification is 2'-OMe. In some embodiments, a 2'-modification is 2'-MOE. In some embodiments, a 2'-modification is a LNA sugar modification (C2–O–CH_2–C4). In some embodiments, a 2'-modification is (C2–O–$C(R)_2$–C4), wherein each R is independently as described in the present disclosure. In some embodiments, a 2'-modification is (C2–O–CHR–C4), wherein R is as described in the present disclosure. In some embodiments, a 2'-modification is (C2–O–(*R*)-CHR–C4), wherein R is as described in the present disclosure and is not hydrogen. In some embodiments, a 2'-modification is (C2–O–(*S*)-CHR–C4), wherein R is as described in the present disclosure and is not hydrogen. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is unsubstituted C_{1-6} alkyl. In some embodiments, R is methyl. In some embodiments, R is ethyl. In some embodiments, a 2'-modification is (C2–O–CHR–C4), wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a 2'-modification is (C2–O–CHR–C4), wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, a 2'-modification is (C2–O–CHR–C4), wherein R is methyl. In some embodiments, a 2'-modification is (C2–O–CHR–C4), wherein R is ethyl. In some embodiments, a 2'-modification is (C2–O–(*R*)-CHR–C4), wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a 2'-modification is (C2–O–(*R*)-CHR–C4), wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, a 2'-modification is (C2–O–(*R*)-CHR–C4), wherein R is methyl. In some embodiments, a 2'-modification is (C2–O–(*R*)-CHR–C4), wherein R is ethyl. In some embodiments, a 2'-modification is (C2–O–(*S*)-CHR–C4), wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a 2'-modification is (C2–O–(*S*)-CHR–C4), wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, a 2'-modification is (C2–O–(*S*)-CHR–C4), wherein R is methyl. In some embodiments, a 2'-modification is (C2–O–(*S*)-CHR–C4),

wherein R is ethyl. In some embodiments, a 2'-modification is C2–O–(*R*)-CH(CH_2CH_3)–C4. In some embodiments, a 2'-modification is C2–O–(*S*)-CH(CH_2CH_3)–C4. In some embodiments, a sugar moiety is a natural DNA sugar moiety. In some embodiments, a sugar moiety is a natural DNA sugar moiety modified at 2' (2'-modification). In some embodiments, a sugar moiety is an optionally substituted natural DNA sugar moiety. In some embodiments, a sugar moiety is an 2'-substituted natural DNA sugar moiety.

[00615] Many modified sugars can be incorporated within oligonucleotides of the present disclosure. In some embodiments, a modified sugar contains one or more substituents at the 2′ position including one of the following: –F; $–CF_3$, –CN, $–N_3$, –NO, $–NO_2$, –OR', –SR', or $–N(R')_2$, wherein each R' is independently as described in the present disclosure; –O–(C_1–C_{10} alkyl), –S–(C_1–C_{10} alkyl), –NH–(C_1–C_{10} alkyl), or –N(C_1–C_{10} alkyl)$_2$; –O–(C_2–C_{10} alkenyl), –S–(C_2–C_{10} alkenyl), –NH–(C_2–C_{10} alkenyl), or –N(C_2–C_{10} alkenyl)$_2$; –O–(C_2–C_{10} alkynyl), –S–(C_2–C_{10} alkynyl), –NH–(C_2–C_{10} alkynyl), or –N(C_2–C_{10} alkynyl)$_2$; or –O—(C_1–C_{10} alkylene)–O—(C_1–C_{10} alkyl), –O–(C_1–C_{10} alkylene)–NH–(C_1–C_{10} alkyl) or –O–(C_1–C_{10} alkylene)–NH(C_1–C_{10} alkyl)$_2$, –NH–(C_1–C_{10} alkylene)–O–(C_1–C_{10} alkyl), or –N(C_1–C_{10} alkyl)–(C_1–C_{10} alkylene)–O–(C_1–C_{10} alkyl), wherein the alkyl, alkylene, alkenyl and alkynyl may be substituted or unsubstituted. Examples of substituents include, and are not limited to, $–O(CH_2)_nOCH_3$, and $–O(CH_2)_nNH_2$, wherein n is from 1 to about 10, MOE, DMAOE, and DMAEOE. Certain modified sugars are described in WO 2001/088198, WO/2017/062862, and Martin *et al.*, *Helv. Chim. Acta*, 1995, *78*, 486-504. In some embodiments, a modified sugar comprises one or more groups selected from a substituted silyl group, an RNA cleaving group, a reporter group, a fluorescent label, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, a group for improving the pharmacodynamic properties of an oligonucleotide, or other substituents having similar properties. In some embodiments, modifications are made at one or more of the the 2′, 3′, 4′, 5′, or 6′ positions of a sugar, including the 3′ position of a sugar on the 3′-terminal nucleoside or in the 5′ position of the 5′-terminal nucleoside. In some embodiments, a RNA comprises a sugar which has, at the 2' position, a 2'-OH, or 2'-OR^1, wherein OR^1 is optionally substituted alkyl, including 2'-OMe.

[00616] In some embodiments, a 2'-modification is 2'-F.

[00617] In some embodiments, the 2'-OH of a ribose is replaced with a substituent (e.g., R^{2s}) including one of the following: –H, –F; $–CF_3$, –CN, $–N_3$, –NO, $–NO_2$, –OR', –SR', or $–N(R')_2$, wherein each R' is independently as defined above and described herein; –O–(C_1–C_{10} alkyl), –S–(C_1–C_{10} alkyl), –NH–(C_1–C_{10} alkyl), or –N(C_1–C_{10} alkyl)$_2$; –O–(C_2–C_{10} alkenyl), –S–(C_2–C_{10} alkenyl), –NH–(C_2–C_{10} alkenyl), or –N(C_2–C_{10} alkenyl)$_2$; –O–(C_2–C_{10} alkynyl), –S–(C_2–C_{10} alkynyl), –NH–(C_2–C_{10} alkynyl), or –N(C_2–C_{10} alkynyl)$_2$; or –O—(C_1–C_{10} alkylene)–O—(C_1–C_{10} alkyl), –O–(C_1–C_{10} alkylene)–NH–(C_1–C_{10}

alkyl) or –O–(C_1–C_{10} alkylene)–NH(C_1–C_{10} alkyl)$_2$, –NH–(C_1–C_{10} alkylene)–O–(C_1–C_{10} alkyl), or –N(C_1–C_{10} alkyl)–(C_1–C_{10} alkylene)–O–(C_1–C_{10} alkyl), wherein the alkyl, alkylene, alkenyl and alkynyl may be substituted or unsubstituted. In some embodiments, the 2'–OH is replaced with –H (deoxyribose). In some embodiments, the 2'–OH is replaced with –F. In some embodiments, the 2'–OH is replaced with –OR'. In some embodiments, the 2'–OH is replaced with –OMe. In some embodiments, the 2'–OH is replaced with –OCH_2CH_2OMe.

[00618] In some embodiments, a modified sugars is a sugar in locked nucleic acids (LNAs). In some embodiments, two substituents on sugar carbon atoms are taken together to form a bivalent moiety. In some embodiments, two substituents are on two different sugar carbon atoms. In some embodiments, a formed bivalent moiety has the structure of –L– as defined herein. In some embodiments, –L– is –O–CH_2–, wherein –CH_2– is optionally substituted. In some embodiments, –L– is –O–CH_2–. In some embodiments, –L– is –O–CH(Me)–. In some embodiments, –L– is –O–CH(Et)–. In some embodiments, –L– is between C2 and C4 of a sugar moiety. In some embodiments, a locked nucleic acid sugar has the structure indicated below, wherein R^{2s} is –OCH_2C4'–:

[00619] In some embodiments, a modified sugar is an ENA sugar or modified ENA sugar such as those described in, *e.g.*, Seth *et al.*, J Am Chem Soc. 2010 October 27; 132(42): 14942–14950. In some embodiments, a modified sugar is any of those found in an XNA (xenonucleic acid), for instance, arabinose, anhydrohexitol, threose, 2'fluoroarabinose, or cyclohexene.

[00620] In some embodiments, a modified sugar is one described in WO 2017/062862.

[00621] In some embodiments, modified sugars are sugar mimetics such as cyclobutyl or cyclopentyl moieties in place of pentofuranosyl. Representative United States patents that teach preparation of such modified sugar structures include, but are not limited to, US Patent Nos.: 4,981,957; 5,118,800; 5,319,080; and 5,359,044. In some embodiments, modified sugars are sugars in which the oxygen atom within the ribose ring is replaced by nitrogen, sulfur, selenium, or carbon. In some embodiments, a modified sugar is a modified ribose wherein the oxygen atom within the ribose ring is replaced with nitrogen, and wherein the nitrogen is optionally substituted with an alkyl group (*e.g.*, methyl, ethyl, isopropyl, *etc*).

[00622] Non-limiting examples of modified sugars include glycerol, which form glycerol nucleic

acid (GNA) analogues. In some embodiments, an GNA analogue is described in Zhang, R *et al.*, *J. Am. Chem. Soc.*, 2008, *130*, 5846-5847; Zhang L, *et al.*, *J. Am. Chem. Soc.*, 2005, *127*, 4174-4175 and Tsai CH *et al.*, *PNAS*, 2007, 14598-14603.

[00623] In some embodiments, another example of a GNA derived analogue, flexible nucleic acid (FNA) based on the mixed acetal aminal of formyl glycerol, is described in Joyce GF *et al.*, *PNAS*, 1987, *84*, 4398-4402 and Heuberger BD and Switzer C, *J. Am. Chem. Soc.*, 2008, *130*, 412-413.

[00624] Additional non-limiting examples of modified sugars include hexopyranosyl (6' to 4'), pentopyranosyl (4' to 2'), pentopyranosyl (4' to 3'), or tetrofuranosyl (3' to 2') sugars.

[00625] In some embodiments, one or more hydroxyl group in a sugar moiety is optionally and independently replaced with halogen, R' $-N(R')_2$, $-OR'$, or $-SR'$, wherein each R' is independently as defined above and described herein.

[00626] In some embodiments, at least 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50% or more (*e.g.*, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more), inclusive, of the sugars in an oligonucleotide, e.g., a chirally controlled oligonucleotide, an oligonucleotide of a plurality of oligonucleotide of an oligonucleotide composition, etc. are modified. In some embodiments, sugars of purine nucleosides and in some embodiments, only purine nucleosides, are modified (*e.g.*, about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50% or more [*e.g.*, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more] of the purine nucleosides are modified). In some embodiments, sugars of pyrimidine nucleosides and in some embodiments, only pyrimidine nucleosides, are modified (*e.g.*, about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50% or more [*e.g.*, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more] of the pyrimidine nucleosides are modified). In some embodiments, both purine and pyrimidine nucleosides are modified.

[00627] In some embodiments, modified sugars include those described in: A. Eschenmoser, Science (1999), 284:2118; M. Bohringer *et al.* Helv. Chim. Acta (1992), 75:1416-1477; M. Egli *et al*, J. Am. Chem. Soc. (2006), 128(33):10847-56; A. Eschenmoser in *Chemical Synthesis: Gnosis to Prognosis*, C. Chatgilialoglu and V. Sniekus, Ed., (Kluwer Academic, Netherlands, 1996), p.293; K.-U. Schoning *et al.* Science (2000), 290:1347-1351; A. Eschenmoser *et al.* Helv. Chim. Acta (1992), 75:218; J. Hunziker *et al.* Helv. Chim. Acta (1993), 76:259; G. Otting *et al.* Helv. Chim. Acta (1993), 76:2701; K. Groebke *et*

al. Helv. Chim. Acta (1998), 81:375; and A. Eschenmoser, Science (1999), 284:2118. Modifications to the 2' modifications can be found in Verma, S. *et al. Annu. Rev. Biochem.* 1998, 67, 99-134 and all references therein. In some embodiments, a modified sugar is one described in WO2012/030683. In some embodiments, a modified sugar is any modified sugar described in any of: Gryaznov, S; Chen, J.-K. J. Am. Chem. Soc. 1994, 116, 3143; Hendrix et al. 1997 Chem. Eur. J. 3: 110; Hyrup et al. 1996 Bioorg. Med. Chem. 4: 5; Jepsen et al. 2004 Oligo. 14: 130-146; Jones et al. J. Org. Chem. 1993, 58, 2983; Koizumi et al. 2003 Nuc. Acids Res. 12: 3267-3273; Koshkin et al. 1998 Tetrahedron 54: 3607-3630; Kumar et al. 1998 Bioo. Med. Chem. Let. 8: 2219-2222; Lauritsen et al. 2002 Chem. Comm. 5: 530-531; Lauritsen et al. 2003 Bioo. Med. Chem. Lett. 13: 253-256; Mesmaeker et al. Angew. Chem., Int. Ed. Engl. 1994, 33, 226; Morita et al. 2001 Nucl. Acids Res. Supp. 1: 241-242; Morita et al. 2002 Bioo. Med. Chem. Lett. 12: 73-76; Morita et al. 2003 Bioo. Med. Chem. Lett. 2211-2226; Nielsen et al. 1997 Chem. Soc. Rev. 73; Nielsen et al. 1997 J. Chem. Soc. Perkins Transl. 1: 3423-3433; Obika et al. 1997 Tetrahedron Lett. 38 (50): 8735-8; Obika et al. 1998 Tetrahedron Lett. 39: 5401-5404; Pallan et al. 2012 Chem. Comm. 48: 8195-8197; Petersen et al. 2003 TRENDS Biotech. 21: 74-81; Rajwanshi et al. 1999 Chem. Commun. 1395-1396; Schultz et al. 1996 Nucleic Acids Res. 24: 2966; Seth et al. 2009 J. Med. Chem. 52: 10-13; Seth et al. 2010 J. Med. Chem. 53: 8309-8318; Seth et al. 2010 J. Org. Chem. 75: 1569-1581; Seth et al. 2012 Bioo. Med. Chem. Lett. 22: 296-299; Seth et al. 2012 Mol. Ther-Nuc. Acids. 1, e47; Seth, Punit P; Siwkowski, Andrew; Allerson, Charles R; Vasquez, Guillermo; Lee, Sam; Prakash, Thazha P; Kinberger, Garth; Migawa, Michael T; Gaus, Hans; Bhat, Balkrishen; et al. From Nucleic Acids Symposium Series (2008), 52(1), 553-554; Singh et al. 1998 Chem. Comm. 1247-1248; Singh et al. 1998 J. Org. Chem. 63: 10035-39; Singh et al. 1998 J. Org. Chem. 63: 6078-6079; Sorensen 2003 Chem. Comm. 2130-2131; Ts'o et al. Ann. N. Y. Acad. Sci. 1988, 507, 220; Van Aerschot et al. 1995 Angew. Chem. Int. Ed. Engl. 34: 1338; Vasseur et al. J. Am. Chem. Soc. 1992, 114, 4006; WO 20070900071; WO 20070900071; or WO 2016/079181.

[00628] In some embodiments, a modified sugar moiety is an optionally substituted pentose or hexose moiety. In some embodiments, a modified sugar moiety is an optionally substituted pentose moiety. In some embodiments, a modified sugar moiety is an optionally substituted hexose moiety. In some embodiments, a modified sugar moiety is an optionally substituted ribose or hexitol moiety. In some embodiments, a modified sugar moiety is an optionally substituted ribose moiety. In some embodiments, a modified sugar moiety is an optionally substituted hexitol moiety.

[00629] In some embodiments, a sugar is D-2-deoxyribose. In some embodiments, a sugar is beta-D-deoxyribofuranose. In some embodiments, a sugar moiety is a beta-D-deoxyribofuranose moiety. In some embodiments, a sugar is D-ribose. In some embodiments, a sugar is beta-D-ribofuranose. In some embodiments, a sugar moiety is a beta-D-ribofuranose moiety. In some embodiments, a sugar is

optionally substituted beta-D-deoxyribofuranose or beta-D-ribofuranose. In some embodiments, a sugar moiety is an optionally substituted beta-D-deoxyribofuranose or beta-D-ribofuranose moiety. In some embodiments, a sugar moiety/unit in an oligonucleotide, nucleic acid, etc. is a sugar which comprises one or more carbon atoms each independently connected to an internucleotidic linkage, e.g., optionally substituted beta-D-deoxyribofuranose or beta-D-ribofuranose whose 5'-C and/or 3'-C are each independently connected to an internucleotidic linkage (e.g., a natural phosphate linkage, a modified internucleotidic linkage, a chirally controlled internucleotidic linkage, etc.).

[00630] In some embodiments, each nucleoside of a provided oligonucleotide comprises a 2'-O-methoxyethyl sugar modification.

[00631] In some embodiments, the oligonucleotide composition comprises at least one locked nucleic acid (LNA) nucleotide. In some embodiments, the oligonucleotide composition comprises at least one modified nucleotide comprising a modified sugar moiety which is modified at the 2'-position.

[00632] In some embodiments, the oligonucleotide composition comprises modified sugar moiety which comprises a 2'-substituent selected from the group consisting of: H, OR, R, halogen, SH, SR, NH_2, NHR, NR_2, and ON, wherein R is an optionally substituted C_1-C_6 alkyl, alkenyl, or alkynyl and halogen is F, Cl, Br or I.

[00633] In some embodiments, a modified nucleobase, sugar, nucleoside, nucleotide, and/or modified internucleotidic linkage is selected from those described in Ts'o et al. Ann. N. Y. Acad. Sci. 1988, 507, 220; Gryaznov, S.; Chen, J.-K. J. Am. Chem. Soc. 1994, 116, 3143; Mesmaeker et al. Angew. Chem., Int. Ed. Engl. 1994, 33, 226; Jones et al. J. Org. Chem. 1993, 58, 2983; Vasseur et al. J. Am. Chem. Soc. 1992, 114, 4006; Van Aerschot et al. 1995 Angew. Chem. Int. Ed. Engl. 34: 1338; Hendrix et al. 1997 Chem. Eur. J. 3: 110; Koshkin et al. 1998 Tetrahedron 54: 3607-3630; Hyrup et al. 1996 Bioorg. Med. Chem. 4: 5; Nielsen et al. 1997 Chem. Soc. Rev. 73; Schultz et al. 1996 Nucleic Acids Res. 24: 2966; Obika et al. 1997 Tetrahedron Lett. 38 (50): 8735–8; Obika et al. 1998 Tetrahedron Lett. 39: 5401-5404; Singh et al. 1998 Chem. Comm. 1247-1248; Kumar et al. 1998 Bioo. Med. Chem. Let. 8: 2219-2222; Nielsen et al. 1997 J. Chem. Soc. Perkins Transl. 1: 3423-3433; Singh et al. 1998 J. Org. Chem. 63: 6078-6079; Seth et al. 2010 J. Org. Chem. 75: 1569-1581; Singh et al. 1998 J. Org. Chem. 63: 10035-39; Sorensen 2003 Chem. Comm. 2130-2131; Petersen et al. 2003 TRENDS Biotech. 21: 74-81; Rajwanshi et al. 1999 Chem. Commun. 1395-1396; Jepsen et al. 2004 Oligo. 14: 130-146; Morita et al. 2001 Nucl. Acids Res. Supp. 1: 241-242; Morita et al. 2002 Bioo. Med. Chem. Lett. 12: 73-76; Morita et al. 2003 Bioo. Med. Chem. Lett. 2211-2226; Koizumi et al. 2003 Nuc. Acids Res. 12: 3267-3273; Lauritsen et al. 2002 Chem. Comm. 5: 530-531; Lauritsen et al. 2003 Bioo. Med. Chem. Lett. 13: 253-256; WO 20070900071; Seth et al., Nucleic Acids Symposium Series (2008), 52(1), 553-554; Seth et al. 2009 J. Med. Chem. 52: 10-13; Seth et al. 2012 Mol. Ther-Nuc. Acids. 1, e47; Pallan et al. 2012 Chem. Comm.

48: 8195-8197; Seth et al. 2010 J. Med. Chem. 53: 8309-8318; Seth et al. 2012 Bioo. Med. Chem. Lett. 22: 296-299; WO 2016/079181; US 6,326,199; US 6,066,500; and US 6,440,739.

[00634] In some embodiments, sugars and nucleosides include 6′ -modified bicyclic sugars and nucleosides, respectively, that have either (*R*) or (*S*)-chirality at the 6′ -position, e.g., those described in US Patent No. 7,399,845. In other embodiments, sugars and nucleosides include 5′ -modified bicyclic sugars and nucleosides, respectively, that have either (*R*) or (*S*)-chirality at the 5′ -position, e.g., those described in US Patent Application Publication No. 20070287831.

[00635] In some embodiments, modified sugars, nucleobases, nucleosides, nucleotides, and/or internucleotidic linkages are described in U.S. Pat. No. 3,687,808, as well as U.S. Pat. Nos. 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,457,191; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,681,941; 5,750,692; 6,015,886; 6,147,200; 6,166,197; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, the sugars, nucleobases, nucleosides, nucleotides, and internucleotidic linkages of each of which are incorporated by reference.

[00636] In some embodiments, modified sugars, nucleobases, nucleosides, nucleotides, and/or internucleotidic linkages are those described in any of: Gryaznov, S; Chen, J.-K. J. Am. Chem. Soc. 1994, 116, 3143; Hendrix et al. 1997 Chem. Eur. J. 3: 110; Hyrup et al. 1996 Bioorg. Med. Chem. 4: 5; Jepsen et al. 2004 Oligo. 14: 130-146; Jones et al. J. Org. Chem. 1993, 58, 2983; Koizumi et al. 2003 Nuc. Acids Res. 12: 3267-3273; Koshkin et al. 1998 Tetrahedron 54: 3607-3630; Kumar et al. 1998 Bioo. Med. Chem. Let. 8: 2219-2222; Lauritsen et al. 2002 Chem. Comm. 5: 530-531; Lauritsen et al. 2003 Bioo. Med. Chem. Lett. 13: 253-256; Mesmaeker et al. Angew. Chem., Int. Ed. Engl. 1994, 33, 226; Morita et al. 2001 Nucl. Acids Res. Supp. 1: 241-242; Morita et al. 2002 Bioo. Med. Chem. Lett. 12: 73-76; Morita et al. 2003 Bioo. Med. Chem. Lett. 2211-2226; Nielsen et al. 1997 Chem. Soc. Rev. 73; Nielsen et al. 1997 J. Chem. Soc. Perkins Transl. 1: 3423-3433; Obika et al. 1997 Tetrahedron Lett. 38 (50): 8735–8; Obika et al. 1998 Tetrahedron Lett. 39: 5401-5404; Pallan et al. 2012 Chem. Comm. 48: 8195-8197; Petersen et al. 2003 TRENDS Biotech. 21: 74-81; Rajwanshi et al. 1999 Chem. Commun. 1395-1396; Schultz et al. 1996 Nucleic Acids Res. 24: 2966; Seth et al. 2009 J. Med. Chem. 52: 10-13; Seth et al. 2010 J. Med. Chem. 53: 8309-8318; Seth et al. 2010 J. Org. Chem. 75: 1569-1581; Seth et al. 2012 Bioo. Med. Chem. Lett. 22: 296-299; Seth et al. 2012 Mol. Ther-Nuc. Acids. 1, e47; Seth, Punit P; Siwkowski, Andrew; Allerson, Charles R; Vasquez, Guillermo; Lee, Sam; Prakash, Thazha P; Kinberger, Garth; Migawa, Michael T; Gaus, Hans; Bhat, Balkrishen; et al. From Nucleic Acids Symposium Series (2008), 52(1), 553-554; Singh et al. 1998 Chem. Comm. 1247-1248; Singh et al. 1998 J. Org. Chem. 63: 10035-39; Singh et al. 1998 J. Org. Chem. 63: 6078-6079; Sorensen 2003 Chem. Comm. 2130-2131; Ts'o et al.

Ann. N. Y. Acad. Sci. 1988, 507, 220; Van Aerschot et al. 1995 Angew. Chem. Int. Ed. Engl. 34: 1338; Vasseur et al. J. Am. Chem. Soc. 1992, 114, 4006; WO 20070900071; WO 20070900071; and WO 2016/079181.

[00637] In some embodiments, modified sugars, nucleobases, nucleosides, nucleotides, and/or internucleotidic linkages include, or include those in, HNA, PNA, 2'-Fluoro N3'-P5'-phosphoramidate, LNA, beta-D-oxy-LNA, 2'-O,3'-C-linked bicyclic, PS-LNA, beta-D-thio-LNA, beta-D-amino-LNA, xylo-LNA [c], alpha-L-LNA, ENA, beta-D-ENA, amide-linked LNA, methylphosphonate-LNA, (*R, S*)-cEt, (*R, S*)-cMOE, (*R, S*)-5'-Me-LNA, S-Me cLNA, Methylene-cLNA, 3'-Me-alpha-L-LNA, R-6'-Me-alpha-L-LNA, *S*-5'-Me-alpha-L-LNA, or *R*-5'-Me-alpha-L-LNA. Certain modified sugars, nucleobases, nucleosides, nucleotides, and/or internucleotidic linkages are described in US 9394333, US 9744183, US 9605019, US 20130178612, US 20150211006, US 9598458, US 20170037399, WO 2017/015555, WO 2017/062862, the modified sugars, nucleobases, nucleosides, nucleotides, and internucleotidic linkages of each of which are incorporated herein by reference.

Dystrophin

[00638] In some embodiments, the present disclosure provides technologies, e.g., oligonucleotides, compositions, methods, etc., related to the dystrophin (DMD) gene or a product encoded thereby (a transcript, a protein (e.g., various variants of the dystrophin protein), etc.). In some embodiments, the base sequence of an oligonucleotide is or comprise a sequence which sequence is, or is complementary (e.g., 85%, 90%, 95%, 100%; in many embodiments, 100%) to, a sequence in the DMD gene or a product thereof (e.g., a transcript, mRNA, etc.) (such an oligonucleotide—DMD oligonucleotide). In some embodiments, such a sequence in the DMD gene or a product thereof comprises 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 20, 31, 32, 33, 34, 35 or more nucleobases. In some embodiments, such a sequence in the DMD gene or a product thereof comprises at least 10 nucleobases. In some embodiments, such a sequence in the DMD gene or a product thereof comprises at least 15 nucleobases. In some embodiments, such a sequence in the DMD gene or a product thereof comprises at least 16 nucleobases. In some embodiments, such a sequence in the DMD gene or a product thereof comprises at least 17 nucleobases. In some embodiments, such a sequence in the DMD gene or a product thereof comprises at least 18 nucleobases. In some embodiments, such a sequence in the DMD gene or a product thereof comprises at least 19 nucleobases. In some embodiments, such a sequence in the DMD gene or a product thereof comprises at least 20 nucleobases. In some embodiments, the present disclosure provides technologies, including DMD oligonucleotides and compositions and methods of use thereof, for treatment of muscular dystrophy, including but not limited to, Duchenne Muscular Dystrophy (also abbreviated as DMD) and

Becker Muscular Dystrophy (BMD). In some embodiments, DMD comprises one or more mutations. In some embodiments, such mutations are associated with reduced biological functions of dystrophin protein in a subject suffering from or susceptible to muscular dystrophy.

[00639] In some embodiments, the dystrophin (DMD) gene or a product thereof, or a variant or portion thereof, may be referred to as DMD, BMD, CMD3B, DXS142, DXS164, DXS206, DXS230, DXS239, DXS268, DXS269, DXS270, DXS272, MRX85, or dystrophin; External IDs: OMIM: 300377 MGI: 94909; HomoloGene: 20856; GeneCards: DMD; In Human: Entrez: 1756; Ensembl: ENSG00000198947; UniProt: P11532; RefSeq (mRNA): NM_000109; NM_004006; NM_004007; NM_004009; NM_004010; RefSeq (protein): NP_000100; NP_003997; NP_004000; NP_004001; NP_004002; Location (UCSC): Chr X: 31.1 – 33.34 Mb; In Mouse: Entrez: 13405; Ensembl: ENSMUSG00000045103; UniProt: P11531; RefSeq (mRNA): NM_007868; NM_001314034; NM_001314035; NM_001314036; NM_001314037; RefSeq (protein): NP_001300963; NP_001300964; NP_001300965; NP_001300966; NP_001300967; Location (UCSC): Chr X: 82.95 – 85.21 Mb.

[00640] The DMD gene reportedly contains 79 exons distributed over 2.3 million bp of genetic real estate on the X chromosome; however, only approximately 14,000 bp (<1%) is reported to be used for translation into protein (coding sequence). It is reported that about 99.5% of the genetic sequence, the intronic sequences, is spliced out of the 2.3 million bp initial heteronuclear RNA transcript to provide a mature 14,000 bp mRNA that includes all key information for dystrophin protein production. In some embodiments, patients with DMD have mutation(s) in the DMD gene that prevent the appropriate construction of the wild-type DMD mRNA and/or the production of the wild-type dystrophin protein, and patients with DMD often show marked dystrophin deficiency in their muscle.

[00641] In some embodiments, a dystrophin transcript, e.g., mRNA, or protein encompasses those related to or produced from alternative splicing. For example, sixteen alternative transcripts of the dystrophin gene were reported following an analysis of splicing patterns of the DMD gene in skeletal muscle, brain and heart tissues. Sironi et al. 2002 FEBS Letters 517: 163-166.

[00642] It is reported that dystrophin has several isoforms. In some embodiments, dystrophin refers to a specific isoform. At least three full-length dystrophin isoforms have been reported, each controlled by a tissue-specific promoter. Klamut et al. 1990 Mol. Cell. Biol. 10: 193-205; Nudel et al. 1989 Nature 337: 76-78; Gorecki et al. 1992 Hum. Mol. Genet. 1: 505-510. The muscle isoform is reportedly mainly expressed in skeletal muscle but also in smooth and cardiac muscles [Bies, R.D., Phelps, S.F., Cortez, M.D., Roberts, R., Caskey, C.T. and Chamberlain, J.S. 1992 Nucleic Acids Res. 20: 1725-1731], the brain dystrophin is reportedly specific for cortical neurons but can also be detected in heart and cerebellar neurons, while the Purkinje-cell type reportedly accounts for nearly all cerebellar dystrophin [Gorecki et al. 1992 Hum. Mol. Genet. 1: 505-510]. Alternative splicing reportedly provides

a means for dystrophin diversification: the 3' region of the gene reportedly undergoes alternative splicing resulting in tissue-specific transcripts in brain neurons, cardiac Purkinje fibers, and smooth muscle cells [Bies et al. 1992 Nucleic Acids Res. 20: 1725-1731; and Feener et al. 1989 Nature 338: 509-511] while 12 patterns of alternative splicing have been reported in the 5' region of the gene in skeletal muscle [Surono et al. 1997 Biochem. Biophys. Res. Commun. 239: 895-899].

[00643] In some embodiments, a dystrophin mRNA, gene or protein is a revertant version. Among others, revertant dystrophins were reported in, for example: Hoffman et al. 1990 J. Neurol. Sci. 99:9-25; Klein et al. 1992 Am. J. Hum. Genet. 50: 950-959; and Chelly et al. 1990 Cell 63: 1239-1348; Arahata et al. 1998 Nature 333: 861-863; Bonilla et al. 1988 Cell 54: 447-452; Fanin et al. 1992 Neur. Disord. 2: 41-45; Nicholson et al. 1989 J. Neurol. Sci. 94: 137-146; Shimizu et al. 1988 Proc. Jpn. Acad. Sci. 64: 205-208; Sicinzki et al. 1989 Science 244: 1578-1580; and Sherratt et al. Am. J. Hum. Genet. 53: 1007-1015.

[00644] Various mutations in the DMD gene can and/or were reported to cause muscular dystrophy.

Muscular Dystrophy

[00645] Compositions comprising one or more DMD oligonucleotides described herein can be used to treat muscular dystrophy. In some embodiments, muscular dystrophy (MD) is any of a group of muscle conditions, diseases, or disorders that results in (increasing) weakening and breakdown of skeletal muscles over time. The conditions, diseases, or disorders differ in which muscles are primarily affected, the degree of weakness, when symptoms begin, and how quickly symptoms worsen. Many MD patients will eventually become unable to walk. In many cases musuclar dystrophy is fatal. Some types are also associated with problems in other organs, including the central nervous system. In some embodiments, the muscular dystrophy is Duchenne (Duchenne's) Muscular Dystrophy (DMD) or Becker (Becker's) Muscular Dystrophy (BMD).

[00646] In some embodiments, a symptom of Duchenne Muscular Dystrophy is muscle weakness associated with muscle wasting, with the voluntary muscles being first affected, especially those of the hips, pelvic area, thighs, shoulders, and calves. Muscle weakness can also occur later, in the arms, neck, and other areas. Calves are often enlarged. Symptoms usually appear before age six and may appear in early infancy. Other physical symptoms are: awkward manner of walking, stepping, or running (in some cases, patients tend to walk on their forefeet, because of an increased calf muscle tone), frequent falls, fatigue, difficulty with motor skills (e.g., running, hopping, jumping), lumbar hyperlordosis, possibly leading to shortening of the hip-flexor muscles, unusual overall posture and/or manner of walking, stepping, or running, muscle contractures of Achilles tendon and hamstrings impair functionality,

progressive difficulty walking, muscle fiber deformities, pseudohypertrophy (enlarging) of tongue and calf muscles, higher risk of neurobehavioral disorders (e.g., ADHD), learning disorders (e.g., dyslexia), and non-progressive weaknesses in specific cognitive skills (e.g., short-term verbal memory), which are believed to be the result of absent or dysfunctional dystrophin in the brain, eventual loss of ability to walk (usually by the age of 12), skeletal deformities (including scoliosis in some cases), and trouble getting up from lying or sitting position.

[00647] In some embodiments, Becker muscular dystrophy (BMD) is caused by mutations that give rise to shortened but in-frame transcripts resulting in the production of truncated but partially functional protein(s). Such partially functional protein(s) were reported to retain the critical amino terminal, cysteine rich and C-terminal domains but usually lack elements of the central rod domains which were reported to be of less functional significance. England et al. 1990 Nature, 343, 180–182.

[00648] In some embodiments, BMD phenotypes range from mild DMD to virtually asymptomatic, depending on the precise mutation and the level of dystrophin produced. Yin et al. 2008 Hum. Mol. Genet. 17: 3909-3918.

[00649] In some embodiments, dystrophy patients with out-of-frame mutations are generally diagnosed with the more severe Duchenne Muscular Dystrophy, and dystrophy patients with in-frame mutations are generally diagnosed with the less severe Becker Muscular Dystrophy. However, a minority of patients with in-frame deletions are diagnosed with Duchenne Muscular Dystrophy, including those with deletion mutations starting or ending in exons 50 or 51, which encode part of the hinge region, such as deletions of exons 47 to 51, 48 to 51, and 49 to 53. Without wishing to be bound by any particular theory, the present disclosure notes that the patient-to-patient variability in disease severity despite the presence of the same exon deletion reportedly may be related to the effect of the specific deletion breakpoints on mRNA splicing efficiency and/or patterns; translation or transcription efficiency after genome rearrangement; and stability or function of the truncated protein structure. Yokota et al. 2009 Arch. Neurol. 66: 32.

Exon Skipping as a Treatment for Muscular Dystrophy

[00650] In some embodiments, a treatment for muscular dystrophy comprises the use of a DMD oligonucleotide which is capable of mediating skipping of one or more Dystrophin exons. In some embodiments, the present disclosure provides methods for treatment of muscular dystrophy comprising administering to a subject suffering therefrom or susceptible thereto an DMD oligonucleotide, or a composition comprising a DMD oligonucleotide. Particularly, among other things, the present disclosure demonstrates that chirally controlled oligonucleotide/chirally controlled oligonucleotide compositions are unexpectedly effective for modulating exon skipping compared to otherwise identical but non-chirally

controlled oligonucleotide/oligonucleotide compositions. In some embodiments, the present disclosure demonstrates incorporation of one or more non-negatively charged internucleotidic linkage can greatly improve delivery and/or overall exon skipping efficiency.

[00651] In some embodiments, a treatment for muscular dystrophy employs the use of a DMD oligonucleotide, wherein the oligonucleotide is capable of providing skipping of one or more exons. Skipping of one or more (e.g., multiple) DMD exons can, for example, remove a mutated exon(s), or compensate for a mutation(s) (e.g., restoring the reading frame if the mutation is a frameshift mutation) in an exon which is not skipped. In some embodiments, a DMD oligonucleotide is capable of mediating the skipping of an exon which comprises a mutation (e.g., a frameshift, insertion, deletion, missense, or nonsense mutation, or other mutation), wherein the skipping of the exon maintains (or restores) the proper reading frame of the DMD gene, and translation produces a truncated but functional (or largely functional) DMD protein. In some embodiments, a DMD oligonucleotide compensates for an exon comprising a frameshift mutation by providing skipping of a different exon (not the one comprising the frameshift mutation), and thus restoring the reading frame of the DMD gene. In some embodiments, a patient having muscular dystrophy has a frameshift mutation in one exon of the DMD gene; and this patient is treated with a DMD oligonucleotide which does not cause skipping of the exon having the mutation, but causes skipping of a different exon, which restores the reading frame of the DMD gene, so that a functional DMD protein is produced (and, if the deleted exon is 3' to the exon which has the frameshift mutation, this functional DMD protein will generally have an amino acid of a normal DMD protein, except for a sequence of amino acids not normally found in DMD, spanning from the frameshift mutation to the exon which is 3' to the deleted exon).

[00652] In some embodiments, a composition comprising a DMD oligonucleotide is useful for treatment of a Dystrophin-related disorder of the central nervous system. In some embodiments, the present disclosure pertains to a method of treatment of a Dystrophin-related disorder of the central nervous system, wherein the method comprises the step of administering a therapeutically effective amount of a DMD oligonucleotide to a patient suffering from a Dystrophin-related disorder of the central nervous system. In some embodiments, a DMD oligonucleotide is administered outside the central nervous system (as non-limiting examples, intravenously or intramuscularly) to a patient suffering from a Dystrophin-related disorder of the central nervous system, and the DMD oligonucleotide is capable of passing through the blood-brain barrier into the central nervous system. In some embodiments, a DMD oligonucleotide is administered directly into the central nervous system (as non-limiting example, via intrathecal, intraventricular, intracranial, etc., delivery).

[00653] In some embodiments, a Dystrophin-related disorder of the central nervous system, or a symptom thereof, can be any one or more of: decreased intelligence, decreased long term memory,

decreased short term memory, language impairment, epilepsy, autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, learning problem, behavioral problem, a decrease in brain volume, a decrease in grey matter volume, lower white matter fractional anisotropy, higher white matter radial diffusivity, an abnormality of skull shape, or a deleterious change in the volume or structure of the hippocampus, globus pallidus, caudate putamen, hypothalamus, anterior commissure, periaqueductal gray, internal capsule, amygdala, corpus callosum, septal nucleus, nucleus accumbens, fimbria, ventricle, or midbrain thalamus. In some embodiments, a patient exhibiting muscle-related symptoms of muscular dystrophy also exhibits symptoms of a Dystrophin-related disorder of the central nervous system.

[00654] In some embodiments, a Dystrophin-related disorder of the central nervous system is related to, associated with and/or caused by an abnormality in the level, activity, expression and/or distribution of a gene product of the Dystrophin gene, such as full-length Dystrophin or a smaller isoform of Dystrophin, including, but not limited to, Dp260, Dp140, Dp116, Dp71 or Dp40. In some embodiments, a DMD oligonucleotide is administered into the central nervous system of a muscular dystrophy patient in order to ameliorate one or more systems of a Dystrophin-related disorder of the central nervous system. In some embodiments, a Dystrophin-related disorder of the central nervous system is related to, associated with and/or caused by an abnormality in the level, activity, expression and/or distribution of a gene product of the Dystrophin gene, such as full-length Dystrophin or a smaller isoform of Dystrophin, including, but not limited to, Dp260, Dp140, Dp116, Dp71 or Dp40. In some embodiments, administration of a DMD oligonucleotide to a patient suffering from a Dystrophin-related disorder of the central nervous system increases the level, activity, and/or expression and/or improves the distribution of a gene product of the Dystrophin gene.

[00655] In some embodiments, the present disclosure provides technologies for modulating dystrophin pre-mRNA splicing, whereby selected exons are excised to either remove nonsense mutations or restore the reading frame around frameshifting mutations from the mature mRNA. In some embodiments, a DMD oligonucleotide capable of skipping an exon is capable of restoring the reading frame.

[00656] As a non-limiting example, in a patient with Duchenne Muscular Dystrophy who has a deletion of exon 50, an out-of-frame transcript is generated in which exon 49 is spliced to exon 51. As a result, a stop codon is generated in exon 51, which prematurely aborts dystrophin synthesis. In some embodiments, the present disclosure provides oligonucleotides that can mediate skipping of exon 51, restore the open reading frame of the transcript, and allow the production of a truncated dystrophin similar to that in patients with Becker muscular dystrophy (BMD).

[00657] In some embodiments, in a DMD patient, a DMD gene comprises an exon comprising a

mutation, and the disorder is at least partially treated by skipping of one or more exons (e.g., the exon comprising the mutation, or an exon adjacent to the exon comprising the mutation, or a set of consecutive exons, including the exon comprising the mutation).

[00658] In some embodiments, in a DMD patient, a DMD gene or transcript has a mutation in an exon(s), which is a missense or nonsense mutation and/or deletion, insertion, inversion, translocation or duplication. In some embodiments, in a DMD patient, a DMD gene or transcript has a mutation in an exon(s) which results in a frameshift, premature stop codon, or otherwise perturbation of the proper reading frame.

[00659] In some embodiments, in a treatment for muscular dystrophy, an exon of DMD is skipped, wherein the exon encodes a string of amino acids not essential for DMD protein function, or whose skipping can provide a fully or partially functional DMD protein. In some embodiments, in a treatment for muscular dystrophy, an exon of DMD is skipped, wherein the exon(s) skipped include an exon which comprises a mutation or is adjacent to (e.g., flanking) an exon comprising a mutation, or wherein multiple exons are skipped, the skipped exons optionally include an exon comprising a mutation. In some embodiments, in a treatment for muscular dystrophy, two or more exons are skipped, wherein the exons skipped include an exon which comprises a mutation or is adjacent to (e.g., flanking) an exon comprising a mutation. In some embodiments, in a treatment for muscular dystrophy, an exon comprises a frameshift mutation, and the skipping of a different exon (while leaving the exon with the frameshift mutation in place) restores the proper reading frame.

[00660] In some embodiments, in a treatment for muscular dystrophy, a DMD oligonucleotide is capable of mediating skipping of one or more DMD exons, thereby either restoring or maintaining the proper reading frame, and/or creating an artificially internally truncated DMD which provides at least partially improved or fully restored biological activity.

[00661] In some embodiments, an DMD oligonucleotide skips an exon(s) which is not exon 64 and exon 70, portions of which are reportedly important for protein function, and/or which is not first or the last exon. In some embodiments, an DMD oligonucleotide skips an exon(s), but skipping of the exon(s) does not cause deletion of one or more or all actin-binding sites in the N-terminal region.

[00662] In some embodiments, an internally truncated DMD protein produced from a dystrophin transcript with a skipped exon(s) is more functional than a terminally truncated DMD protein e.g., produced from a dystrophin transcript with an out-of-frame deletion.

[00663] In some embodiments, an internally truncated DMD protein produced from a dystrophin transcript with a skipped exon(s) is more resistant to nonsense-mediated decay, which can degrade a terminally truncated DMD protein, e.g., produced from a dystrophin transcript with an out-of-frame deletion.

[00664] In some embodiments, a treatment for muscular dystrophy employs the use of a DMD oligonucleotide, wherein the oligonucleotide is capable of providing skipping of one or more exons. Skipping of one or more (e.g., multiple) DMD exons can, for example, remove a mutated exon, or compensate for a mutation (e.g., restoring from for a frameshift mutation) in an exon which is not skipped.

[00665] In some embodiments, the present disclosure encompasses the recognition that the nature and location of a DMD mutation may be utilized to design exon-skipping strategy. In some embodiments, if a DMD patient has a mutation in an exon, skipping of the mutated exon can produce an internally truncated (internally shortened) but at least partially functional DMD protein product.

[00666] In some embodiments, a DMD patient has a mutation which alters splicing of a DMD transcript, e.g., by inactivating a site required for splicing, or activating a cryptic site so that it becomes active for splicing, or by creating an alternative (e.g., unnatural) splice site. In some embodiments, such a mutation causes production of proteins with low or no activities. In some embodiments, splicing modulation, e.g., exon skipping, suppression of such a mutation, etc., can be employed to remove or reduce effects of such a mutation, e.g., by restoring proper splicing to produce proteins with restored activities, or producing an internally truncated dystrophin protein with improved or restored activities, etc.

[00667] In some embodiments, a DMD patient has a mutation which is a duplication of one or several exons, and the present disclosure provides exon skipping technologies to delete the duplication and/or to restore the reading frame.

[00668] In some embodiments, a DMD patient has a mutation which causes the skipping of an exon, which in turn can cause a frameshift. In some embodiments, the present disclosure provides technologies that can provide skipping of an additional exon(s) to restore the reading frame. For example, deletion of exon 51, which causes a frame shift, may be addressed by skipping of exon 50 or 52, which restores the reading frame. In some embodiments, a DMD patient has a mutation in one exon which causes a frame shift, and a deletion of a different exon(s) (e.g., a different exon, or an adjacent or flanking exon(s) immediately 5' or 3' to the mutated exon) restores the reading frame.

[00669] In some embodiments, restoring the reading frame can convert an out-of-frame mutation to an in-frame mutation; in some embodiments, in humans, such a change can transform severe Duchenne Muscular Dystrophy into milder Becker Muscular Dystrophy.

[00670] In some embodiments, a DMD patient or a patient suspected to have DMD is analyzed for DMD genotype prior to administration of a composition comprising a DMD oligonucleotide.

[00671] In some embodiments, a DMD patient or a patient suspected to have DMD is analyzed for DMD phenotype prior to administration of a composition comprising a DMD oligonucleotide.

[00672] In some embodiments, a DMD patient is analyzed for genotype and phenotype to

determine the relationship of DMD genotype and DMD phenotype prior to administration of a composition comprising a DMD oligonucleotide.

[00673] In some embodiments, a patient is genetically verified to have dystrophy prior to administration of a composition comprising a DMD oligonucleotide.

[00674] In some embodiments, analysis of DMD genotype or genetic verification of DMD or a patient comprises determining if the patient has one or more deleterious mutations in DMD.

[00675] In some embodiments, analysis of DMD genotype or genetic verification of DMD or a patient comprises determining if the patient has one or more deleterious mutations in DMD and/or analyzing DMD splicing and/or detecting splice variants of DMD, wherein a splice variant is produced by an abnormal splicing of DMD.

[00676] In some embodiments, analysis of DMD genotype or genetic verification of DMD informs the selection of a composition comprising a DMD oligonucleotide useful for treatment.

[00677] In some embodiments, an abnormal or mutant DMD gene or a portion thereof is removed or copied from a patient or a patient's cell(s) or tissue(s) and the abnormal or mutant DMD gene, or a portion thereof comprising the abnormality or mutation, or a copy thereof, is inserted into a cell. In some embodiments, this cell can be used to test various compositions comprising a DMD oligonucleotide to predict if such a composition would be useful as a treatment for the patient. In some embodiments, the cell is a myoblast or myotubule.

[00678] In some embodiments, an individual or patient can produce, prior to treatment with a DMD oligonucleotide, one or more splice variants of DMD, often each variant being produced at a very low level. In some embodiments, a method such as that described in Example 20 can be used to detect low levels of splice variants being produced in a patient prior to, during or after administration of a DMD oligonucleotide.

[00679] In some embodiments, a patient and/or the tissues thereof are analyzed for production of various splicing variants of a DMD gene prior to administration of a composition comprising a DMD oligonucleotide.

[00680] In some embodiments, the present disclosure provides methods for designing a DMD oligonucleotide (e.g., an oligonucleotide capable of mediating skipping of one or more exons of DMD). In some embodiments, the present disclosure utilizes rationale design described herein and optionally sequence walks to design oligonucleotides, e.g., for testing exon skipping in one or more assays and/or conditions. In some embodiments, an efficacious oligonucleotide is developed following rational design, including using various information of a given biological system.

[00681] In some embodiments, in a method for developing DMD oligonucleotides, oligonucleotides are designed to anneal to one or more potential splicing-related motifs and then tested

for their ability to mediate exon skipping. In some embodiments, splicing-related motifs include, but are not limited to, any one or more of: an acceptor, exon recognition sequence (ERS), exonic splice enhancer (ESE) site, splicing enhancer sequence (SES), branch point sequence, and donor splice site of a target exon. Certain sequences that may be involved in splicing were reported in, for example: Disset et al. 2006 Human Mol. Gen. 15: 999–1013.

[00682] In some embodiments, software packages, such as RESCUE-ESE, ESEfinder, and the PESX server, may be utilized to predict putative ESE sites (Fairbrother et al. 2002 Science 297: 1007-1013; Cartegni et al. 2003 Nat. Struct. Biol. 120-125; Zhang and Chasin 2004 Gen. Dev. 18: 1241-1250; Smith et al. 2006 Hum. Mol. Genet. 15: 2490-2508).

[00683] In some embodiments, a DMD oligonucleotide which targets or interacts with an acceptor, exon recognition sequence (ERS), exonic splice enhancer (ESE) site, or donor splice site of a DMD exon does not interact or significantly interact with a sequence in another (e.g., off-target) gene.

[00684] In some embodiments, in a rational approach to DMD oligonucleotide design, oligonucleotides are designed with consideration of secondary structures of dystrophin transcripts, e.g., mRNA. Designed oligonucleotide can then be assessed for exon skipping. A number of effective DMD oligonucleotides have been designed using rational approaches described in the present disclosure.

[00685] In some embodiments, alternatively or additionally, sequence walk, e.g., of an exon sequence can be performed to search for efficacious DMD oligonucleotide sequences.

[00686] In some embodiments, provided methods comprise sequence walking. In some embodiments, a set of overlapping oligonucleotides is generated. In some embodiments, oligonucleotides in a set have the same length, and the 5' ends of the oligonucleotides in the set are evenly spaced apart. In some embodiments, a set of overlapping oligonucleotides encompasses an entire exon or a portion(s) thereof. The 5' ends of the oligonucleotides in a walk can be evenly spaced at a suitable distance, e.g., 1 base apart, 2 bases apart, 3 bases apart, etc. Among other things, the present disclosure demonstrates that sequences can be optimized and in combination with chemistry and/or stereochemistry technologies of the present disclosure, highly effective oligonucleotides (and compositions and methods of use thereof) can be prepared.

Example Technologies for Assessing Oligonucleotides and Oligonucleotide Compositions

[00687] Various technologies for assessing properties and/or activities of oligonucleotides can be utilized in accordance with the present disclosure, e.g., US 20170037399, WO 2017/015555, WO 2017/015575, WO 2017/192664, WO 2017/062862, WO 2017/192679, WO 2017/210647, etc.

[00688] For example, DMD oligonucleotides can be evaluated for their ability to mediate exon

skipping in various assays, including in vitro and in vivo assays, in accordance with the present disclosure. In vitro assays can be performed in various test cells described herein or known in the art, including but not limited to, Δ48-50 Patient-Derived Myoblast Cells. In vivo tests can be performed in test animals described herein or known in the art, including but not limited to, a mouse, rat, cat, pig, dog, monkey, or non-human primate.

[00689] As non-limiting examples, a number of assays are described below for assessing properties/activities of DMD oligonucleotides. Various other suitable assays are available and may be utilized to assess oligonucleotide properties/activities, including those of oligonucleotides not designed for exon skipping (e.g., for oligonucleotides that may involve RNase H for reducing levels of target transcripts, assays described in US 20170037399, WO 2017/015555, WO 2017/015575, WO 2017/192664, WO 2017/192679, WO 2017/210647, etc.).

[00690] A DMD oligonucleotide can be evaluated for its ability to mediate skipping of an exon in the Dystrophin RNA, which can be tested, as non-limiting examples, using nested PCR, qRT-PCR, and/or sequencing.

[00691] A DMD oligonucleotide can be evaluated for its ability to mediate protein restoration (e.g., production of an internally truncated protein lacking the amino acids corresponding to the codons encoded in the skipped exon, which has improved functions compared to proteins (if any) produced prior to exon skipping), which can be evaluated by a number of methods for protein detection and/or quantification, such as western blot, immunostaining, etc. Antibodies to dystrophin are commercially available or if desired, can be developed for desired purposes.

[00692] A DMD oligonucleotide can be evaluated for its ability to mediate production of a stable restored protein. Stability of restored protein can be tested, in non-limiting examples, in assays for serum and tissue stability.

[00693] A DMD oligonucleotide can be evaluated for its ability to bind protein, such as albumin. Example related technologies include those described, e.g., in WO 2017/015555, WO 2017/015575, etc.

[00694] A DMD oligonucleotide can be evaluated for immuno activity, e.g., through assays for cytokine activation, complement activation, TLR9 activity, etc. Example related technologies include those described, e.g., in WO 2017/015555, WO 2017/015575, WO 2017/192679, WO 2017/210647, etc.

[00695] In some embodiments, efficacy of a DMD oligonucleotide can be tested, e.g., in in silico analysis and prediction, a cell-free extract, a cell transfected with artificial constructs, an animal such as a mouse with a human Dystrophin transgene or portion thereof, normal and dystrophic human myogenic cell lines, and/or clinical trials. It may be desirable to utilize more than one assay, as normal and dystrophic human myogenic cell lines may sometimes produce different efficacy results under certain conditions (Mitrpant et al. 2009 Mol. Ther. 17: 1418).

[00696] In some embodiments, DMD oligonucleotides can be tested in vitro in cells. In some embodiments, testing in vitro in cells involves gymnotic delivery of the oligonucleotide(s), or delivery using a delivery agent or transfectant, many of which are known in the art and may be utilized in accordance with the present disclosure.

[00697] In some embodiments, DMD oligonucleotides can be tested in vitro in normal human skeletal muscle cells (hSkMCs). See, for example, Arechavala et al. 2007 Hum. Gene Ther. 18: 798-810.

[00698] In some embodiments, DMD oligonucleotides can be tested in a muscle explant from a DMD patient. Muscle explants from DMD patients are reported in, for example, Fletcher et al. 2006 J. Gene Med. 8: 207-216; McClorey et al. 2006 Neur. Dis. 16: 583-590; and Arechavala et al. 2007 Hum. Gene Ther. 18: 798-810.

[00699] In some embodiments, cells are or comprise cultured muscle cells from DMD patients. See, for example: Aartsma-Rus et al. 2003 Hum. Mol. Genet. 8: 907-914.

[00700] In some embodiments, an individual DMD oligonucleotide may demonstrate experiment-to-experiment variability in its ability to skip an exon under certain circumstances. In some embodiments, an individual DMD oligonucleotide can demonstrate variability in its ability to skip an exon(s) depending on which cells are used, the growth conditions, and other experimental factors. To control variations, typically oligonucleotides to be tested and control oligonucleotides are assayed under the same or substantially the same conditions.

[00701] In vitro experiments also include those conducted with patient-derived myoblasts. Certain results from such experiments were described herein. In certain such experiments, cells were cultured in skeletal growth media to keep them in a dividing / immature myoblast state. The media was then changed to 'differentiation' media (containing insulin and 2% horse serum) concurrent with spiking oligonucleotides in the media for dosing. The cells differentiated into myotubes as they were getting dosed for a suitable period of time, e.g., a total of 4d for RNA experiments and 6d for protein experiments (such conditions referenced as '0d pre-differentiation' (0d + 4d for RNA, 0d + 6d for protein)).

[00702] Without wishing to be bound by any particular theory, the present disclosure notes that it may be desirable to know if DMD oligonucleotides are able to enter mature myotubes and induce skipping in these cells as well as 'immature' cells. In some embodiments, the present disclosure provided assays to test effects of DMD oligonucleotides in myotubes. In some embodiments, a dosing schedule different from the '0d pre-differentiation' was used, wherein the myoblasts were pre-differentiated into myotubes in differentiation media for several days (4d or 7d or 10d) and then DMD oligonucleotides were administered. Certain related protocols are described in Example 19.

[00703] In some embodiments, the present disclosure demonstrated that, in the pre-differentiation experiments, DMD oligonucleotides (excluding those which are PMOs) usually give about the same level

of RNA skipping and dystrophin protein restoration, regardless of the number of days cells were cultured in differentiation media prior to dosing. In some embodiments, the present disclosure provides oligonucleotides that may be able to enter and be active in myoblasts and in myotubes. In some embodiments, a DMD oligonucleotide is tested in vitro in Δ45-52 DMD patient cells (also designated D45-52 or del45-52) or Δ52 DMD patient cells (also designated D52 or del52) with 0, 4 or 7 days of pre-differentiation.

[00704] In some embodiments, DMD oligonucleotides can be tested in any one or more of various animal models, including non-mammalian and mammalian models; including, as non-limiting examples, Caenorhabditis, Drosophila, zebrafish, mouse, rat, cat, dog and pig. See, for example, a review in McGreevey et al. 2015 Dis. Mod. Mech. 8: 195-213.

[00705] Example use of mdx mice is reported in, for example: Lu et al. 2003 Nat. Med. 9: 1009; Jearawiriyapaisarn et al. 2008 Mol. Ther., 16, 1624–1629; Yin et al. 2008 Hum. Mol. Genet., 17, 3909–3918; Wu et al. 2009 Mol. Ther., 17, 864–871; Wu et al. 2008 Proc. Natl Acad. Sci. USA, 105, 14814–14819; Mann et al. 2001 Proc. Nat. Acad. Sci. USA 98: 42-47; and Gebski et al. 2003 Hum. Mol. Gen. 12: 1801–1811.

[00706] Efficacy of DMD oligonucleotides can be tested in dogs, such as the Golden Retriever Muscular Dystrophy (GRMD) animal model. Lu et al. 2005 Proc. Natl. Acad. Sci. U S A 102:198-203; Alter et al. 2006 Nat. Med. 12:175-7; McClorey et al. 2006 Gene Ther. 13:1373-81; and Yokota et al. 2012 Nucl. Acid Ther. 22: 306.

[00707] A DMD oligonucleotide can be evaluated in vivo in a test animal for efficient delivery to various tissues (e.g., skeletal, heart and/or diaphragm muscle); this can be tested, in non-limiting examples, by hybridization ELISA and tests for distribution in animal tissue.

[00708] A DMD oligonucleotide can be evaluated in vivo in a test animal for plasma PK; this can be tested, as non-limiting examples, by assaying for AUC (area under the curve) and half-life.

[00709] In some embodiments, DMD oligonucleotides can be tested in vivo, via an intramuscular administration a muscle of a test animal.

[00710] In some embodiments, DMD oligonucleotides can be tested in vivo, via an intramuscular administration into the gastrocnemius muscle of a test animal.

[00711] In some embodiments, DMD oligonucleotides can be tested in vivo, via an intramuscular administration into the gastrocnemius muscle of a mouse.

[00712] In some embodiments, DMD oligonucleotides can be tested in vivo, via an intramuscular administration into the gastrocnemius muscle of a mouse model transgenic for the entire human dystrophin locus. See, for example: Bremmer-Bout et al. 2004 Mol. Ther. 10, 232–240.

[00713] Additional tests which can be performed to evaluate the efficacy of DMO oligonucleotides include centrally nucleated fiber counts and dystrophin-positive fiber counts, and functional grip strength analysis. See, as non-limiting examples, experimental protocols reported in: Yin et al. 2009 Hum. Mol. Genet. 18: 4405-4414.

[00714] Additional methods of testing DMD oligonucleotides include, as non-limiting example, methods reported in: Kinali et al. 2009 Lancet 8: 918; Bertoni et al. 2003 Hum. Mol. Gen. 12: 1087–1099.

Certain Embodiments of Oligonucleotides and Compositions Thereof

[00715] Among other things, the present disclosure provides oligonucleotides, and compositions and methods of use thereof, useful for targeting various genes, including products encoded thereby and/or conditions, diseases and/or disorders associated therewith. In some embodiments, the present disclosure provides oligonucleotides, and compositions and methods of use thereof, for DMD. In some embodiments, the present disclosure provides a DMD oligonucleotide, wherein the base sequence of the DMD oligonucleotide is or comprises at least 15 contiguous bases of the sequence of any DMD oligonucleotide listed herein. In some embodiments, the present disclosure provides a DMD oligonucleotide, wherein the base sequence of the DMD oligonucleotide is or comprises at least 15 contiguous bases of the sequence of any DMD oligonucleotide listed herein, and wherein the DMD oligonucleotide is less than about 50 bases long. In some embodiments, the present disclosure provides an oligonucleotide or an oligonucleotide composition which comprises a non-negatively charged internucleotidic linkage.

[00716] In some embodiments, the present disclosure provides a chirally controlled composition of a DMD oligonucleotide (a plurality of DMD oligonucleotides), wherein the base sequence of the DMD oligonucleotide is or comprises at least 15 contiguous bases of the sequence of any DMD oligonucleotide listed herein. In some embodiments, the present disclosure provides a chirally controlled composition of a DMD oligonucleotide, wherein the base sequence of the DMD oligonucleotide is or comprises at least 15 contiguous bases of the sequence of any DMD oligonucleotide listed herein, and wherein the DMD oligonucleotide is less than about 50 bases long.

[00717] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide having a sequence consisting of or comprising a sequence or a 15 base portion thereof found in any oligonucleotide listed in Table A1, wherein one or more U may be optionally and independently replaced with T or vice versa.

[00718] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence of UCAAGGAAGAUGGCAUUUCU,

CUCCGGUUCUGAAGGUGUUC, or UUCUGAAGGUGUUCUUGUAC, or a portion thereof at least 15 bases long, wherein each U can be optionally and independently replaced by T, wherein at least one internucleotidic linkage is a chirally controlled internucleotidic linkage. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence of UCAAGGAAGAUGGCAUUUCU, CUCCGGUUCUGAAGGUGUUC, or UUCUGAAGGUGUUCUUGUAC, or a portion thereof at least 15 bases long, wherein each U can be optionally and independently replaced by T, wherein at least one chirally controlled internucleotidic linkage has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, **III**, or a salt form thereof. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence of UCAAGGAAGAUGGCAUUUCU, CUCCGGUUCUGAAGGUGUUC, or UUCUGAAGGUGUUCUUGUAC, or a portion thereof at least 15 bases long, wherein each U can be optionally and independently replaced by T, wherein at least one chirally controlled internucleotidic linkage has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence of UCAAGGAAGAUGGCAUUUCU, CUCCGGUUCUGAAGGUGUUC, or UUCUGAAGGUGUUCUUGUAC, or a portion thereof at least 15 bases long, wherein each U can be optionally and independently replaced by T, wherein each internucleotidic linkage has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence of UCAAGGAAGAUGGCAUUUCU, CUCCGGUUCUGAAGGUGUUC, or UUCUGAAGGUGUUCUUGUAC, or a portion thereof at least 15 bases long, wherein each U can be optionally and independently replaced by T, wherein at least one internucleotidic linkage has the structure of formula **I-c** or a salt form thereof. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence of UCAAGGAAGAUGGCAUUUCU, CUCCGGUUCUGAAGGUGUUC, or UUCUGAAGGUGUUCUUGUAC, or a portion thereof at least 15 bases long, wherein each U can be optionally and independently replaced by T, wherein at least one internucleotidic linkage has the structure of formula **I-c** or a salt form thereof, and at least one internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence of UCAAGGAAGAUGGCAUUUCU, CUCCGGUUCUGAAGGUGUUC, or UUCUGAAGGUGUUCUUGUAC, or a portion thereof at least 15 bases long, wherein each U can be optionally and independently replaced by T, wherein at least one

internucleotidic linkage is a chirally controlled phosphorothioate internucleotidic linkage, and at least one internucleotidic linkage is a non-negatively charged internucleotidic linkage having the structure of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence of UCAAGGAAGAUGGCAUUUCU, CUCCGGUUCUGAAGGUGUUC, or UUCUGAAGGUGUUCUUGUAC, or a portion thereof at least 15 bases long, wherein each U can be optionally and independently replaced by T, wherein each internucleotidic linkage is a phosphodiester.

[00719] In some embodiments, an oligonucleotide comprises one or more internucleotidic linkages which comprise a phosphorus modification prone to "autorelease" under certain conditions. That is, under certain conditions, a particular phosphorus modification is designed such that it self-cleaves from the oligonucleotide to provide, *e.g.*, a phosphate diester such as those found in naturally occurring DNA and RNA. In some embodiments, such a phosphorus modification has a structure of $-O-L-R^1$, wherein each of L and R^1 is independently as described in the present disclosure.

[00720] In some embodiments, a provided oligonucleotide of the present disclosure comprises chemical modifications and/or stereochemistry that delivers desirable properties, e.g., delivery to target cells/tissues/organs, pharmacodynamics, pharmacokinetics, etc.

[00721] In some embodiments, an oligonucleotide comprises a modification at a linkage phosphorus which can be transformed to a natural phosphate linkage by one or more esterases, nucleases, and/or cytochrome P450 enzymes, including but not limited to: CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A7, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2F1, CYP2J2, CYP2R1, CYP2S1, CYP2U1, CYP2W1, CYP3A4, CYP3A5, CYP3A7, CYP3A43, CYP4A11, CYP4A22, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4F22, CYP4V2, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1 (prostacyclin synthase), CYP8B1 (bile acid biosynthesis), CYP11A1, CYP11B1, CYP11B2, CYP17A1, CYP19A1, CYP20A1, CYP21A2, CYP24A1, CYP26A1, CYP26B1, CYP26C1, CYP27A1 (bile acid biosynthesis), CYP27B1 (vitamin D3 1-alpha hydroxylase, activates vitamin D3), CYP27C1 (unknown function), CYP39A1, CYP46A1, and CYP51A1 (lanosterol 14-alpha demethylase).

[00722] In some embodiments, an oligonucleotide comprises a modification at a linkage phosphorus that is a pro-drug moiety, *e.g.*, a P-modification moiety facilitates delivery of an oligonucleotide to a desired location prior to removal. For instance, in some embodiments, a P-modification moiety results from PEGylation at the linkage phosphorus. One of skill in the relevant arts will appreciate that various PEG chain lengths are useful and that the selection of chain length will be determined in part by the result that is sought to be achieved by PEGylation. For instance, in some embodiments, PEGylation is effected in order to reduce RES uptake and extend *in vivo* circulation

lifetime of an oligonucleotide.

[00723] In some embodiments, a PEGylation reagent for use in accordance with the present disclosure is of a molecular weight of about 300 g/mol to about 100,000 g/mol. In some embodiments, a PEGylation reagent is of a molecular weight of about 300 g/mol to about 10,000 g/mol. In some embodiments, a PEGylation reagent is of a molecular weight of about 300 g/mol to about 5,000 g/mol. In some embodiments, a PEGylation reagent is of a molecular weight of about 500 g/mol. In some embodiments, a PEGylation reagent of a molecular weight of about 1000 g/mol. In some embodiments, a PEGylation reagent is of a molecular weight of about 3000 g/mol. In some embodiments, a PEGylation reagent is of a molecular weight of about 5000 g/mol.

[00724] In certain embodiments, a PEGylation reagent is PEG500. In certain embodiments, a PEGylation reagent is PEG1000. In certain embodiments, a PEGylation reagent is PEG3000. In certain embodiments, a PEGylation reagent is PEG5000.

[00725] In some embodiments, an oligonucleotide comprises a P-modification moiety that acts as a PK enhancer, *e.g.*, lipids, PEGylated lipids, *etc.*

[00726] In some embodiments, oligonucleotides of the present disclosure, e.g., DMD oligonucleotides, comprise a P-modification moiety that promotes cell entry and/or endosomal escape, such as a membrane-disruptive lipid or peptide.

[00727] In some embodiments, an oligonucleotide comprises a P-modification moiety that acts as a targeting moiety. In some embodiments, a P-modification moiety is or comprises a targeting moiety. In some embodiments, a target moiety is an entity that is associates with a payload of interest (*e.g.*, with an oligonucleotide or oligonucleotide composition) and also interacts with a target site of interest so that the payload of interest is targeted to the target site of interest when associated with the targeting moiety to a materially greater extent than is observed under otherwise comparable conditions when the payload of interest is not associated with the targeting moiety. A targeting moiety may be, or comprise, any of a variety of chemical moieties, including, for example, small molecule moieties, nucleic acids, polypeptides, carbohydrates, *etc.* Targeting moieties are described, e.g., in Adarsh *et al.*, "Organelle Specific Targeted Drug Delivery – A Review," International Journal of Research in Pharmaceutical and Biomedical Sciences, 2011, p. 895.

[00728] Examples of such targeting moieties include, but are not limited to, proteins (*e.g.* Transferrin), oligopeptides (*e.g.*, cyclic and acyclic RGD-containing oligopeptides), antibodies (monoclonal and polyclonal antibodies, *e.g.* IgG, IgA, IgM, IgD, IgE antibodies), sugars / carbohydrates (*e.g.*, monosaccharides and/or oligosaccharides (mannose, mannose-6-phosphate, galactose, and the like)), vitamins (*e.g.*, folate), or other small biomolecules. In some embodiments, a targeting moiety is a steroid molecule (*e.g.*, bile acids including cholic acid, deoxycholic acid, dehydrocholic acid; cortisone;

digoxigenin; testosterone; cholesterol; cationic steroids such as cortisone having a trimethylaminomethyl hydrazide group attached via a double bond at the 3-position of the cortisone ring, *etc.*). In some embodiments, a targeting moiety is a lipophilic molecule (*e.g.*, alicyclic hydrocarbons, saturated and unsaturated fatty acids, waxes, terpenes, and polyalicyclic hydrocarbons such as adamantine and buckminsterfullerenes). In some embodiments, a lipophilic molecule is a terpenoid such as vitamin A, retinoic acid, retinal, or dehydroretinal. In some embodiments, a targeting moiety is a peptide.

[00729] In some embodiments, a P-modification moiety is a targeting moiety having the structure of $-X-L-R^1$ wherein each of X, L, and R^1 is independently as described in the present disclosure.

[00730] In some embodiments, a P-modification moiety facilitates cell specific delivery.

[00731] In some embodiments, a P-modification moiety may perform one or more than one functions. For instance, in some embodiments, a P-modification moiety acts as a PK enhancer and a targeting ligand. In some embodiments, a P-modification moiety acts as a pro-drug and an endosomal escape agent. Numerous other such combinations are possible and are included in the present disclosure.

Certain Examples of Oligonucleotides and Compositions

[00732] In some embodiments, the present disclosure provides oligonucleotides and/or oligonucleotide compositions that are useful for various purposes, e.g., modulating skipping, reducing levels of transcripts, improving levels of beneficial proteins, treating conditions, diseases and disorders, etc. In some embodiments, the present disclosure provides oligonucleotide compositions with improved properties, *e.g.*, increased activities, reduced toxicities, *etc.* Among other things, oligonucleotides of the present disclosure comprise chemical modifications, stereochemistry, and/or combinations thereof which can improve various properties and activities of oligonucleotides. Non-limiting examples are listed in **Table A1**. In some embodiments, an oligonucleotide type is a type as defined by the base sequence, pattern of backbone linkages, pattern of backbone chiral centers and pattern of backbone phosphorus modifications of an oligonucleotide in Table A1, wherein the oligonucleotide comprises at least one chirally controlled internucleotidic linkage (at least one R or S in "Stereochemistry/Linkage"). In some embodiments, a plurality of oligonucleotides of a particular oligonucleotide type is a plurality of an oligonucleotide in Table A1 (e.g., a plurality of oligonucleotides is a plurality of WV-1095). In some embodiments, a plurality of oligonucleotides in a chirally controlled oligonucleotide composition is a plurality of an oligonucleotide in Table A1 (e.g., a plurality of oligonucleotides is a plurality of WV-1095), wherein the oligonucleotide comprises at least one chirally controlled internucleotidic linkage (at least one R or S in "Stereochemistry/Linkage").

[00733] Table A1 lists non-limiting examples of DMD oligonucleotides. All of the oligonucleotides in Table A1 are DMD oligonucleotides, except for WV-12915, WV-12914, WV-12913,

WV-12912, WV-12911, WV-12910, WV-12909, WV-12908, WV-12907, WV-12906, WV-12905, WV-12904, WV-15887, WV-24100, WV-24101, WV-24102, WV-24103, WV-24104, WV-24105, WV-24106, WV-24107, WV-24108, WV-24109, WV-24110, WV-XBD108, WV-XBD 109, WV-XBD 110, WV-XKCD108, WV-XKCD 109, WV-XKCD 110, which all target Malat-1, which is a gene target different than DMD.

[00734] In some embodiments, the present disclosure pertains to an oligonucleotide or oligonucleotide composition, wherein the base sequence of the oligonucleotide comprises at least 15 contiguous bases, with 1-3 mismatches, of the base sequence of a DMD oligonucleotide disclosed in Table A1. In some embodiments, the present disclosure pertains to an oligonucleotide or oligonucleotide composition, wherein the base sequence of the oligonucleotide comprises at least 15 contiguous bases of the base sequence of a DMD oligonucleotide disclosed in Table A1. In some embodiments, the present disclosure pertains to an oligonucleotide or oligonucleotide composition, wherein the base sequence of the oligonucleotide comprises the base sequence of a DMD oligonucleotide disclosed in Table A1. In some embodiments, the present disclosure pertains to an oligonucleotide or oligonucleotide composition, wherein the base sequence of the oligonucleotide is the base sequence of a DMD oligonucleotide disclosed in Table A1.

[00735] In some embodiments, the present disclosure pertains to an oligonucleotide or oligonucleotide composition, wherein the base sequence of the oligonucleotide comprises at least 15 contiguous bases, with 1-3 mismatches, of the base sequence of a DMD oligonucleotide disclosed in Table A1, or wherein the base sequence of the oligonucleotide comprises at least 15 contiguous bases of the base sequence of a DMD oligonucleotide disclosed in Table A1, or wherein the base sequence of the oligonucleotide comprises the base sequence of a DMD oligonucleotide disclosed in Table A1, or wherein the base sequence of the oligonucleotide is the base sequence of a DMD oligonucleotide disclosed in Table A1; and wherein the oligonucleotide is stereorandom (e.g., not chirally controlled), or the oligonucleotide is chirally controlled, and/or the oligonucleotide comprises at least one internucleotidic linkage which is chirally controlled, and/or the oligonucleotide optionally comprises a sugar modification which is a LNA, and/or the oligonucleotide comprises a sugar which is a natural deoxyribose, a 2'-OMe or a 2'-MOE. In some embodiments, the present disclosure pertains to an oligonucleotide capable of mediating skipping of a DMD exon, wherein the oligonucleotide comprises at least one LNA.

[00736] In the following table ID indicates identification or oligonucleotide number; and Description indicates the modified sequence.

Table A1. Example Oligonucleotides.

ID	Description	Naked Base Sequence	Linkage / Stereochemistry
ONT-395	mU*S mC*S mA*S mA*S mG*S mG*S mA*S mA*S mG*S mA*S mU*S mG*S mG*S mC*S mA*S mU*S mU*S mU*S mC*S mU	UCAAGGAAGAUGGCAUUUCU	SSSSSSSSSSSSSSSSSS
WV-1093	G * G * C * C * A * A * A * C * C * T * C * G * G * C * T * T * A * C * C * T	GGCCAAACCTCGGCTTACCT	XXXXX XXXXX XXXXX XXXX
WV-1094	mG mG mC mC mA mA mA mC mC mU mC mG mG mC mU mU mA mC mC mU	GGCCAAACCUCGGCUUACCU	OOOOO OOOOO OOOOOOOOO
WV-1095	G * RG * RC * RC * RA * RA * RA * RC * RC * RT * RC * RG * RG * RC * RT * RT * RA * RC * RC * RT	GGCCAAACCTCGGCTTACCT	RRRRRRRRRRRRRRRRRRR
WV-1096	G * SG * SC * SC * SA * SA * SA * SC * SC * ST * SC * SG * SG * SC * ST * ST * SA * SC * SC * ST	GGCCAAACCTCGGCTTACCT	SSSSSSSSSSSSSSSSSS
WV-1097	G * SG * SC * SC * SA * S mA mA mC mC mU mC mG mG mCT * ST * SA * SC * SC * ST	GGCCAAACCUCGGCTTACCT	SSSSSOOOOOOOOOSSSSS
WV-1098	mG mG mC mCA * SA * SA * S mCC * ST * SC * SG * S mGC * ST * ST * S mA mC mC mU	GGCCAAACCTCGGCTTACCU	OOOOSSSOSSSSOSSSOOO
WV-1099	G * S mGC * S mCA * S mAA * S mCC * S mUC * S mGG * S mCT * S mUA * S mCC * S mU	GGCCAAACCUCGGCTUACCU	SOSOSOSOSOSOSOSOSOS
WV-1100	mGG * S mCC * S mAA * S mAC * S mCT * S mCG * S mGC * S mUT * S mAC * S mC mU	GGCCAAACCTCGGCUTACCU	OSOSOSOSOSOSOSOSOSO
WV-1101	G * SG * S mC mCA * SA * S mA mCC * ST * SC * S mG mGC * ST * S mU mAC * SC * S mU	GGCCAAACCTCGGCTUACCU	SSOOSSOOSSSOOSSOOSS
WV-1102	G * SG * SC * S mC mA mAA * SC * S mC mU mCG * SG * S mC mU mUA * SC * SC * S mU	GGCCAAACCUCGGCUUACCU	SSSOOOSSOOOSSSOOOSS
WV-1103	G * SG * SC * SC * S mA mA mA mCC * ST * SC * S mG mG mC mUT * SA * SC * SC * S mU	GGCCAAACCTCGGCUTACCU	SSSSOOOOSSSOOOOSSSS
WV-1104	G * SG * SC * S mCA * SA * SA * S mCC * ST * SC * S mGG * SC * ST * S mUA * SC * SC * S mU	GGCCAAACCTCGGCTUACCU	SSSOSSSOSSSOSSSOSSS
WV-1105	mG mG mC mCA * SA * SA * SC * SC * S mU mC mG mG mCT * ST * SA * SC * SC * S mU	GGCCAAACCUCGGCTTACCU	OOOOSSSSSOOOOOSSSSS
WV-1106	G * SG * S mC mC mA mA mA mC mC mUC * S mG mGC * S mUT * SA * SC * SC * S mU	GGCCAAACCUCGGCUTACCU	SSOOOOOOOOSOOSOSSSS
WV-1107	T * C * A * A * G * G * A * A * G * A * T * G * G * C * A * T * T * T * C * T	TCAAGGAAGATGGCATTTCT	XXXXX XXXXX XXXXX XXXX

WV-1108	mU mC mA mA mG mG mA mA mG mA mU mG mG mC mA mU mU mU mC mU	UCAAGGAAGAU GGCAUUUCU	OOOOO OOOOO O OOOOOOO
WV-1109	T * RC * RA * RA * RG * RG * RA * RA * RG * RA * RT * RG * RG * RC * RA * RT * RT * RT * RC * RT	TCAAGGAAGATGGCA TTTCT	RRRRRRRRRRRR RRRRRR
WV-1110	T * SC * SA * SA * SG * SG * SA * SA * SG * SA * ST * SG * SG * SC * SA * ST * ST * ST * SC * ST	TCAAGGAAGATGGCA TTTCT	SSSSSSSSSSSSS SSSS
WV-1111	T * SC * SA * SA * SG * S mG mA mA mG mA mU mG mG mCA * ST * ST * ST * SC * ST	TCAAGGAAGAUGGCA TTTCT	SSSSSOOOOOOOO OSSSS
WV-1112	mU mC mA mAG * SG * SA * S mAG * SA * ST * SG * S mGC * SA * ST * S mU mU mC mU	UCAAGGAAGATGGCA TUUCU	OOOOSSSSOSSSSOS SSOOO
WV-1113	T * S mCA * S mAG * S mGA * S mAG * S mAT * S mGG * S mCA * S mUT * S mUC * S mU	TCAAGGAAGATGGCA UTUCU	SOSOSOSOSOSOS OSOSOS
WV-1114	mUC * S mAA * S mGG * S mAA * S mGA * S mUG * S mGC * S mAT * S mUT * S mC mU	UCAAGGAAGAUGGCA TUTCU	OSOSOSOSOSOSO SOSOSO
WV-1115	T * SC * S mA mAG * SG * S mA mAG * SA * ST * S mG mGC * SA * S mU mUT * SC * S mU	TCAAGGAAGATGGCA UUTCU	SSOOSSOOSSSOOS SOOSS
WV-1116	T * SC * SA * S mA mG mGA * SA * S mG mA mUG * SG * S mC mA mUT * ST * SC * S mU	TCAAGGAAGAUGGCA UTTCU	SSSOOOSSOOOSS OOOSSS
WV-1117	T * SC * SA * SA * S mG mG mA mAG * SA * ST * S mG mG mC mAT * ST * ST * SC * S mU	TCAAGGAAGATGGCA TTTCU	SSSSOOOOSSSOO OOSSSS
WV-1118	T * SC * SA * S mAG * SG * SA * S mAG * SA * ST * S mGG * SC * SA * S mUT * ST * SC * S mU	TCAAGGAAGATGGCA UTTCU	SSSOSSSOSSSOSS SOSSS
WV-1119	mU mC mA mAG * SG * SA * SA * SG * S mA mU mG mG mCA * ST * ST * ST * SC * S mU	UCAAGGAAGAUGGCA TTTCU	OOOOSSSSSOOOO OSSSSS
WV-1120	T * SC * S mA mA mG mG mA mA mG mAT * S mG mGC * S mAT * ST * ST * SI * SC * S mU	TCAAGGAAGATGGCA TTTCU	SSOOOOOOOOSO OSOSSSS
WV-1121	G * G * C * C * A * mA mA mC mC mU mC mG mG mCT * T * A * C * C * T	GGCCAAACCUCGGCT TACCT	XXXXXOOOOOO OOXXXXX
WV-1122	mG mG mC mCA * A * A * mCC * T * C * G * mGC * T * T * mA mC mC mU	GGCCAAACCTCGGCT TACCU	OOOOXXXOXXXX OXXXOOO
WV-1123	G * mGC * mCA * mAA * mCC * mUC * mGG * mCT * mUA * mCC * mU	GGCCAAACCUCGGCT UACCU	XOXOXOXOXOXO XOXOXOX
WV-1124	mGG * mCC * mAA * mAC * mCT * mCG * mGC * mUT * mAC * mC mU	GGCCAAACCTCGGCU TACCU	OXOXOXOXOXOX OXOXOXO
WV-1125	G * G * mC mCA * A * mA mC mCT * C * mG mGC * T * mU mAC * C * mU	GGCCAAACCTCGGCT UACCU	XXOOXXOOOXXO OXXOOXX

WV-1126	G * G * C * mC mA mAA * C * mC mU mCG * G * mC mU mUA * C * C * mU	GGCCAAACCUCGGCU UACCU	XXX000XX000X X000XXX
WV-1127	G * G * C * C * mA mA mA mCC * T * C * mG mG mC mUT * A * C * C * mU	GGCCAAACCTCGGCU TACCU	XXXX00000XXX0 000XXXX
WV-1128	G * G * C * mCA * A * A * mCC * T * C * mGG * C * T * mUA * C * C * mU	GGCCAAACCTCGGCT UACCU	XXX0XXX0XXX0 XXX0XXX
WV-1129	mG mG mC mCA * A * A * C * C * mU mC mG mG mCT * T * A * C * C * mU	GGCCAAACCUCGGCT TACCU	0000XXXX0000 00XXXXX
WV-1130	G * G * mC mC mA mA mA mC mC mUC * mG mGC * mUT * A * C * C * mU	GGCCAAACCUCGGCU TACCU	XX0000000X0 0X0XXXX
WV-1131	T * C * A * A * G * mG mA mA mG mA mU mG mG mCA * T * T * T * T * C * T	TCAAGGAAGAUGGCA TTTCT	XXXX0000000 00XXXXX
WV-1132	mU mC mA mAG * G * A * mAG * A * T * G * mGC * A * T * mU mU mC mU	UCAAGGAAGAUGGCA TUUCU	0000XXX0XXXX 0XXX000
WV-1133	T * mCA * mAG * mGA * mAG * mAT * mGG * mCA * mUT * mUC * mU	TCAAGGAAGAUGGCA UTUCU	X0X0X0X0X0X0 X0X0X0X	
WV-1134	mUC * mAA * mGG * mAA * mGA * mUG * mGC * mAT * mUT * mC mU	UCAAGGAAGAUGGCA TUTCU	0X0X0X0X0X0X 0X0X0X0
WV-1135	T * C * mA mAG * G * mA mAG * A * T * mG mGC * A * mU mUT * C * mU	TCAAGGAAGAUGGCA UUTCU	XX0OXX0OXXX0 0XX00XX
WV-1136	T * C * A * mA mG mGA * A * mG mA mUG * G * mC mA mUT * T * C * mU	TCAAGGAAGAUGGCA UTTCU	XXX000XX000X X000XXX
WV-1137	T * C * A * A * mG mG mA mAG * A * T * mG mG mC mAT * T * T * T * C * mU	TCAAGGAAGATGGCA TTTCU	XXXX0000XXX0 000XXXX
WV-1138	T * C * A * mAG * G * A * mAG * A * T * mGG * C * A * mUT * T * C * mU	TCAAGGAAGATGGCA UTTCU	XXX0XXX0XXX0 XXX0XXX
WV-1139	mU mC mA mAG * G * A * A * G * mA mU mG mG mCA * T * T * T * T * C * mU	UCAAGGAAGAUGGCA TTTCU	0000XXXX000 00XXXXX
WV-1140	T * C * mA mA mG mG mA mA mG mAT * mG mGC * mAT * T * T * T * C * mU	TCAAGGAAGATGGCA TTTCU	XX0000000X0 0X0XXXX
WV-1141	mG * mG * mC * mC * mA * mA mA mC mC mU mC mG mG mC mU * mU * mA * mC * mC * mU	GGCCAAACCUCGGCU UACCU	XXXX0000000 00XXXXX
WV-1142	mG mG mC mC mA * mA * mA * mC mC * mU * mC * mG * mG mC * mU * mU * mA mC mC mU	GGCCAAACCUCGGCU UACCU	0000XXX0XXXX 0XXX000
WV-1143	mG * mG mC * mC mA * mA mA * mC mC * mU mC * mG mG * mC mU * mU mA * mC mC * mU	GGCCAAACCUCGGCU UACCU	X0X0X0X0X0X0 X0X0X0X

WV-1144	mG mG * mC mC * mA mA * mA mC * mC mU * mC mG * mG mC * mU mU * mA mC * mC mU	GGCCAAACCUCGGCU UACCU	0X0X0X0X0X0X 0X0X0X0
WV-1145	mG * mG * mC mC mA * mA * mA mC mC mU * mC * mG mG mC * mU * mU mA mC * mC * mU	GGCCAAACCUCGGCU UACCU	XX00XX000XX0 0XX00XX
WV-1146	mG * mG * mC * mC mA mA mA * mC * mC mU mC mG * mG * mC mU mU mA * mC * mC * mU	GGCCAAACCUCGGCU UACCU	XXX000X0000X X000XXX
WV-1147	mG * mG * mC * mC * mA mA mA mC mC * mU * mC * mG mG mG mC mU mU * mA * mC * mC * mU	GGCCAAACCUCGGCU UACCU	XXXX0000XXX0 000XXXX
WV-1148	mG * mG * mC * mC mA * mA * mA * mC mC * mU * mC * mG mG * mC * mU * mU mA * mC * mC * mU	GGCCAAACCUCGGCU UACCU	XXX0XXX0XXX0 XXX0XXX
WV-1149	mG mG mC mC mA * mA * mA * mC * mC * mU mC mG mG mC mU * mU * mA * mC * mC * mU	GGCCAAACCUCGGCU UACCU	0000XXXXX000 00XXXXX
WV-1150	mG * mG * mC mC mA mA mA mC mC mU mC * mG mG mC * mU mU * mA * mC * mC * mU	GGCCAAACCUCGGCU UACCU	XX0000000X0 0X0XXXX
WV-1151	mU * mC * mA * mA * mG * mG mA mA mG mA mU mG mG mC mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX0000000 00XXXXX
WV-1152	mU mC mA mA mG * mG * mA * mA mG * mA * mU * mG * mG mC * mA * mU * mU mU mC mU	UCAAGGAAGAUGGCA UUUCU	0000XXX0XXXX 0XXX000
WV-1153	mU * mC mA * mA mG * mG mA * mA mG * mA mU * mG mG * mC mA * mU mU mU * mU mC * mU	UCAAGGAAGAUGGCA UUUCU	X0X0X0X0X0X0 X0X0X0X	
WV-1154	mU mC * mA mA * mG mG * mA mA * mG mA * mU mG * mG mC * mA mU * mU mU * mC mU	UCAAGGAAGAUGGCA UUUCU	0X0X0X0X0X0X 0X0X0X0
WV-1155	mU * mC * mA mA mG * mG * mA mA mG * mA * mU * mG mG mC * mA * mU mU mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XX00XX00XXX0 0XX00XX
WV-1156	mU * mC * mA * mA mG mG mA * mA * mG mA mU mG * mG * mC mA mU mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXX000XX0X00X X000XXX
WV-1157	mU * mC * mA * mA * mG mG mA mA mG * mA * mU * mG mG mC mA mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXX00000XXX0 000XXXX
WV-1158	mU * mC * mA * mA mG * mG * mA * mA mG * mA * mU * mG mG * mC * mA * mU mU mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXX0XXX0XXX0 XXX0XXX
WV-1159	mU mC mA mA mG * mG * mA * mG * mA mU mG mG mC mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	0000XXXXX000 00XXXXX
WV-1160	mU * mC * mA mA mG mG mA mA mG mA mU * mG mG mC * mA mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XX0000000X0 0X0XXXX
WV-1678	fG * fG * fC * fC * fC * fA * fA * fA * fC * fC * fU * fC * fG * fG * fC * fU * fU * fA * fC * fC * fC * fU	GGCCAAACCUCGGCU UACCU	XXXXX XXXXX XXXX XXXX

WV-1679	mG * mG * fC * fC * mA * mA * mA * fC * fC * fU * fC * mG * mG * fC * fU * fU * mA * fC * fC * fU	GGCCAAACCUCGGCU UACCU	XXXXX XXXXX XXXXX XXXX
WV-1680	fG * fG * mC * mC * fA * fA * fA * mC * mC * mU * mC * fG * fG * mC * mU * mU * fA * mC * mC * mU	GGCCAAACCUCGGCU UACCU	XXXXX XXXXX XXXXX XXXX
WV-1681	mG * fG * mC * fC * mA * fA * mA * fC * mC * fU * mC * fG * mG * fC * mU * fU * mA * fC * mC * fU	GGCCAAACCUCGGCU UACCU	XXXXX XXXXX XXXXX XXXX
WV-1682	mG * mG * mC * mC * mA * mA * fA * fC * fC * fU * fC * fG * fG * fC * mU * mU * mA * mC * mC * mU	GGCCAAACCUCGGCU UACCU	XXXXX XXXXX XXXXX XXXX
WV-1683	fG * fG * fC * fC * fA * fA * mA * mC * mC * mU * mC * mG * mG * mC * fU * fU * fA * fC * fC * fU	GGCCAAACCUCGGCU UACCU	XXXXX XXXXX XXXXX XXXX
WV-1684	fG * fG * fC * fC * mA * mA * mA * fC * fC * mU * fC * fG * fG * fC * mU * mU * mA * fC * fC * mU	GGCCAAACCUCGGCU UACCU	XXXXX XXXXX XXXXX XXXX
WV-1685	mG * mG * mC * mC * fA * fA * fA * mC * mC * fU * mC * mG * mG * mC * fU * fU * fA * mC * mC * fU	GGCCAAACCUCGGCU UACCU	XXXXX XXXXX XXXXX XXXX
WV-1687	rA rG rA rA rA rU rG rC rC rA rU rU rC rC rU rU rG rA	AGAAAUGCCAUCUUC CUUGA	OOOOO OOOOO OOOOOOOO
WV-1709	fU * fC * fA * fA * fG * fG * fA * fA * fG * fA * fU * fG * fG * fC * fA * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-1710	fU * fC * mA * mA * mG * mG * mA * mA * mG * mA * fU * mG * mG * fC * mA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-1711	mU * mC * fA * fA * fG * fG * fA * fA * fG * fA * mU * fG * fG * mC * fA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-1712	mU * fC * mA * fA * mG * fG * mA * fA * mG * fA * mU * fG * mG * fC * mA * fU * mU * fU * mC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-1713	mU * mC * mA * mA * mG * mG * fA * fA * fG * fA * fU * fG * fG * fC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-1714	fU * fC * fA * fA * fG * fG * mA * mA * mG * mA * mU * mG * mG * mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-1715	mU * fC * mA * mA * fG * fG * mA * mA * fG * mA * mU * fG * fG * fC * mA * mU * mU * mU * fC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-1716	fU * mC * fA * fA * mG * mG * fA * fA * mG * fA * fU * mG * mG * mC * fA * fU * fU * fU * mC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-2095	fU * fC * fA * fA * fG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-2096	fU * fC * fA * fA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX

WV-2097	fU * fC * fA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-2098	fU * fC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-2099	fU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-2100	fU * fC * fA * fA * fG * fG mA * mA * mG * mA * mU * mG * mG * mCfA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXOXXXXX XOXXXXX
WV-2101	fU * fC * fA * fA * fGfG mA * mA * mG * mA * mU * mG * mG * mCfAfU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXX00XXXXX X00XXXX
WV-2102	fU * fC * fA * fAfGfG mA * mA * mG * mA * mU * mG * mG * mCfAfUfU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXX000XXXXX X000XXX
WV-2103	fU * fC * fAfAfGfG mA * mA * mG * mA * mU * mG * mG * mCfAfUfUfU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XX0000XXXXX X0000XX
WV-2104	fU * fCfAfAfGfG mA * mA * mG * mA * mU * mG * mG * mCfAfUfUfUfC * fU	UCAAGGAAGAUGGCA UUUCU	X000000XXXXX X000000X
WV-2105	fUfCfAfAfGfG mA * mA * mG * mA * mU * mG * mG * mCfAfUfUfUfCfU	UCAAGGAAGAUGGCA UUUCU	0000000XXXXX X000000
WV-2106	fU * fC * fA * fA * fG * fG * fA * fA * fG * fA * mU * mG * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-2107	mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * fU * fG * fG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-2108	fU * fC * fA * fA * fG * fG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-2109	mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX

WV-2165	mC * mU * mC * mC * mA * mA * mC * mA * mU * mC * mA * mA * mG * mG * mA * mA * mG * mU * mG * mC * mA * mU * mU * mU * mC * mU * mA * mG	CUCCAACAUCAAGGA AG AUGGCAUUUCUAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-2179	mA * mC * mC * mC * mA * mG * mA * mG * mU * mA * mA * mC * mC * mA * mG * mU * mC * mU * mG * mA * mU * mA * mG * mG * mA * mG	ACCAGAGUAACAG UCUGAGUAGGAG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-2180	mC * mA * mC * mC * mC * mA * mG * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU * mG * mA * mG * mU * mA * mG * mG * mA	CACCAGAGUAACAG UCUGAGUAGGA	XXXXX XXXXX XXXXX XXXXX XXXX

WV-2181	mU * mC * mA * mC * mC * mA * mG * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU * mG * mA * mG * mU * mA * mG * mG	UCACCAGAGUAACA GUCUGAGUAGG	XXXXX XXXXX XXXXX XXXX
WV-2182	mG * mU * mC * mA * mC * mC * mA * mG * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU * mG * mA * mG * mU * mA * mG	GUCACCAGAGUAAC AGUCUGAGUAG	XXXXX XXXXX XXXXX XXXX
WV-2183	mG * mU * mU * mG * mU * mG * mU * mC * mA * mC * mC * mA * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU * mG	GUUGUGUCACCAGA GUAACAGUCUG	XXXXX XXXXX XXXXX XXXX
WV-2184	mG * mG * mU * mU * mG * mU * mG * mU * mC * mA * mC * mC * mC * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mC * mU	GGUUGUGUCACCAG AGUAACAGUCU	XXXXX XXXXX XXXXX XXXX
WV-2185	mA * mG * mG * mU * mU * mG * mU * mG * mU * mC * mA * mC * mC * mA * mG * mG * mU * mA * mA * mC * mA * mG * mU * mC	AGGUUGUGUCAC CAGAGUAACAGUC	XXXXX XXXXX XXXXX XXXX
WV-2186	mC * mA * mG * mG * mU * mU * mG * mU * mG * mU * mC * mA * mC * mC * mA * mG * mU * mA * mA * mC * mA * mG * mG * mU	CAGGUUGUGUCA CCAGAGUAACAGU	XXXXX XXXXX XXXXX XXXX
WV-2187	mA * mC * mA * mG * mG * mU * mU * mG * mU * mG * mU * mU * mC * mA * mC * mC * mA * mG * mU * mA * mA * mC * mC * mA * mG	ACAGGUUGUGUC ACCAGAGUAACAG	XXXXX XXXXX XXXXX XXXX
WV-2188	mC * mC * mA * mC * mA * mG * mG * mU * mU * mG * mU * mU * mG * mG * mC * mC * mA * mG * mA * mG * mU * mA * mA * mC	CCACAGGUUGUG UCACCAGAGUAAC	XXXXX XXXXX XXXXX XXXX
WV-2189	mA * mC * mC * mA * mC * mA * mG * mG * mU * mU * mG * mU * mC * mC * mA * mC * mA * mG * mG * mA * mG * mU * mA * mA	ACCACAGGUUGUG UCACCAGAGUAA	XXXXX XXXXX XXXXX XXXX
WV-2190	mA * mA * mC * mC * mC * mA * mC * mA * mG * mG * mU * mU * mG * mU * mC * mC * mA * mA * mG * mG * mA * mG * mU * mA	AACCACAGGUUGU GUCACCAGAGUA	XXXXX XXXXX XXXXX XXXX
WV-2191	mU * mA * mA * mC * mC * mC * mA * mA * mG * mG * mU * mU * mG * mU * mC * mA * mC * mC * mC * mA * mG * mA * mG * mU	UAACCACAGGUUG UGUCACCAGAGU	XXXXX XXXXX XXXXX XXXX
WV-2192	mG * mU * mA * mA * mC * mC * mA * mA * mC * mC * mA * mA * mG * mG * mU * mU * mG * mU * mC * mC * mC * mA * mA * mG * mG	GUAACCACAGGUU GUGUCACCAGAG	XXXXX XXXXX XXXXX XXXX

WV-2193	mA * mG * mU * mA * mA * mC * mC * mA * mC * mA * mG * mG * mU * mU * mG * mU * mG * mU * mC * mA * mC * mC * mA * mG * mA	AGUAACCACAGGU UGUGUCACCAGA	XXXXX XXXXX XXXXX XXXX
WV-2194	mU * mA * mG * mU * mA * mA * mC * mC * mA * mC * mA * mG * mG * mU * mU * mG * mU * mU * mG * mC * mA * mC * mC * mA * mG mG	UAGUAACCACAGG UUGUGUCACCAG	XXXXX XXXXX XXXXX XXXX
WV-2195	mU * mU * mA * mG * mU * mA * mA * mC * mC * mA * mC * mA * mA * mG * mG * mU * mU * mG * mG * mU * mU * mG * mC * mA * mC * mC * mA mA	UUAGUAACCACAG GUUGUGUCACCA	XXXXX XXXXX XXXXX XXXX
WV-2196	mC * mU * mU * mA * mG * mU * mA * mA * mC * mC * mC * mA * mC * mA * mG * mG * mU * mU * mU * mG * mG * mU * mU * mG * mC * mA * mC * mC mC	CUUAGUAACCACA GGUUGUGUCACC	XXXXX XXXXX XXXXX XXXX
WV-2197	mC * mC * mU * mU * mA * mG * mU * mA * mA * mC * mC * mC * mA * mC * mA * mG * mG * mU * mU * mU * mG * mG * mU * mC * mC * mA * mC mC	CCUUAGUAACCACA GGUUGUGUCAC	XXXXX XXXXX XXXXX XXXX
WV-2198	mU * mC * mC * mU * mU * mA * mG * mU * mA * mA * mA * mC * mC * mC * mA * mA * mG * mG * mU * mU * mG * mU * mG * mU * mU * mC * mC * mA mA	UCCUUAGUAACCAC AGGUUGUGUCA	XXXXX XXXXX XXXXX XXXX
WV-2199	mG * mU * mU * mU * mC * mC * mU * mU * mA * mA * mG * mU * mA * mA * mC * mA * mC * mA * mG * mG * mU * mU * mG * mU * mU * mG mG	GUUUCCUUAGUAAC CACAGGUUGUG	XXXXX XXXXX XXXXX XXXX
WV-2200	mA * mG * mU * mU * mU * mC * mC * mU * mU * mA * mA * mG * mU * mA * mA * mC * mC * mA * mG * mG * mU * mU * mU * mG * mG * mU mU	AGUUUCCUUAGUAA CCACAGGUUGU	XXXXX XXXXX XXXXX XXXX
WV-2201	mC * mA * mG * mU * mU * mU * mC * mC * mC * mU * mU * mA * mA * mA * mC * mC * mA * mA * mC * mC * mA * mG * mG * mU * mU * mU * mG mG	CAGUUUCCUUAGU AACCACAGGUUG	XXXXX XXXXX XXXXX XXXX
WV-2202	mG * mC * mA * mG * mU * mU * mU * mC * mC * mC * mU * mU * mA * mG * mU * mA * mA * mC * mC * mA * mA * mC * mA * mG * mG * mU * mU mU	GCAGUUUCCUUAGU AACCACAGGUU	XXXXX XXXXX XXXXX XXXX
WV-2203	mG * mG * mC * mA * mG * mU * mU * mU * mC * mC * mC * mU * mU * mA * mG * mU * mA * mA * mC * mC * mA * mA * mC * mA * mG * mG * mU mU	GGCAGUUUCCUUAG UAACCACAGGU	XXXXX XXXXX XXXXX XXXX
WV-2204	mU * mG * mG * mC * mA * mG * mU * mU * mU * mC * mC * mU * mU * mG * mU * mA * mA * mC * mC * mA * mC * mA * mA * mG * mG	UGGCAGUUUCCUUA GUAACCACAGG	XXXXX XXXXX XXXXX XXXX

WV-2205	mA * mU * mG * mG * mC * mA * mG * mU * mU * mU * mC * mC * mU * mU * mA * mG * mU * mA * mA * mC * mC * mA * mC * mA * mG	AUGGCAGUUUCCUU AGUAACCACAG	XXXXX XXXXX XXXXX XXXX
WV-2206	mA * mG * mA * mU * mG * mG * mC * mA * mG * mU * mU * mU * mU * mC * mU * mA * mG * mU * mA * mA * mC * mC * mA * mC	AGAUGGCAGUUUCCU UAGUAACCAC	XXXXX XXXXX XXXXX XXXX
WV-2207	mG * mA * mG * mA * mU * mG * mG * mC * mA * mG * mU * mU * mU * mC * mC * mU * mU * mA * mA * mG * mU * mA * mA * mC * mC * mC * mA	GAGAUGGCAGUUUCC UUAGUAACCA	XXXXX XXXXX XXXXX XXXX
WV-2208	mG * mG * mA * mG * mA * mU * mG * mG * mC * mA * mG * mU * mU * mU * mC * mC * mU * mU * mA * mG * mU * mA * mA * mC * mC * mC	GGAGAUGGCAGUUUC CUUAGUAACC	XXXXX XXXXX XXXXX XXXX
WV-2209	mU * mG * mG * mA * mG * mA * mU * mG * mG * mC * mA * mG * mU * mU * mC * mC * mU * mA * mG * mU * mA * mA * mC	UGGAGAUGGCAGUUU CCUUAGUAAC	XXXXX XXXXX XXXXX XXXX
WV-2210	mU * mU * mG * mG * mA * mG * mA * mU * mG * mG * mC * mA * mG * mU * mU * mC * mC * mU * mU * mA * mG * mU * mA * mA	UUGGAGAUGGCAGUU UCCUUAGUAA	XXXXX XXXXX XXXXX XXXX
WV-2211	mU * mU * mG * mG * mA * mG * mA * mU * mG * mG * mC * mA * mG * mU * mU * mC * mC * mU * mU * mA * mG * mU * mA * mA	UUUGGAGAUGGCAGU UUCCUUAGUA	XXXXX XXXXX XXXXX XXXX
WV-2212	mA * mG * mU * mU * mG * mG * mA * mG * mA * mU * mU * mG * mG * mC * mA * mG * mU * mU * mC * mC * mU * mU * mA * mG	AGUUUGGAGAUGGCA GUUUCCUUAG	XXXXX XXXXX XXXXX XXXX
WV-2213	mU * mA * mG * mU * mU * mG * mG * mA * mG * mA * mA * mU * mG * mG * mC * mA * mG * mU * mU * mU * mC * mC * mU * mU * mA	UAGUUUGGAGAUGGC AGUUUCCUUA	XXXXX XXXXX XXXXX XXXX
WV-2214	mC * mU * mA * mG * mU * mU * mU * mG * mG * mA * mG * mA * mU * mG * mC * mA * mG * mU * mU * mU * mC * mC * mC * mU * mU	CUAGUUUGGAGAUGG CAGUUUCCUU	XXXXX XXXXX XXXXX XXXX
WV-2215	mU * mC * mU * mA * mG * mU * mU * mU * mG * mG * mA * mG * mA * mU * mG * mC * mA * mG * mU * mU * mU * mC * mC * mC * mU	UCUAGUUUGGAGAUG GCAGUUUCCU	XXXXX XXXXX XXXXX XXXX
WV-2216	mU * mU * mC * mU * mA * mG * mU * mU * mU * mG * mG * mA * mG * mA * mU * mG * mG * mC * mA * mG * mU * mU * mU * mC * mC	UUCUAGUUUGGAGAU GGCAGUUUCC	XXXXX XXXXX XXXXX XXXX

WV-2217	mC * mA * mU * mU * mU * mC * mU * mA * mG * mU * mU * mU * mG * mG * mA * mG * mU * mG * mG * mC * mA * mG * mU * mU	CAUUUCUAGUUUGGA GAUGGCAGUU	XXXXX XXXXX XXXXX XXXX
WV-2218	mG * mC * mA * mU * mU * mU * mC * mU * mA * mG * mU * mU * mU * mG * mG * mA * mG * mU * mG * mC * mA * mG * mU	GCAUUUCUAGUUUGG AGAUGGCAGU	XXXXX XXXXX XXXXX XXXX
WV-2219	mA * mU * mG * mG * mC * mA * mU * mU * mU * mU * mC * mU * mA * mG * mU * mU * mG * mG * mA * mG * mU * mU * mC	AUGGCAUUUCUAGUU UGGAGAUGGC	XXXXX XXXXX XXXXX XXXX
WV-2220	mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mU * mC * mU * mA * mG * mU * mU * mG * mG * mA * mG * mU * mA	GAAGAUGGCAUUUCU AGUUUGGAGA	XXXXX XXXXX XXXXX XXXX
WV-2221	mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mC * mU * mA * mG * mU * mU * mG * mG * mA	AGGAAGAUGGCAUUU CUAGUUUGGA	XXXXX XXXXX XXXXX XXXX
WV-2222	mA * mA * mG * mG * mA * mA * mG * mA * mU * mU * mG * mG * mG * mC * mA * mU * mU * mC * mU * mA * mG * mU * mU * mG	AAGGAAGAUGGCAUU U CUAGUUUGG	XXXXX XXXXX XXXXX XXXX
WV-2223	mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mC * mU * mA * mG * mU * mU * mG	CAAGGAAGAUGGCAU UU CUAGUUUG	XXXXX XXXXX XXXXX XXXX
WV-2224	mC * mA * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU * mA * mG * mU	CAUCAAGGAAGAUGG CAU UUCUAGU	XXXXX XXXXX XXXXX XXXX
WV-2225	mA * mC * mA * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU * mA * mG	ACAUCAAGGAAGAUG GCA UUUCUAG	XXXXX XXXXX XXXXX XXXX
WV-2226	mA * mA * mC * mA * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU * mA	AACAUCAAGGAAGAU GGC AUUUCUA	XXXXX XXXXX XXXXX XXXX
WV-2227	mC * mA * mA * mC * mA * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU	CAACAUCAAGGAAGA UGG CAUUUCU	XXXXX XXXXX XXXXX XXXX
WV-2228	mC * mU * mC * mC * mA * mA * mC * mA * mU * mC * mA * mA * mG * mG * mA * mA * mG * mG * mC * mA * mU * mG * mC * mA * mU	CUCCAACAUCAAGGA AGAU GGCAUU	XXXXX XXXXX XXXXX XXXX

WV-2229	mA * mC * mC * mU * mC * mC * mA * mA * mC * mA * mU * mC * mA * mA * mG * mG * mA * mA * mU * mG * mG * mC * mA	ACCUCCAACAUCAAG GAAGAUGGCA	XXXXX XXXXX XXXXX XXXX
WV-2230	mG * mU * mA * mC * mC * mU * mC * mC * mA * mA * mC * mA * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG	GUACCUCCAACAUCA AGGAAGAUGG	XXXXX XXXXX XXXXX XXXX
WV-2231	mA * mG * mG * mU * mA * mC * mC * mU * mC * mC * mA * mA * mC * mA * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mA * mU	AGGUACCUCCAACAU CAAGGAAGAU	XXXXX XXXXX XXXXX XXXX
WV-2232	mA * mG * mA * mG * mC * mA * mG * mG * mU * mA * mC * mC * mU * mC * mC * mA * mA * mC * mU * mC * mA * mA * mG * mG	AGAGCAGGUACCUCC AACAUCAAGG	XXXXX XXXXX XXXXX XXXX
WV-2233	mC * mA * mG * mA * mG * mC * mA * mG * mG * mU * mA * mC * mC * mU * mC * mC * mA * mA * mU * mC * mA * mA * mG	CAGAGCAGGUACCUC CAACAUCAAG	XXXXX XXXXX XXXXX XXXX
WV-2234	mC * mU * mG * mC * mC * mA * mG * mA * mG * mC * mA * mG * mG * mU * mA * mC * mC * mU * mC * mC * mA * mC * mA * mA	CUGCCAGAGCAGGUA CCUCCAACAU	XXXXX XXXXX XXXXX XXXX
WV-2235	mU * mC * mU * mG * mC * mC * mA * mG * mA * mG * mC * mA * mG * mG * mU * mA * mC * mC * mU * mC * mA * mA * mC * mA	UCUGCCAGAGCAGGU ACCUCCAACA	XXXXX XXXXX XXXXX XXXX
WV-2236	mA * mU * mC * mU * mG * mC * mC * mA * mG * mA * mG * mC * mA * mG * mU * mA * mC * mC * mU * mC * mC * mA * mA * mC	AUCUGCCAGAGCAGG UACCUCCAAC	XXXXX XXXXX XXXXX XXXX
WV-2237	mA * mA * mU * mC * mU * mG * mC * mC * mA * mG * mA * mG * mC * mA * mG * mU * mA * mC * mC * mU * mC * mC * mA * mA	AAUCUGCCAGAGCAG GUACCUCCAA	XXXXX XXXXX XXXXX XXXX
WV-2238	mA * mA * mA * mU * mC * mU * mG * mC * mC * mA * mG * mA * mG * mC * mA * mG * mU * mA * mC * mC * mU * mC * mC * mA	AAAUCUGCCAGAGCA GGUACCUCCA	XXXXX XXXXX XXXXX XXXX
WV-2239	mG * mA * mA * mA * mU * mC * mU * mG * mC * mC * mA * mA * mG * mA * mG * mC * mA * mG * mU * mA * mC * mC * mU * mC * mC	GAAAUCUGCCAGAGC AGGUACCUCC	XXXXX XXXXX XXXXX XXXX
WV-2240	mU * mG * mA * mA * mA * mU * mC * mU * mG * mC * mC * mA * mG * mA * mG * mC * mA * mG * mU * mA * mC * mC * mU * mC	UGAAAUCUGCCAGAG CAGGUACCUC	XXXXX XXXXX XXXXX XXXX

WV-2241	mU * mU * mG * mA * mA * mA * mU * mC * mU * mG * mC * mC * mA * mG * mA * mG * mC * mA * mG * mU * mA * mC * mC * mU	UUGAAAUCUGCCAGA GCAGGUACCU	XXXXX XXXXX XXXXX XXXX
WV-2242	mC * mC * mC * mG * mG * mU * mU * mG * mA * mA * mA * mU * mC * mU * mG * mC * mC * mA * mG * mA * mC * mC * mG	CCCGGUUGAAAUCUG CCAGAGCAGG	XXXXX XXXXX XXXXX XXXX
WV-2243	mC * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU * mU * mG * mA * mA * mU * mC * mU * mG * mC * mC * mA * mA * mG * mA	CCAAGCCCGGUUGAA AUCUGCCAGA	XXXXX XXXXX XXXXX XXXX
WV-2244	mU * mC * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU * mU * mG * mA * mA * mA * mU * mC * mC * mU * mG * mC * mC * mA * mA * mG	UCCAAGCCCGGUUGA AAUCUGCCAG	XXXXX XXXXX XXXXX XXXX
WV-2245	mG * mU * mC * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU * mU * mG * mA * mA * mA * mU * mC * mC * mU * mG * mC * mC * mA	GUCCAAGCCCGGUU GAAAUCUGCCA	XXXXX XXXXX XXXXX XXXX
WV-2246	mU * mC * mU * mG * mU * mC * mC * mC * mA * mA * mA * mG * mC * mC * mC * mG * mG * mU * mU * mG * mA * mA * mA * mU * mC * mC * mU * mG	UCUGUCCAAGCCCGG UUGAAAUCUG	XXXXX XXXXX XXXXX XXXX
WV-2247	mU * mU * mC * mC * mU * mG * mU * mC * mC * mC * mA * mA * mG * mA * mA * mA * mU * mC * mC * mC * mG * mG * mU * mU * mG * mA * mA * mA * mU * mC * mC * mU	UUCUGUCCAAGCCCG GUUGAAAUCU	XXXXX XXXXX XXXXX XXXX
WV-2248	mG * mU * mU * mC * mC * mU * mG * mU * mC * mC * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU * mU * mG * mG * mA * mA * mA * mU * mC	GUUCUGUCCAAGCCC GGUUGAAAUC	XXXXX XXXXX XXXXX XXXX
WV-2249	mA * mG * mU * mU * mC * mU * mG * mU * mU * mC * mC * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU * mU * mG * mG * mA * mA * mA * mU	AGUUCUGUCCAAGC CCGGUUGAAAU	XXXXX XXXXX XXXXX XXXX
WV-2250	mA * mA * mG * mU * mU * mC * mU * mG * mU * mU * mC * mC * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU * mU * mG * mG * mA * mA * mA	AAGUUCUGUCCAA GCCCGGUUGAAA	XXXXX XXXXX XXXXX XXXX
WV-2251	mU * mA * mA * mG * mU * mU * mC * mC * mU * mG * mU * mU * mC * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU * mU * mG * mG * mA * mA	UAAGUUCUGUCC AAGCCCGGUUGAA	XXXXX XXXXX XXXXX XXXX
WV-2252	mG * mU * mA * mA * mG * mU * mU * mC * mC * mU * mU * mG * mC * mA * mG * mC * mC * mC * mG * mG * mU * mU * mG * mC * mA	GUAAGUUCUGU CCAAGCCCGGUUGA	XXXXX XXXXX XXXXX XXXX

WV-2253	mG * mG * mU * mA * mA * mG * mU * mU * mC * mU * mG * mU * mC * mC * mA * mA * mG * mC * mC * mG * mG * mU * mU * mG	GGUAAGUUCUGUCCA AGCCCGGUUG	XXXXX XXXXX XXXXX XXXX
WV-2254	mC * mG * mG * mU * mA * mA * mG * mU * mU * mC * mC * mU * mG * mU * mC * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU	CGGUAAGUUCUGUCC AAGCCCGGUU	XXXXX XXXXX XXXXX XXXX
WV-2255	mU * mC * mG * mG * mU * mA * mA * mG * mU * mU * mC * mU * mG * mU * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU	UCGGUAAGUUCUGUC CAAGCCCGGU	XXXXX XXXXX XXXXX XXXX
WV-2256	mG * mU * mC * mG * mG * mU * mA * mA * mG * mU * mU * mC * mU * mG * mU * mC * mC * mA * mA * mG * mC * mC * mC * mG * mG	GUCGGUAAGUUCUGU CCAAGCCCGG	XXXXX XXXXX XXXXX XXXX
WV-2257	mA * mG * mU * mC * mG * mG * mU * mA * mA * mG * mU * mU * mC * mU * mU * mC * mC * mA * mA * mG * mC * mC * mC * mG	AGUCGGUAAGUUCUG UCCAAGCCCG	XXXXX XXXXX XXXXX XXXX
WV-2258	mC * mA * mG * mU * mC * mG * mG * mU * mA * mA * mG * mU * mU * mC * mU * mG * mU * mC * mC * mA * mA * mG * mC * mC * mC	CAGUCGGUAAGUUCU GUCCAAGCCC	XXXXX XXXXX XXXXX XXXX
WV-2259	mA * mA * mA * mG * mC * mC * mA * mG * mU * mC * mG * mG * mU * mA * mA * mG * mU * mU * mC * mU * mG * mU * mC * mC * mC * mA	AAAGCCAGUCGGUAA GUUCUGUCCA	XXXXX XXXXX XXXXX XXXX
WV-2260	mG * mA * mA * mA * mG * mC * mC * mA * mG * mU * mC * mG * mG * mU * mA * mA * mG * mU * mC * mU * mG * mU * mC * mC * mC	GAAAGCCAGUCGGUA AGUUCUGUCC	XXXXX XXXXX XXXXX XXXX
WV-2261	mG * mU * mC * mA * mC * mC * mA * mC * mC * mC * mA * mU * mC * mA * mC * mC * mU * mC * mU * mG * mU * mG * mA * mU	GUCACCCACCAUCAC CCUCUGUGAU	XXXXX XXXXX XXXXX XXXX
WV-2262	mG * mG * mU * mC * mA * mC * mC * mC * mA * mC * mC * mC * mA * mU * mC * mC * mC * mC * mU * mC * mU * mG * mU * mG * mA	GGUCACCCACCAUCA CCCUCUGUGA	XXXXX XXXXX XXXXX XXXX
WV-2263	mA * mA * mG * mG * mU * mC * mA * mC * mC * mC * mA * mC * mC * mA * mU * mC * mA * mC * mC * mC * mU * mC * mU * mG * mU	AAGGUCACCCACCAU CACCCUCUGU	XXXXX XXXXX XXXXX XXXX
WV-2264	mC * mA * mA * mG * mG * mU * mC * mA * mA * mC * mC * mC * mA * mC * mC * mA * mU * mC * mA * mC * mC * mU * mC * mU * mG	CAAGGUCACCCACCA UCACCCUCUG	XXXXX XXXXX XXXXX XXXX

WV-2265	mU * mC * mA * mA * mG * mG * mU * mC * mA * mC * mC * mC * mA * mC * mA * mU * mC * mA * mC * mC * mU * mC * mU	UCAAGGUCACCCACC AUCACCCUCU	XXXXX XXXXX XXXXX XXXX
WV-2266	mC * mU * mC * mA * mA * mG * mG * mU * mC * mA * mC * mC * mC * mA * mC * mC * mA * mU * mC * mA * mC * mC * mU * mC	CUCAAGGUCACCCAC CAUCACCCUC	XXXXX XXXXX XXXXX XXXX
WV-2267	mC * mU * mU * mG * mA * mU * mC * mA * mA * mA * mG * mC * mA * mG * mA * mG * mA * mA * mG * mC * mC * mA * mG * mU * mC	CUUGAUCAAGCAGAG AAAGCCAGUC	XXXXX XXXXX XXXXX XXXX
WV-2268	mA * mU * mA * mA * mC * mU * mU * mG * mA * mU * mC * mA * mA * mG * mC * mA * mG * mA * mA * mA * mG * mC * mC	AUAACUUGAUCAAGC AGAGAAAGCC	XXXXX XXXXX XXXXX XXXX

WV-2273	mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU * mG * mA * mG * mU * mA * mG * mA * mG	AGUAACAGUCUGAGU AGGAG	XXXXX XXXXX XXXX
WV-2274	mG * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU * mG * mA * mG * mU * mA * mG * mG * mA	GAGUAACAGUCUGAG UAGGA	XXXXX XXXXX XXXX
WV-2275	mA * mG * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU * mG * mA * mU * mA * mG * mG	AGAGUAACAGUCUGA GUAGG	XXXXX XXXXX XXXX
WV-2276	mC * mA * mG * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU * mG * mA * mU * mA * mG	CAGAGUAACAGUCUG AGUAG	XXXXX XXXXX XXXX
WV-2277	mG * mU * mC * mA * mC * mC * mA * mG * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU * mG	GUCACCAGAGUAACA GUCUG	XXXXX XXXXX XXXX
WV-2278	mU * mG * mU * mC * mA * mC * mC * mA * mG * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU	UGUCACCAGAGUAAC AGUCU	XXXXX XXXXX XXXX
WV-2279	mG * mU * mG * mU * mC * mC * mA * mC * mC * mA * mG * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC	GUGUCACCAGAGUAA CAGUC	XXXXX XXXXX XXXX
WV-2280	mU * mG * mU * mG * mU * mC * mA * mC * mC * mA * mG * mA * mG * mU * mG * mU * mA * mC * mA * mG * mU	UGUGUCACCAGAGUA ACAGU	XXXXX XXXXX XXXX
WV-2281	mU * mU * mG * mU * mG * mU * mC * mA * mC * mC * mA * mG * mG * mA * mG * mU * mA * mA * mC * mA * mG	UUGUGUCACCAGAGU AACAG	XXXXX XXXXX XXXX
WV-2282	mG * mG * mU * mU * mU * mG * mU * mU * mC * mA * mC * mC * mA * mG * mA * mG * mU * mA * mA * mC	GGUUGUGUCACCAGA GUAAC	XXXXX XXXXX XXXX
WV-2283	mA * mG * mG * mU * mU * mG * mU * mG * mU * mC * mA * mC * mC * mA * mA * mG * mU * mA * mA * mA	AGGUUGUGUCACCAG AGUAA	XXXXX XXXXX XXXX
WV-	mC * mA * mG * mG * mU * mU * mG * mU * mC * mA *	CAGGUUGUGUCACCA	XXXXX XXXXX

2284	mC * mC * mA * mG * mA * mG * mU * mA	GAGUA	XXXXX XXXX
WV-2285	mA * mC * mA * mG * mG * mU * mU * mG * mU * mC * mA * mC * mC * mA * mG * mA * mG * mU	ACAGGUUGUGUCACC AGAGU	XXXXX XXXXX XXXXX XXXX
WV-2286	mC * mA * mC * mA * mG * mG * mU * mU * mG * mU * mG * mU * mC * mA * mC * mC * mA * mG * mA * mG	CACAGGUUGUGUCAC CAGAG	XXXXX XXXXX XXXXX XXXX
WV-2287	mC * mC * mA * mC * mA * mG * mG * mU * mU * mG * mU * mG * mU * mC * mA * mC * mC * mA * mG * mA	CCACAGGUUGUGUCA CCAGA	XXXXX XXXXX XXXXX XXXX
WV-2288	mA * mC * mC * mA * mC * mA * mG * mG * mU * mU * mG * mU * mU * mC * mC * mA * mC * mC * mA * mG	ACCACAGGUUGUGUC ACCAG	XXXXX XXXXX XXXXX XXXX
WV-2289	mA * mA * mC * mC * mA * mC * mA * mG * mG * mU * mU * mG * mU * mG * mU * mC * mC * mC * mA	AACCACAGGUUGUGU CACCA	XXXXX XXXXX XXXXX XXXX
WV-2290	mU * mA * mA * mC * mC * mC * mA * mA * mG * mG * mU * mU * mG * mU * mU * mC * mA * mC * mC	UAACCACAGGUUGUG UCACC	XXXXX XXXXX XXXXX XXXX
WV-2291	mG * mU * mA * mA * mC * mC * mC * mA * mA * mG * mG * mU * mU * mG * mU * mC * mC * mA * mC	GUAACCACAGGUUGU GUCAC	XXXXX XXXXX XXXXX XXXX
WV-2292	mA * mG * mU * mA * mA * mC * mC * mC * mA * mC * mA * mG * mG * mU * mG * mU * mG * mC * mA	AGUAACCACAGGUUG UGUCA	XXXXX XXXXX XXXXX XXXX
WV-2293	mC * mU * mU * mA * mG * mU * mA * mA * mC * mC * mC * mA * mA * mG * mG * mU * mU * mG	CUUAGUAACCACAGG UUGUG	XXXXX XXXXX XXXXX XXXX
WV-2294	mC * mC * mU * mU * mA * mG * mU * mA * mA * mC * mC * mC * mA * mC * mA * mG * mG * mU * mU * mG	CCUUAGUAACCACAG GUUGU	XXXXX XXXXX XXXXX XXXX
WV-2295	mU * mC * mC * mC * mU * mU * mA * mG * mU * mA * mA * mC * mC * mC * mA * mA * mC * mG * mU * mU * mG	UCCUUAGUAACCACA GGUUG	XXXXX XXXXX XXXXX XXXX
WV-2296	mU * mU * mC * mC * mU * mU * mA * mG * mU * mA * mA * mC * mC * mA * mC * mC * mA * mG * mU * mU	UUCCUUAGUAACCAC AGGUU	XXXXX XXXXX XXXXX XXXX
WV-2297	mU * mU * mU * mC * mC * mU * mU * mA * mG * mU * mA * mA * mC * mC * mA * mC * mA * mG * mU	UUUCCUUAGUAACCA CAGGU	XXXXX XXXXX XXXXX XXXX
WV-2298	mG * mU * mU * mU * mC * mC * mU * mU * mA * mG * mU * mU * mA * mC * mC * mA * mC * mA * mG	GUUUCCUUAGUAACC ACAGG	XXXXX XXXXX XXXXX XXXX
WV-2299	mA * mG * mU * mU * mU * mC * mC * mU * mU * mA * mG * mU * mA * mA * mC * mC * mC * mA * mG	AGUUUCCUUAGUAAC CACAG	XXXXX XXXXX XXXXX XXXX
WV-2300	mG * mC * mA * mG * mU * mU * mC * mC * mU * mU * mA * mG * mU * mA * mA * mC * mC * mA * mC	GCAGUUUCCUUAGUA ACCAC	XXXXX XXXXX XXXXX XXXX
WV-2301	mG * mG * mC * mA * mG * mU * mU * mC * mC * mU * mU * mA * mA * mG * mU * mA * mA * mC * mC * mA	GGCAGUUUCCUUAGU AACCA	XXXXX XXXXX XXXXX XXXX
WV-	mU * mG * mG * mC * mA * mG * mU * mU * mU * mC * mC * mU *	UGGCAGUUUCCUUAG	XXXXX XXXXX

2302	mU * mA * mG * mU * mA * mA * mC * mC	UAACC	XXXXX XXXX
WV-2303	mA * mU * mG * mG * mC * mA * mG * mU * mU * mC * mC * mU * mU * mA * mG * mU * mA * mC	AUGGCAGUUUCCUUA GUAAC	XXXXX XXXXX XXXXX XXXX
WV-2304	mG * mA * mU * mG * mC * mA * mG * mU * mU * mU * mC * mC * mU * mU * mA * mG * mU * mA * mA	GAUGGCAGUUUCCUU AGUAA	XXXXX XXXXX XXXXX XXXX
WV-2305	mA * mG * mA * mU * mG * mG * mC * mA * mG * mU * mU * mU * mC * mC * mU * mU * mA * mG * mU * mA	AGAUGGCAGUUUCCU UAGUA	XXXXX XXXXX XXXXX XXXX
WV-2306	mG * mG * mA * mG * mA * mU * mG * mG * mC * mA * mG * mU * mU * mU * mC * mC * mU * mU * mA * mG	GGAGAUGGCAGUUUC CUUAG	XXXXX XXXXX XXXXX XXXX
WV-2307	mU * mG * mA * mG * mA * mU * mG * mG * mC * mA * mG * mG * mU * mU * mC * mC * mU * mU * mA	UGGAGAUGGCAGUU UCCUUA	XXXXX XXXXX XXXXX XXXX
WV-2308	mU * mU * mG * mG * mA * mG * mA * mU * mG * mG * mC * mA * mG * mU * mU * mU * mC * mC * mU * mU	UUGGAGAUGGCAGU UUCCUU	XXXXX XXXXX XXXXX XXXX
WV-2309	mU * mU * mU * mG * mG * mA * mG * mA * mU * mG * mG * mC * mA * mG * mU * mU * mC * mC * mU	UUUGGAGAUGGCAG UUUCCU	XXXXX XXXXX XXXXX XXXX
WV-2310	mG * mU * mU * mU * mG * mG * mA * mG * mA * mU * mG * mG * mC * mA * mG * mU * mU * mC * mC	GUUUGGAGAUGGCA GUUUCC	XXXXX XXXXX XXXXX XXXX
WV-2311	mC * mU * mA * mG * mU * mU * mG * mG * mA * mG * mA * mU * mG * mC * mA * mG * mU * mU	CUAGUUUGGAGAUG GCAGUU	XXXXX XXXXX XXXXX XXXX
WV-2312	mU * mC * mU * mA * mG * mU * mU * mG * mG * mA * mG * mA * mU * mG * mC * mA * mG * mU	UCUAGUUUGGAGAU GGCAGU	XXXXX XXXXX XXXXX XXXX
WV-2313	mA * mU * mU * mU * mC * mU * mA * mG * mU * mU * mU * mG * mG * mA * mG * mU * mG * mC	AUUUCUAGUUUGGA GAUGGC	XXXXX XXXXX XXXXX XXXX
WV-2314	mU * mG * mG * mC * mA * mU * mU * mC * mU * mA * mG * mU * mU * mU * mG * mA * mG * mA	UGGCAUUUCUAGUUU GGAGA	XXXXX XXXXX XXXXX XXXX
WV-2315	mG * mA * mU * mG * mC * mA * mU * mU * mU * mC * mU * mA * mG * mU * mU * mG * mA	GAUGGCAUUUCUAGU UUGGA	XXXXX XXXXX XXXXX XXXX
WV-2316	mA * mG * mA * mU * mG * mC * mA * mU * mU * mU * mC * mU * mA * mG * mU * mU * mG	AGAUGGCAUUUCUAG UUUGG	XXXXX XXXXX XXXXX XXXX
WV-2317	mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mU * mC * mU * mA * mG * mU * mU * mG	AAGAUGGCAUUUCUA GUUUG	XXXXX XXXXX XXXXX XXXX
WV-2318	mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mU * mC * mU * mA * mG * mU	AGGAAGAUGGCAUU UCUAGU	XXXXX XXXXX XXXXX XXXX
WV-2319	mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mC * mU * mA * mG	AAGGAAGAUGGCAU UUCUAG	XXXXX XXXXX XXXXX XXXX
WV-	mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mC * mA * mG	CAAGGAAGAUGGCAU	XXXXX XXXXX

2320	mC * mA * mU * mU * mU * mC * mU * mA	UUCUA	XXXXX XXXX
WV-2321	mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-2322	mA * mC * mA * mU * mC * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU	ACAUCAAGGAAGAUG GCAUU	XXXXX XXXXX XXXXX XXXX
WV-2323	mC * mA * mA * mC * mA * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA	CAACAUCAAGGAAGA UGGCA	XXXXX XXXXX XXXXX XXXX
WV-2324	mU * mC * mC * mA * mA * mC * mA * mU * mC * mA * mA * mG * mG * mA * mA * mG * mU * mG * mG	UCCAACAUCAAGGAA GAUGG	XXXXX XXXXX XXXXX XXXX
WV-2325	mC * mC * mU * mC * mC * mC * mA * mA * mC * mA * mU * mC * mC * mA * mA * mG * mG * mA * mA * mU	CCUCCAACAUCAAGG AAGAU	XXXXX XXXXX XXXXX XXXX
WV-2326	mA * mG * mG * mU * mA * mC * mC * mU * mC * mC * mA * mA * mC * mA * mU * mC * mA * mA * mG * mG	AGGUACCUCCAACAU CAAGG	XXXXX XXXXX XXXXX XXXX
WV-2327	mC * mA * mG * mG * mU * mA * mC * mC * mU * mC * mC * mA * mA * mC * mA * mU * mC * mA * mA * mG	CAGGUACCUCCAACA UCAAG	XXXXX XXXXX XXXXX XXXX
WV-2328	mA * mG * mA * mG * mC * mA * mG * mU * mA * mC * mC * mA * mU * mC * mC * mA * mA * mU	AGAGCAGGUACCUCC AACAU	XXXXX XXXXX XXXXX XXXX
WV-2329	mC * mA * mG * mA * mG * mC * mA * mG * mU * mA * mC * mC * mU * mC * mC * mA * mA	CAGAGCAGGUACCUC CAACA	XXXXX XXXXX XXXXX XXXX
WV-2330	mC * mC * mA * mG * mA * mG * mC * mA * mG * mG * mU * mA * mC * mC * mU * mC * mC * mA * mA * mC	CCAGAGCAGGUACCU CCAAC	XXXXX XXXXX XXXXX XXXX
WV-2331	mG * mC * mC * mA * mG * mA * mG * mC * mA * mG * mG * mU * mA * mC * mC * mU * mC * mC * mA * mA	GCCAGAGCAGGUACC UCCAA	XXXXX XXXXX XXXXX XXXX
WV-2332	mU * mG * mC * mC * mA * mG * mA * mG * mC * mA * mG * mG * mU * mA * mC * mC * mU * mC * mC * mA	UGCCAGAGCAGGUAC CUCCA	XXXXX XXXXX XXXXX XXXX
WV-2333	mC * mU * mG * mC * mC * mA * mG * mA * mG * mC * mA * mG * mG * mU * mA * mC * mC * mU * mC * mC	CUGCCAGAGCAGGUA CCUCC	XXXXX XXXXX XXXXX XXXX
WV-2334	mU * mC * mU * mG * mC * mC * mA * mG * mA * mG * mC * mA * mG * mG * mU * mA * mC * mC * mU * mC	UCUGCCAGAGCAGGU ACCUC	XXXXX XXXXX XXXXX XXXX
WV-2335	mA * mU * mC * mU * mG * mC * mC * mA * mG * mA * mG * mC * mA * mG * mG * mU * mA * mC * mC * mU	AUCUGCCAGAGCAGG UACCU	XXXXX XXXXX XXXXX XXXX
WV-2336	mU * mU * mG * mA * mA * mA * mU * mC * mU * mG * mC * mC * mA * mG * mA * mG * mC * mA * mG * mG	UUGAAAUCUGCCAGA GCAGG	XXXXX XXXXX XXXXX XXXX
WV-2337	mC * mC * mC * mG * mG * mU * mU * mG * mA * mA * mA * mU * mC * mU * mG * mC * mC * mA * mG * mA	CCCGGUUGAAAUCUG CCAGA	XXXXX XXXXX XXXXX XXXX
WV-	mG * mC * mC * mC * mG * mG * mU * mU * mG * mA * mA * mA *	GCCCGGUUGAAAUCU	XXXXX XXXXX

2338	mU * mC * mU * mG * mC * mC * mA * mG	GCCAG	XXXXX XXXX
WV-2339	mA * mG * mC * mC * mC * mG * mU * mU * mG * mA * mA * mA * mU * mC * mU * mG * mC * mC * mA	AGCCCGGUUGAAAUC UGCCA	XXXXX XXXXX XXXXX XXXX
WV-2340	mC * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU * mU * mG * mA * mA * mU * mC * mU * mG	CCAAGCCCGGUUGAA AUCUG	XXXXX XXXXX XXXXX XXXX
WV-2341	mU * mC * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU * mU * mG * mA * mA * mU * mC * mU	UCCAAGCCCGGUUGA AAUCU	XXXXX XXXXX XXXXX XXXX
WV-2342	mG * mU * mC * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU * mU * mG * mA * mA * mU * mC	GUCCAAGCCCGGUUG AAAUC	XXXXX XXXXX XXXXX XXXX
WV-2343	mU * mG * mU * mC * mC * mA * mA * mG * mC * mC * mC * mG * mU * mU * mG * mA * mA * mU	UGUCCAAGCCCGGUU GAAAU	XXXXX XXXXX XXXXX XXXX
WV-2344	mC * mU * mG * mU * mC * mC * mA * mA * mG * mC * mC * mC * mC * mG * mG * mU * mU * mG * mA * mA * mA	CUGUCCAAGCCCGGU UGAAA	XXXXX XXXXX XXXXX XXXX
WV-2345	mU * mC * mU * mG * mU * mC * mC * mA * mA * mG * mC * mC * mC * mC * mG * mU * mU * mG * mA * mA	UCUGUCCAAGCCCGG UUGAA	XXXXX XXXXX XXXXX XXXX
WV-2346	mU * mU * mC * mU * mG * mU * mC * mC * mA * mA * mG * mC * mC * mG * mG * mU * mU * mG * mA	UUCUGUCCAAGCCCG GUUGA	XXXXX XXXXX XXXXX XXXX
WV-2347	mG * mU * mU * mC * mU * mG * mU * mC * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU * mU * mG	GUUCUGUCCAAGCCC GGUUG	XXXXX XXXXX XXXXX XXXX
WV-2348	mA * mG * mU * mU * mC * mU * mG * mU * mC * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU * mU	AGUUCUGUCCAAGCC CGGUU	XXXXX XXXXX XXXXX XXXX
WV-2349	mA * mA * mG * mU * mU * mC * mU * mG * mU * mC * mC * mA * mA * mG * mC * mC * mC * mG * mG * mU	AAGUUCUGUCCAAGC CCGGU	XXXXX XXXXX XXXXX XXXX
WV-2350	mU * mA * mA * mG * mU * mU * mC * mU * mG * mU * mC * mC * mA * mA * mG * mC * mC * mC * mG * mG	UAAGUUCUGUCCAAG CCCGG	XXXXX XXXXX XXXXX XXXX
WV-2351	mG * mU * mA * mA * mG * mU * mU * mC * mU * mG * mU * mC * mC * mA * mG * mC * mC * mC * mG	GUAAGUUCUGUCCAA GCCCG	XXXXX XXXXX XXXXX XXXX
WV-2352	mG * mG * mU * mA * mA * mG * mU * mU * mC * mU * mG * mU * mC * mC * mA * mG * mC * mC * mC	GGUAAGUUCUGUCCA AGCCC	XXXXX XXXXX XXXXX XXXX
WV-2353	mC * mA * mG * mU * mC * mG * mU * mA * mA * mG * mU * mU * mC * mU * mG * mU * mC * mC * mA	CAGUCGGUAAGUUCU GUCCA	XXXXX XXXXX XXXXX XXXX
WV-2354	mC * mC * mA * mG * mU * mC * mG * mG * mU * mA * mA * mG * mU * mU * mC * mU * mG * mU * mC * mC	CCAGUCGGUAAGUUC UGUCC	XXXXX XXXXX XXXXX XXXX
WV-2355	mC * mC * mA * mC * mC * mA * mU * mC * mA * mC * mC * mC * mU * mC * mU * mG * mU * mG * mA * mU	CCACCAUCACCCUCU GUGAU	XXXXX XXXXX XXXXX XXXX
WV-	mC * mC * mC * mA * mC * mC * mA * mU * mC * mA * mC * mC *	CCCACCAUCACCCUC	XXXXX XXXXX

2356	mC * mU * mC * mU * mG * mU * mG * mA	UGUGA	XXXXX XXXX
WV-2357	mC * mA * mC * mC * mC * mA * mC * mC * mA * mU * mC * mA * mC * mC * mC * mU * mC * mU * mG * mU	CACCCACCAUCACCC UCUGU	XXXXX XXXXX XXXXX XXXX
WV-2358	mU * mC * mA * mC * mC * mC * mA * mC * mC * mA * mU * mC * mA * mC * mC * mC * mU * mC * mU * mG	UCACCCACCAUCACC CUCUG	XXXXX XXXXX XXXXX XXXX
WV-2359	mG * mU * mC * mA * mC * mC * mC * mA * mC * mC * mA * mU * mC * mA * mC * mC * mC * mU * mC * mU	GUCACCCACCAUCAC CCUCU	XXXXX XXXXX XXXXX XXX
WV-2360	mG * mG * mU * mC * mA * mC * mC * mC * mA * mC * mC * mA * mU * mC * mA * mC * mC * mC * mU * mC	GGUCACCCACCAUCA CCCUC	XXXXX XXXXX XXXXX XXX
WV-2361	mU * mC * mA * mG * mC * mC * mA * mG * mA * mC * mA * mA * mA * mG * mC * mC * mA * mG * mU * mC	UCAAGCAGAGAAAGC CAGUC	XXXXX XXXXX XXXXX XXX
WV-2362	mU * mU * mG * mA * mU * mC * mA * mA * mG * mC * mA * mG * mA * mG * mA * mA * mG * mC * mC	UUGAUCAAGCAGAGA AAGCC	XXXXX XXXXX XXXX XXX
WV-2363	mU * S mC * S mA * R mA * R mG * R mG * R mA * R mA * R mG * R mA * R mU * R mG * R mG * R mC * R mA * R mU * R mU * R mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSRRRRRRRRRR RRRSS
WV-2364	mU * S mC * S mA * S mG * R mG * R mA * R mA * R mG * R mA * R mU * R mG * R mG * R mC * R mA * R mU * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSRRRRRRRR RRSSSS
WV-2365	mU * S mC * S mA * S mA * S mG * S mG * R mA * R mA * R mG * R mA * R mU * R mG * R mC * R mA * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSRRRRRRR RSSSSS
WV-2366	mU * S mC mA mA mG mG mA mA mG mA mU mG mG mC mA mU mU mU mC * S mU	UCAAGGAAGAUGGCA UUUCU	SOOOOO OOOOO OOOOOOS
WV-2367	mU * S mC * S mC * S mA mA mG mG mA mA mG mA mU mG mG mC mA mU mU mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSOOOOO OOOOO OOOOSS
WV-2368	mU * S mC * S mA * S mA mG mG mA mA mG mA mU mG mG mC mA mU mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSOOOOO OOOOO OOOSSS
WV-2369	mU * S mC * S mA * S mA * S mG mG mA mA mG mA mU mG mG mC mA mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSOOOOO OOOOO OSSSS
WV-2370	mU * S mC * S mA * S mA * S mG * S mG mA mA mG mA mU mG mG mC mA * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSOOOOOOO OSSSSS
WV-2381	mU * mC mA mA mG mG mA mA mG mA mU mG mG mC mA mU mU mU mC * mU	UCAAGGAAGAUGGCA UUUCU	XOOOOO OOOOO OOOOOOX
WV-2382	mU * mC * mA mA mG mG mA mA mG mA mU mG mG mC mA mU mU mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXOOOOO OOOOO

			00000XX
WV-2383	mU * mC * mA * mA mG mG mA mA mG mA mU mG mG mC mA mU mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXX00000 00000 000XXX
WV-2384	mU * mC * mA * mA * mG mG mA mA mG mA mU mG mG mC mA mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXX00000 00000 0XXXX
WV-2385	mU * mC * mA * mA * mG * mG mA mA mG mA mU mG mG mC mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX000000 00XXXXX
WV-2432	fU * fC * fA * fA * fG * fG * mA mA mG mA mU mG mG mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX000000 0XXXXXX
WV-2433	fU * fC * fA * fA * fG * mG mA mA mG mA mU mG mG mC mA * fU * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX000000 00XXXXX
WV-2434	fU * fC * fA * fA * mG mG mA mA mG mA mU mG mG mC mA mU * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXX00000 00000 0XXXX
WV-2435	fU * fC * fA * mA mG mG mA mA mG mA mU mG mG mC mA mU mU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXX00000 00000 000XXX
WV-2436	fU * fC * mA mA mG mG mA mA mG mA mU mG mG mC mA mU mU mU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XX00000 00000 00000XX
WV-2437	fU * mC mA mA mG mG mA mA mG mA mU mG mG mC mA mU mU mU mC * fU	UCAAGGAAGAUGGCA UUUCU	X00000 00000 00000X
WV-2438	fU * SfC * SfA * SfA * SfG * SfG * S mA mA mG mA mU mG mG mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSS00000 SSSSS
WV-2439	fU * SfC * SfA * SfA * SfG * S mG mA mA mG mA mU mG mG mC mA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSS00000 0SSSS
WV-2440	fU * SfC * SfA * SfA * S mG mG mA mA mG mA mU mG mG mC mA mU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSS00000 00000 0SSSS
WV-2441	fU * SfC * SfA * S mA mG mG mA mA mG mA mU mG mG mC mA mU mU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSS00000 00000 00SSS
WV-2442	fU * SfC * S mA mA mG mG mA mA mG mA mU mG mG mC mA mU mU mU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SS00000 00000 0000SS
WV-2443	fU * S mC mA mA mG mG mA mA mG mA mU mG mG mC mA mU mU mU mC * SfU	UCAAGGAAGAUGGCA UUUCU	S00000 00000 0000000S
WV-2444	fU * SfC * SfA * SfA * SfG * SfG * S mA * R mA * R mG * R mA * R mU * R mG * R mG * R mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSRRRRRRS SSSSS
WV-2445	fU * SfC * SfA * SfA * SfG * S mG * R mA * R mA * R mG * R mA * R mU * R mG * R mG * R mC * R mA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSRRRRRRR RSSSSS

WV-2446	fU * SfC * SfA * SfA * S mG * R mG * R mA * R mA * R mG * R mA * R mU * R mG * R mG * R mC * R mA * R mU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSRRRRRRRRR RRSSSS
WV-2447	fU * SfC * SfA * S mA * R mG * R mG * R mA * R mG * R mA * R mU * R mG * R mG * R mC * R mA * R mU * R mU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSRRRRRRRRRR RRRSSS
WV-2448	fU * SfC * S mA * R mA * R mG * R mG * R mA * R mA * R mG * R mA * R mU * R mG * R mG * R mC * R mA * R mU * R mU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSRRRRRRRRRRR RRRRSS
WV-2449	fU * S mC * R mA * R mA * R mG * R mG * R mA * R mA * R mG * R mA * R mU * R mG * R mG * R mC * R mA * R mU * R mU * R mU * R mC * SfU	UCAAGGAAGAUGGCA UUUCU	SRRRRRRRRRRRR RRRRRS
WV-2526	fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * R mG * R mA * R mU * R mG * R mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSRRRRRSS SSSSS
WV-2527	fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * S mG * R mA * R mU * R mG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSRRRSSSS SSSS
WV-2528	fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * SfG * S mA * R mU * SfG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSSRSSSSS SSSS
WV-2529	fU * SfC * SfA * SfG * SfG * SfA * SfA mG mA mU mG mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSOOOOOSS SSSSS
WV-2530	fU * SfC * SfA * SfG * SfG * SfA * SfA * S mG mA mU mG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSOOOSSS SSSSS
WV-2531	fU * SfC * SfA * SfG * SfG * SfA * SfA * SfG * S mA mU * SfG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSSOSSSS SSSS
WV-2532	fU * SfC * SfA * SfG * SfG * SfA * mA * mG * mA * mU * mG * mG * fC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSXXXXXXX SSSSSS
WV-2533	mU * S mC * S mA * S mA * S mG * S mG * S mA * R mA * R mG * R mA * R mU * R mG * R mG * R mC * S mA * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSRRRRRRS SSSSS
WV-2534	mU * S mC * S mA * S mA * S mG * S mG * S mA * S mA * R mG * R mA * R mU * R mG * S mG * S mC * S mA * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSRRRRSS SSSSS
WV-2535	mU * S mC * S mA * S mA * S mG * S mG * S mA * S mA * S mG * R mA * R mU * R mG * S mG * S mC * S mA * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSRRRSSSS SSSS
WV-2536	mU * S mC * S mA * S mA * S mG * S mG * S mA * S mA * S mG * S mA * R mU * S mG * S mG * S mC * S mA * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSSRSSSSS SSSS
WV-2537	mU * S mC * S mA * S mA * S mG * S mG * S mA * S mA * mG * mA * mU * mG * mG * mC * S mA * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSXXXXXXX SSSSSS
WV-2538	L001 * mU * mC * mA * mA * mG * mG * mA * mA * mU	UCAAGGAAGAUGGCA	XXXXXXXXXXX

2538	* mG * mG * mC * mA * mU * mU * mC * mU	UUUCU	XXXXX XXXXX
WV-2578	Mod013L001 * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXXX
WV-2579	Mod014L001 * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXXX
WV-2580	Mod005L001 * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXXX
WV-2581	Mod015L001 * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXXX
WV-2582	Mod016L001 * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXXX
WV-2583	Mod017L001 * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXXX
WV-2584	Mod018L001 * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXXX
WV-2585	Mod019L001 * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXXX
WV-2586	Mod006L001 * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXXX
WV-2587	Mod020L001 * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXXX
WV-2588	Mod021 * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXXX
WV-2625	mC * mA * mA * mA * mG * mA * mA * mG * mA * mU * mG * mG * mG * mC * mA * mU * mU * mC * mU * mA * mG * mU * mU * mC * mU	CAAAGAAGAUGGCAU UUCUA GUUUG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-2627	mG * mC * mA * mA * mA * mG * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mC * mU	GCAAAGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-2628	fG * fC * fA * fA * fA * fG * mA * mG * mA * mU * mG * mG * mC * fA * fU * fU * fU * fC * fU	GCAAAGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-2660	mU * mC * mA * mA * mG * mG * mA mA mG mA mU mG mG mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXXOOOOOO OXXXXXX
WV-2661	mU * mC * mA * mA * mG * mG * mA * mA mG mA mU mG mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOOOOO XXXXXXX
WV-2662	mU * mC * mA * mA * mG * mG * mA * mA * mG mA mU mG * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXOOOX XXXXXX

WV-2663	mU * mC * mA * mA * mG * mG * mA * mA * mG * mA mU * mG * mG * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXOXXXXX XXXX
WV-2664	mU * S mC * S mA * S mA * S mG * S mG * S mA mA mG mA mU mG mG mC * S mA * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOOOOOOO SSSSSS
WV-2665	mU * S mC * S mA * S mA * S mG * S mG * S mA * S mA mG mA mU mG mG * S mC * S mA * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSOOOOOSS SSSSS
WV-2666	mU * S mC * S mA * S mA * S mG * S mG * S mA * S mA * S mG mA mU mG * S mG * S mC * S mA * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSOOOSSS SSSSS
WV-2667	mU * S mC * S mA * S mA * S mG * S mG * S mA * S mA * S mG * S mA mU * S mG * S mC * S mA * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSSOSSSSS SSSS
WV-2668	fU * fC * fA * fA * fG * fG * fA * mA mG mA mU mG mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXOOOOO XXXXXX
WV-2669	fU * fC * fA * fA * fG * fG * fA * fA * mG mA mU mG * fG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXOOOX XXXXXX
WV-2670	fU * fC * fA * fA * fG * fG * fA * fA * fG * mA mU * fG * fG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX
WV-2733	L001 * mG * mG * mC * mC * mA * mA * mA * mC * mC * mU * mC * mG * mG * mC * mU * mA * mC * mU	GGCCAAACCUCGGCU UACCU	XXXXX XXXXX XXXX
WV-2734	L001 * mG * mG * mC * mC * mA * mA * mA * mC * mC * mU * mC * mG * mG * mC * mU * mA * mC * mC * mU * mA * mU	GGCCAAACCUC GGCUUACCUGAAAU	XXXXX XXXXX XXXX
WV-2737	fU * SfC * SfA * SfA * SfG * SfG * S mA mA mG mA * R mU mG mG mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOOORROOO SSSSSS
WV-2738	fU * SfC * SfA * SfA * SfG * SfG * S mA mA mG * R mA * R mU * R mG mG mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOORRROO SSSSSS	
WV-2739	fU * SfC * SfA * SfA * SfG * SfG * S mA mA * R mG * R mA * R mU * R mG * R mG mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSORRRRROS SSSSS	
WV-2740	fU * SfC * SfA * SfA * SfG * SfG * S mA * R mA * R mG mA mU mG * R mG * R mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSRROOOORRS SSSSS	
WV-2741	fU * SfC * SfA * SfA * SfG * SfG * S mA * R mA mG mA mU mG mG * R mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSROOOOOR SSSSSS	
WV-2742	fU * SfC * SfA * SfA * SfG * SfG * S mA * S mA * S mG mA mU mG * S mG * S mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSOOOOSSS SSSSS	
WV-	fU * SfC * SfA * SfA * SfG * SfG * S mA * S mA mG mA mU mG mG * S mC	UCAAGGAAGAUGGCA	SSSSSSSOOOOOSS

2743	* SfA * SfU * SfU * SfU * SfC * SfU	UUUCU	SSSSS
WV-2744	fU * SfC * SfA * SfA * SfG * SfG * S mA * S mA * S mG * S mA * S mU * S mG * S mG * S mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSSSSSSS SSSS
WV-2745	fU * SfC * SfA * SfA * SfG * SfG * S mA mA mG mAfU * S mG mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOOOOSOSS SSSSS
WV-2746	fU * SfC * SfA * SfA * SfG * SfG * S mA * R mA * R mG * R mA * RfU * S mG * R mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSRRRRSRSS SSSSS
WV-2747	fU * SfC * SfA * SfA * S mG * S mG * SfAfA mG mAfU * S mG mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOOOOSOSS SSSSS
WV-2748	fU * SfC * SfA * SfA * S mG * S mG * SfA * RfA * R mG * R mA * RfU * S mG * R mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSRRRRSRSS SSSSS
WV-2749	fU * SfC * SfA * SfA * SfG * SfG * SfA * S mA mG mA mU mG mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOOOOOSS SSSSS
WV-2750	fU * SfC * SfA * SfA * SfG * SfG * SfA * S mA * R mG * R mA * R mU * R mG * R mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSRRRRRSS SSSSS
WV-2752	TCAAGGAAGATGGCATTTCT	TCAAGGAAGATGGCA TTTCT	OOOOO OOOOO OOOOOOOO
WV-2783	mU * S mC * S mA * S mA * SfG * SfG * S mA * R mA * R mG * R mA * R mU * R mG * R mC * SfA * SfU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSRRRRRRRS SSSSS
WV-2784	mU * S mC * S mA * S mA * SfG * SfG * SfA * S mA * R mG * R mA * R mU * R mG * R mG * SfC * SfA * SfU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSRRRRRSS SSSSS
WV-2785	mU * S mC * S mA * S mA * SfG * SfG * SfA * S mG * R mA * R mU * R mG * SfG * SfC * SfA * SfU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSRRRSSSS SSSS	
WV-2786	mU * S mC * S mA * S mA * SfG * SfG * SfA * SfA * SfG * S mA * R mU * SfG * SfG * SfC * SfA * SfU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSSRSSSSS SSSS	
WV-2787	mU * S mC * S mA * S mA * SfG * SfG * S mA mA mG mA mU mG mG mC * SfA * SfU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOOOOOOO SSSSSS	
WV-2788	mU * S mC * S mA * S mA * SfG * SfG * SfA * S mA mG mA mU mG mG * SfC * SfA * SfU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSOOOOOSS SSSSS	
WV-2789	mU * S mC * S mA * S mA * SfG * SfG * SfA * SfA * S mG mA mU mG * SfG * SfC * SfA * SfU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSOOOSSS SSSSS	
WV-2790	mU * S mC * S mA * S mA * SfG * SfG * SfA * SfA * SfG * S mA mU * SfG * SfG * SfC * SfA * SfU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSSOSSSSS SSSS	
WV-2791	mU * S mC * S mA * SfA * SfG * SfG * S mA * R mA * R mG * R mA * R mU * R mG * R mG * R mC * SfA * SfU * SfU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSRRRRRRRS SSSSS	
WV-	mU * S mC * S mA * SfA * SfG * SfG * SfA * S mA * R mG * R mA * R	UCAAGGAAGAUGGCA	SSSSSSRRRRRSS

2792	mU * R mG * R mG * SfC * SfA * SfU * SfU * S mU * S mC * S mU	UUUCU	SSSSS
WV-2793	mU * S mC * S mA * SfA * SfG * SfG * SfA * SfA * S mG * R mA * R mU * R mG * SfG * SfC * SfA * SfU * SfU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSRRRSSSS SSSS
WV-2794	mU * S mC * S mA * SfA * SfG * SfG * SfA * SfA * SfG * S mA * R mU * SfG * SfG * SfC * SfA * SfU * SfU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSSRSSSSS SSSS
WV-2795	mU * S mC * S mA * SfA * SfG * SfG * SfA * SfA * S mG mA mU mG * SfG * SfC * SfA * SfU * SfU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSOOOSSS SSSSS
WV-2796	mU * S mC * S mA * SfA * SfG * SfG * SfA * SfA * SfG * S mA mU * SfG * SfG * SfC * SfA * SfU * SfU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSSOSSSSS SSSS
WV-2797	fU * fC * fA * fA * fG * fG * fA * fA * mG * mA * mU * mG * mA * mU * mG * fC * fA * fU * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX
WV-2798	fU * fC * fA * fA * fG * fG * fA * fA * mG * mA * mU * mG * fG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX
WV-2799	fU * fC * fA * fA * fG * fG * fA * fA * fG * mA * mU * fG * fG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX
WV-2800	fU * fC * fA * fA * fG * fG * fA * mA * mG * mA * mU * mG * mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX
WV-2801	mU * mC * mA * fA * fG * fG * mA * mA * mG * mA * mU * mG * mG * mC * fA * fU * fU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX
WV-2802	mU * mC * mA * fA * fG * fG * fA * mA * mG * mA * mU * mG * mG * fC * fA * fU * fU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX
WV-2803	mU * mC * mA * fA * fG * fG * fA * fA * mG * mA * mU * mG * fG * fC * fA * fU * fU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX
WV-2804	mU * mC * mA * fA * fG * fG * fA * fA * fG * mA * mU * fG * fG * fC * fA * fU * fU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX
WV-2805	mU * mC * mA * fA * fG * fG * fA * fA * mG mA mU mG * fG * fC * fA * fU * fU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXXOOOX XXXXXXX
WV-2806	mU * mC * mA * fA * fG * fG * fA * fA * fG * mA mU * fG * fG * fC * fA * fU * fU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXOXXXXX XXXX
WV-2807	Mod024L001 * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX
WV-2808	Mod026L001 * mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX
WV-2812	fU * fC * fA * fA * fG * fG * mA * mA * mG * mA * BrdU * mG * mG * mC * fA * fU * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXX

WV-2813	fU * fC * fA * fA * fG * fG * fA * fG * mA * BrdU * fG * fG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-2814	mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * BrdU * mG * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-3017	fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * S mG mA BrdU mG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGATGGCA UUUCU	SSSSSSSSOOOSSS SSSSS
WV-3018	fU * fC * fA * fA * fG * fG * fA * fA * mG mA BrdU mG * fG * fC * fA * fU * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXXXXXXOOOX XXXXXXX
WV-3019	fU * SfC * SfA * SfA * SfG * SfG * S mA mA mG mA BrdU mG mG mC * SfA * SfU * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGATGGCA UUUCU	SSSSSSOOOOOOO SSSSSS
WV-3020	fU * fC * fA * fA * fG * fG * mA mA mG mA BrdU mG mG mC * fA * fU * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXXXOOOOOO OXXXXXX
WV-3022	L001 * fU * SfC * SfA * SfA * SfG * SfG * S mA mA mG mA mU mG mG mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	XSSSSSSOOOOOO OSSSSS
WV-3023	Mod015L001 * fU * SfC * SfA * SfA * SfG * SfG * S mA mA mG mA mU mG mG mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	XSSSSSSOOOOOO OSSSSS
WV-3024	Mod006L001 * fU * SfC * SfA * SfA * SfG * SfG * S mA mA mG mA mU mG mG mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	XSSSSSSOOOOOO OSSSSS
WV-3025	L001 * fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * S mG mA mU mG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	XSSSSSSSSOOOSS SSSSS
WV-3026	Mod015L001 * fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * S mG mA mU mG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	XSSSSSSSSOOOSS SSSSS
WV-3027	Mod006L001 * fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * S mG mA mU mG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	XSSSSSSSSOOOSS SSSSS
WV-3028	fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * S mG mA mU mG mG * SfC * SfA * SfU * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSOOOOSS SSSSS
WV-3029	L001 * fU * fC * fA * fA * fG * fG * mA * mA * mG * mA * mU * mG * mG * mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-3030	Mod015L001 * fU * fC * fA * fA * fG * fG * mA * mA * mG * mA * mU * mG * mG * mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-3031	Mod006L001 * fU * fC * fA * fA * fG * fG * mA * mA * mG * mA * mU * mG * mG * mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-3032	Mod020L001 * fU * fC * fA * fA * fG * fG * mA * mA * mG * mA * mU * mG * mG * mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-3033	Mod019L001 * fU * fC * fA * fA * fG * fG * mA * mA * mG * mA * mU * mG * mG * mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX

WV-3034	L001 * fU * fC * fA * fA * fG * fA * fA * mG mA mU mG * fG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXOOOXXXXX XXX
WV-3035	Mod015L001 * fU * fC * fA * fA * fG * fG * fA * fA * mG mA mU mG * fG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXOOOXXXXX XXX
WV-3036	Mod006L001 * fU * fC * fA * fA * fG * fG * fA * fA * mG mA mU mG * fG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXOOOXXXXX XXX
WV-3037	Mod020L001 * fU * fC * fA * fA * fG * fG * fA * fA * mG mA mU mG * fG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXOOOXXXXX XXX
WV-3038	Mod019L001 * fU * fC * fA * fA * fG * fG * fA * fA * mG mA mU mG * fG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXOOOXXXXX XXX
WV-3039	fU * fC * fA * fA * fG * fG * mA mA mG mA * mU mG mG mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXOOOXOO OXXXXX
WV-3040	fU * fC * fA * fA * fG * fG * mA mA mG * mA * mU * mG mG mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXOOOXXXO OXXXXX
WV-3041	fU * fC * fA * fA * fG * fG * mA mA * mG * mA * mU * mG * mG mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXOXXXXX OXXXXX
WV-3042	fU * fC * fA * fA * fG * fG * mA * mA * mG mA mU mG * mG * mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXXOOOX XXXXXX
WV-3043	fU * fC * fA * fA * fG * fG * mA * mA mG mA mU mG mG * mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOOOOO XXXXXX
WV-3044	fU * fC * fA * fA * fG * fG * mA * mA * mG mA mU mG * mG * mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXOOOX XXXXXX
WV-3045	fU * fC * fA * fA * fG * fG * mA * mA mG mA mU mG mG * mC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOOOOO XXXXXX
WV-3046	fU * fC * fA * fA * fG * fG * mA mA mG mAfU * mG mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXOOOOXO XXXXXX
WV-3047	fU * fC * fA * fA * fG * fG * mA * mA * mG * mA * fU * mG * mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX XXX
WV-3048	fU * fC * fA * fA * mG * mG * fAfA mG mAfU * mG mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXOOOOXO XXXXXX
WV-	fU * fC * fA * fA * mG * mG * fA * fA * mG * mA * fU * mG * mG * fC *	UCAAGGAAGAUGGCA	XXXXX XXXXX

3049	fA * fU * fU * fU * fC * fU	UUUCU	XXXXX XXXX
WV-3050	fU * fC * fA * fA * fG * fG * mA * mA * mG * mA * fU * mG * mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-3051	fU * fC * fA * fA * mG * mG * fA * fA * mG * mA * fU * mG * mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-3052	fU * fC * fA * fA * mG * mG * fA * fA * mG mA mU mG * mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXXOOOX XXXXXXX
WV-3053	fU * fC * fA * fA * mG * mG * mA * mA * mG mAfU mG * mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXXOOOX XXXXXXX
WV-3054	fU * fC * fA * fA * mG * mG * fA * fA * mG * mA * mU * mG * mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-3055	fU * fC * fA * fA * mG * mG * mA * mA * mG * mA * fU * mG * mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX XXXX
WV-3056	fU * fC * fA * fA * mG * mG * fAfA mG mA * fU * mG mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOOOXXO XXXXXXX
WV-3057	fU * fC * fA * fA * mG * mG * fA * fA * mG * mA * fU * mG * mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX XXXX
WV-3058	fU * fC * fA * fA * mG * mG * fA * fA * mG * fA * fU * mG * mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX XXXX
WV-3059	fU * fC * fA * fA * mG * mG * fA * fA * mG mA mU mG mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXXOOOO XXXXXXX
WV-3060	fU * fC * fA * fA * mG * mG * fA * fA * mG mAfU * mG mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXXOOXO XXXXXXX
WV-3061	fU * fC * fA * fA * mG * mG * mA * mA * mG mAfU * mG mG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXXOOXO XXXXXXX
WV-3070	fU * SfC * SfA * SfA * SfG * SfG * S mA mA mG mA mU: mG mG mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOOOODOO SSSSSS
WV-3071	fU * SfC * SfA * SfA * SfG * SfG * S mA mA: mG mA: mU mG: mG mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSODODODO SSSSSS
WV-3072	fU * SfC * SfA * SfA * SfG * SfG * S mA: mA mG: mA mU: mG mG: mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSDODODOD SSSSSS
WV-3073	fU * SfC * SfA * SfA * SfG * SfG * S mA: mA mG mA mU: mG mG: mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSDOOODOD SSSSSS
WV-3074	fU * SfC * SfA * SfA * fG:fG: mA mA mG mA mU: mG mG mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSXDDOOOODO OSSSSSS
WV-	fU * SfC * SfA * SfA * mG: mG: mA mA mG mA mU: mG mG mC * SfA *	UCAAGGAAGAUGGCA	SSSXDDOOOODO

3075	SfU * SfU * SfU * SfC * SfU	UUUCU	OSSSSSS
WV-3076	fU * SfC * SfA * SfA * SfG * SfG * SfA * S mA mG mA mU: mG mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSOOODOSS SSSSS
WV-3077	fU * SfC * SfA * SfA * fG:fG:fA * S mA mG mA mU: mG mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSXDDSOOODOS SSSSSS
WV-3078	fU * SfC * SfA * SfA * mG: mG:fA * S mA mG mA mU: mG mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSXDDSOOODOS SSSSSS
WV-3079	fU * SfC * SfA * SfA * SfG * SfG * SfA * S mG mA mU: mG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSOODSSS SSSSS
WV-3080	fU * SfC * SfA * SfA * SfG * SfG * SfA * S mG: mA: mU: mG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSDDDSSS SSSSS
WV-3081	fU * SfC * SfA * SfA * SfG * SfG * SfA * S mG: mA mU: mG * SfG * SfC * SfA * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSDODSSS SSSSS
WV-3082	fU * SfC * SfA * SfA * fG:fG:fA * SfA * S mG mA mU: mG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSXDDSSOODSS SSSSSS
WV-3083	fU * SfC * SfA * SfA * mG: mG:fA * SfA * S mG mA mU: mG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSXDDSSOODSS SSSSSS
WV-3084	Mod015L001 mU * mC * mA * mA * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	OXXXXX XXXXX XXXX XXXX
WV-3085	Mod019L001 mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	OXXXXX XXXXX XXXX XXXX
WV-3086	Mod020L001 mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	OXXXXX XXXXX XXXX XXXX
WV-3087	Mod015L001: mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	DXXXXX XXXXX XXXX XXXX
WV-3088	Mod019L001: mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	DXXXXX XXXXX XXXX XXXX
WV-3089	Mod020L001: mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	DXXXXX XXXXX XXXX XXXX
WV-3113	fU * SfC * SfA * SfA * SfG:fG: mA mA mG mA mU: mG mG mC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSDDOOOODOO SSSSSS
WV-3114	fU * SfC * SfA * SfA * S mG: mG: mA mA mG mA mU: mG mG mC. * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSDDOOOODOO SSSSSS
WV-3115	fU * SfC * SfA * SfA * SfG:fG:fA * S mA mG mA mU: mG mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSDDS0OODOS SSSSSS
WV-	fU * SfC * SfA * SfA * S mG: mG:fA * S mA mG mA mU: mG mG * SfC *	UCAAGGAAGAUGGCA	SSSSDDS0OODOS

3116	SfA * SfU * SfU * SfU * SfC * SfU	UUUCU	SSSSS
WV-3117	fU * SfC * SfA * SfA * SfG:fG:fA * SfA * S mG mA mU: mG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSDDSSOODSSS SSSSS
WV-3118	fU * SfC * SfA * SfA * S mG: mG:fA * SfA * S mG mA mU: mG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSDDSSOODSSS SSSSS
WV-3120	fU * SfC * SfA * SfA * SfG * SfG * SfA * SfG * S mA mU mG * SfG * SfC * SfA * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSSOOSSSS SSSS
WV-3121	fU * fC * fA * fA * fG * fG * fA * fA * fG * mA mU mG * fG * fC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXOOXXXXXX XX
WV-3152	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * S mUfG * S mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSOSOS SSSSS
WV-3153	fU * SfC * SfA * SfA * SfG * SfG * SfA * S mGfA * S mUfG * S mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSOSOSSSS SSSS
WV-3357	L001 mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	OXXXXX XXXXX XXXXX XXXX
WV-3358	L001fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * SfG * S mA mU * SfG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSSSSOSSSS SSSSS
WV-3359	Mod013L001 mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	OXXXXX XXXXX XXXXX XXXX	
WV-3360	Mod013L001fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * SfG * S mA mU * SfG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSSSSOSSSS SSSSS
WV-3361	Mod014L001fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * SfG * S mA mU * SfG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSSSSOSSSS SSSSS
WV-3362	Mod005L001fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * SfG * S mA mU * SfG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSSSSOSSSS SSSSS
WV-3363	Mod015L001fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * SfG * S mA mU * SfG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSSSSOSSSS SSSSS
WV-3364	Mod020L001fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * SfG * S mA mU * SfG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSSSSOSSSS SSSSS
WV-3365	Mod027L001fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * SfG * S mA mU * SfG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSSSSOSSSS SSSSS
WV-3366	Mod029L001fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * SfG * S mA mU * SfG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSSSSOSSSS SSSSS
WV-3463	fU * SfC * SfA * SfA * SfG * SfGfA * S mAfU * S mGfGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSOSOSOSOOS SSSSS

WV-3464	fU * SfC * SfA * SfA * SfG * SfG * SfA * SfAfG * S mAfU * S mG * S mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSOSOSSSSS SSSS
WV-3465	fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * SfG * S mAfU * S mG * SfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSSOSSSSS SSSS
WV-3466	fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * S mG mAfU * S mG mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSOOSOSS SSSSS
WV-3467	fU * SfC * SfA * SfA * SfG * SfG * SfA * SfA * SfG * S mAfU * S mGfG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSSOSOSSS SSSS
WV-3468	fU * SfC * SfA * SfA * SfG * SfG * mA mA mG mAfU * S mG mG * SfC * SfA * SfU * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSXOOOOSOS SSSSS
WV-3469	fU * SfC * SfA * SfA * SfG * SfG * S mA * S mA * S mG * S mA * SfU * S mG * S mG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSSSSSSSSS SSSS
WV-3470	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * SfUfG * S mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSOSOS SSSSS
WV-3471	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * SfU mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSOOOS SSSSS
WV-3472	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSSOOS SSSSS
WV-3473	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSSOOS SSSSS
WV-3506	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfAfU * S mG mGfC * SfA * SfU * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOOSOOS SSSSS
WV-3507	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mAfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOOSOOS SSSSS
WV-3508	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * SfU * S mG mGfC * SfAfU * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSSOOS OSSSS
WV-3509	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfAfU * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSSOOS OSSSS
WV-3510	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfAfU * S mG mGfC * S mA * SfU * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOOSOOS SSSSS
WV-3511	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mAfU * S mG mGfC * S mA * SfU * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOOSOOS SSSSS
WV-3512	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfAfU * S mG mGfC * S mAfU * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOOSOOS OSSSS
WV-3513	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mAfU * S mG mGfC * S mAfU * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOOSOOS OSSSS

WV-3514	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfAfU * S mG mGfC * SfAfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOOSOOS OSSSS
WV-3515	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mAfU * S mG mGfC * SfAfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOOSOOS OSSSS
WV-3516	fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXOX OXXXXXX
WV-3517	Mod030fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXXXXXOXOXO XOXXXXXX
WV-3518	Mod031fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXXXXXOXOXO XOXXXXXX
WV-3519	Mod032fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXXXXXOXOXO XOXXXXXX
WV-3520	Mod033fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXXXXXOXOXO XOXXXXXX
WV-3543	Mod013L001fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSSOO SSSSSS
WV-3544	Mod005L001fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSSOO SSSSSS
WV-3545	Mod015L001fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSSOO SSSSSS
WV-3546	Mod020L001fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSSOO SSSSSS
WV-3547	Mod027L001fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSSOO SSSSSS
WV-3548	Mod029L001fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSSOO SSSSSS
WV-3549	Mod030fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSSOO SSSSSS
WV-3550	Mod032fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSSOO SSSSSS
WV-3551	Mod033fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSSOO SSSSSS
WV-3552	Mod020L001 * fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OXSSSSSSOSOSSO OSSSSSS
WV-3553	Mod005L001 * fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OXSSSSSSOSOSSO OSSSSSS

WV-3554	Mod014L001fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OOSSSSSSOSOSSO OSSSSSS
WV-3555	Mod030 * fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	XSSSSSSOSOSSOO SSSSSS
WV-3556	Mod032 * fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	XSSSSSSOSOSSOO SSSSSS
WV-3557	Mod033 * fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	XSSSSSSOSOSSOO SSSSSS
WV-3558	Mod033 * fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXOXOXO XOXXXXXX
WV-3559	Mod020L001fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXXXXXOXOXO XOXXXXXX
WV-3560	Mod020L001 * fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXOXOXO XOXXXXXX
WV-3753	L001 * fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	XSSSSSSOSOSSOO SSSSSS	
WV-3754	L001fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSSOO SSSSSS	
WV-3820	L001 * fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXOXOXO XOXXXXXX	
WV-3821	L001fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXXXXXOXOXO XOXXXXXX	
WV-3855	Mod015L001 * fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXXOXOXO XOXXXXXX	
WV-3856	Mod015L001fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXXXXXOXOXO XOXXXXXX	
WV-3971	Mod033L001 * fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	XSSSSSSOSOSSOO SSSSSS	
WV-4106	Mod015L001 * fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	XSSSSSSOSOSSOO SSSSSS	
WV-4107	Mod015L001 * SfU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSOSOSSOO SSSSSS	
WV-4191	L001 * SfU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSSOSOSSOO SSSSSS	
WV-4231	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC	UCAAGGAAGAUGGCA UUUC	SSSSSSOSOSSOOS SSSS	

WV-4232	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU	UCAAGGAAGAUGGCA UUU	SSSSSSOSOSSOOS SSS
WV-4233	fC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	CAAGGAAGAUGGCAU UUCU	SSSSSOSOSSOOSS SSSS
WV-4610	Mod020L001 mG * mG * mC * mC * mA * mA * mC * mC * mU * mC * mG * mG * mC * mU * mU * mA * mC * mC * mU	GGCCAAACCUCGGCU UACCU	OXXXXX XXXXX XXXX XXXX
WV-4611	Mod015L001 mG * mG * mC * mC * mA * mA * mC * mC * mU * mC * mG * mG * mC * mU * mU * mA * mC * mC * mU	GGCCAAACCUCGGCU UACCU	OXXXXX XXXXX XXXX XXXX
WV-4614	fU * fU * fC * fU * fG * fU * mA * mA * mG * mG * mU * mU * mU * mU * fU * fA * fU * fG * fU * fG	UUCUGUAAGGUUUU UAUGUG	XXXXX XXXXX XXXX XXXX
WV-4615	fA * fU * fU * fU * fC * fU * mG * mU * mA * mA * mG * mG * mU * mU * fU * fU * fU * fA * fU * fG	AUUUCUGUAAGGUU UUUAUG	XXXXX XXXXX XXXX XXXX
WV-4616	fC * fC * fA * fU * fU * fU * mC * mU * mG * mU * mA * mA * mG * mG * fU * fU * fU * fU * fU * fA	CCAUUUCUGUAAGGU UUUUA	XXXXX XXXXX XXXX XXXX
WV-4617	fA * fU * fC * fC * fA * fU * mU * mC * mU * mG * mU * mA * mA * fG * fG * fU * fU * fU * fU	AUCCAUUUCUGUAAG GUUUU	XXXXX XXXXX XXXX XXXX
WV-4618	fC * fA * fU * fC * fC * fA * mU * mU * mC * mU * mG * mU * mA * fA * fG * fG * fU * fU * fU	CAUCCAUUUCUGUAA GGUUU	XXXXX XXXXX XXXX XXXX
WV-4619	fC * fC * fA * fU * fC * fC * mA * mU * mU * mC * mU * mG * mU * fA * fA * fA * fG * fG * fU * fU	CCAUCCAUUUCUGUA AGGUU	XXXXX XXXXX XXXX XXXX
WV-4620	fG * fC * fC * fA * fU * fC * mC * mA * mU * mU * mC * mU * mG * fU * fA * fA * fG * fG * fU	GCCAUCCAUUUCUGU AAGGU	XXXXX XXXXX XXXX XXXX
WV-4621	fA * fG * fC * fC * fA * fU * mC * mC * mA * mU * mU * mC * mU * fG * fU * fA * fA * fG * fG	AGCCAUCCAUUUCUG UAAGG	XXXXX XXXXX XXXX XXXX
WV-4622	fC * fA * fG * fC * fC * fC * fA * mU * mC * mC * mA * mU * mU * mC * fU * fG * fU * fA * fA * fG	CAGCCAUCCAUUUCU GUAAG	XXXXX XXXXX XXXX XXXX
WV-4623	fU * fC * fA * fG * fC * fC * mA * mU * mC * mC * mA * mU * mU * mU * fC * fU * fG * fU * fA * fA	UCAGCCAUCCAUUUC UGUAA	XXXXX XXXXX XXXX XXXX
WV-4624	fU * fU * fC * fA * fG * fC * mC * mA * mU * mC * mC * mA * mU * mU * fC * fU * fG * fU * fA	UUCAGCCAUCCAUUU CUGUA	XXXXX XXXXX XXXX XXXX
WV-4625	fC * fU * fU * fU * fC * fA * fG * mC * mC * mA * mU * mC * mC * mA * mU * fU * fU * fC * fU * fG * fU	CUUCAGCCAUCCAUU UCUGU	XXXXX XXXXX XXXX XXXX
WV-4626	fA * fC * fU * fU * fC * fA * mG * mC * mC * mA * mU * mC * mC * mA * fU * fU * fU * fU * fC * fU * fG	ACUUCAGCCAUCCAU UUCUG	XXXXX XXXXX XXXX XXXX
WV-4627	fA * fA * fC * fU * fU * fC * mA * mG * mC * mC * mA * mU * mC * mC * fA * fU * fU * fU * fC * fU	AACUUCAGCCAUCCA UUUCU	XXXXX XXXXX XXXX XXXX

WV-4628	fC * fA * fA * fC * fU * fU * mC * mA * mG * mC * mC * mA * mU * mC * fC * fA * fU * fU * fU * fC	CAACUUCAGCCAUCC AUUUC	XXXXX XXXXX XXXXX XXXX
WV-4629	fU * fC * fA * fA * fC * fU * mU * mC * mA * mG * mC * mC * mA * mU * fC * fC * fA * fU * fU * fU	UCAACUUCAGCCAUC CAUUU	XXXXX XXXXX XXXXX XXXX
WV-4630	fA * fU * fC * fA * fA * fC * mU * mU * mC * mA * mG * mC * mC * mA * fU * fC * fC * fA * fU * fU	AUCAACUUCAGCCAU CCAUU	XXXXX XXXXX XXXXX XXXX
WV-4631	fC * fA * fU * fC * fA * fA * mC * mU * mU * mC * mA * mG * mC * mC * fA * fU * fC * fC * fA * fU	CAUCAACUUCAGCCA UCCAU	XXXXX XXXXX XXXXX XXXX
WV-4632	fA * fC * fC * fA * fU * fC * fA * mA * mC * mU * mU * mC * mA * mG * mC * fC * fA * fU * fC * fC * fA	ACAUCAACUUCAGCC AUCCA	XXXXX XXXXX XXXXX XXXX
WV-4633	fA * fA * fC * fC * fA * fU * fC * mA * mA * mC * mU * mU * mC * mA * mG * fC * fC * fC * fA * fU * fC * fC	AACAUCAACUUCAGC CAUCC	XXXXX XXXXX XXXXX XXXX
WV-4634	fG * fA * fA * fA * fA * fC * mA * mU * mC * mA * mA * mC * mU * mU * fC * fC * fA * fG * fC * fC * fA	GAAAACAUCAACUUC AGCCA	XXXXX XXXXX XXXXX XXXX
WV-4635	fC * fA * fG * fG * fA * fA * mA * mA * mC * mA * mU * mC * mA * mA * fU * fC * fC * fA * fG	CAGGAAAACAUCAAC UUCAG	XXXXX XXXXX XXXXX XXXX
WV-4636	fU * fU * fU * fC * fA * fG * mG * mA * mA * mA * mA * mC * mA * mU * fC * fA * fA * fC * fU * fU	UUUCAGGAAAACAUC AACUU	XXXXX XXXXX XXXXX XXXX
WV-4637	fC * fU * fC * fU * fU * fU * mC * mA * mG * mA * mA * mA * mA * mA * fC * fA * fU * fC * fA * fA	CUCUUUCAGGAAAAC AUCAA	XXXXX XXXXX XXXXX XXXX
WV-4638	fU * fU * fC * fC * fU * fC * mU * mU * mC * mA * mG * mG * mA * fA * fA * fA * fC * fA * fU	UUCCUCUUUCAGGAA AACAU	XXXXX XXXXX XXXXX XXXX
WV-4639	fG * fC * fC * fA * fU * fU * mC * mC * mU * mU * mU * mU * mC * fA * fG * fG * fA * fA * fA	GCCAUUCCUCUUUCA GGAAA	XXXXX XXXXX XXXXX XXXX
WV-4640	fG * fG * fC * fC * fA * fU * mU * mC * mC * mU * mC * mU * mU * mU * fC * fC * fA * fG * fG * fA * fA	GGCCAUUCCUCUUUC AGGAA	XXXXX XXXXX XXXXX XXXX
WV-4641	fA * fG * fG * fC * fC * fA * mU * mU * mC * mC * mU * mC * mU * mU * fU * fC * fA * fG * fG * fA	AGGCCAUUCCUCUUU CAGGA	XXXXX XXXXX XXXXX XXXX
WV-4642	fC * fA * fG * fG * fC * fC * mA * mU * mU * mC * mC * mU * mC * mU * fU * fC * fA * fG * fG	CAGGCCAUUCCUCUU UCAGG	XXXXX XXXXX XXXXX XXXX
WV-4643	fG * fC * fA * fG * fG * fC * mC * mA * mU * mU * mC * mC * mU * mC * fU * fU * fU * fC * fA * fG	GCAGGCCAUUCCUCU UUCAG	XXXXX XXXXX XXXXX XXXX
WV-4644	fG * fG * fC * fA * fG * fG * mC * mC * mA * mU * mU * mU * mC * mC * mC * fU * fC * fU * fU * fC * fA	GGCAGGCCAUUCCUC UUUCA	XXXXX XXXXX XXXXX XXXX
WV-4645	fG * fG * fG * fC * fA * fG * mG * mC * mC * mA * mU * mU * mC * mC * fU * fC * fU * fU * fU * fC	GGGCAGGCCAUUCCU CUUUC	XXXXX XXXXX XXXXX XXXX

WV-4646	fA * fG * fG * fG * fC * fA * mG * mG * mC * mC * mA * mU * mU * mC * fC * fU * fC * fU * fU * fU	AGGGCAGGCCAUUCC UCUUU	XXXXX XXXXX XXXXX XXXX
WV-4647	fC * fA * fG * fG * fG * fC * mA * mG * mG * mC * mC * mA * mU * mU * fC * fC * fU * fC * fU * fU	CAGGGCAGGCCAUUC CUCUU	XXXXX XXXXX XXXXX XXXX
WV-4648	fC * fC * fA * fG * fG * fG * mC * mA * mG * mG * mC * mC * mA * mU * fU * fC * fC * fU * fC * fU	CCAGGGCAGGCCAUU CCUCU	XXXXX XXXXX XXXXX XXXX
WV-4649	fC * fC * fC * fC * fA * fG * fG * mG * mC * mA * mG * mG * mC * mC * mA * fU * fU * fC * fC * fU * fC	CCCAGGGCAGGCCAU UCCUC	XXXXX XXXXX XXXXX XXXX
WV-4650	fC * fC * fC * fC * fC * fA * fG * mG * mC * mA * mG * mG * mC * mC * fA * fU * fU * fC * fC * fC * fU	CCCCAGGGCAGGCCA UUCCU	XXXXX XXXXX XXXXX XXXX
WV-4651	fC * fC * fC * fC * fC * fC * fA * mG * mG * mC * mA * mG * mG * mC * fC * fA * fU * fU * fC * fC * fC	CCCCCAGGGCAGGCC AUUCC	XXXXX XXXXX XXXXX XXXX
WV-4652	fU * fC * fC * fC * fC * fC * mA * mG * mG * mC * mA * mG * mG * fC * fC * fC * fA * fU * fU * fU * fC	UCCCCCAGGGCAGGC CAUUC	XXXXX XXXXX XXXXX XXXX
WV-4653	fA * fU * fC * fC * fC * fC * mC * mA * mG * mG * mC * mC * mA * mG * fG * fC * fC * fC * fA * fU * fU	AUCCCCCAGGGCAGG CCAUU	XXXXX XXXXX XXXXX XXXX
WV-4654	fC * fA * fU * fC * fC * fC * mC * mC * mA * mG * mG * mC * mC * mA * fG * fG * fC * fC * fC * fA * fU	CAUCCCCCAGGGCAG GCCAU	XXXXX XXXXX XXXXX XXXX
WV-4655	fG * fC * fA * fU * fC * fC * mC * mC * mC * mA * mG * mG * mG * mC * fA * fG * fG * fC * fC * fC * fA	GCAUCCCCCCAGGGCA GGCCA	XXXXX XXXXX XXXXX XXXX
WV-4656	fA * fG * fC * fA * fU * fC * mC * mC * mC * mA * mG * mG * mG * mG * fC * fA * fG * fG * fG * fC * fC	AGCAUCCCCCCAGGGC AGGCC	XXXXX XXXXX XXXXX XXXX
WV-4657	fC * fA * fG * fC * fC * fA * fU * mC * mC * mC * mC * mA * mG * mG * fG * fC * fA * fG * fG * fG * fC	CAGCAUCCCCCCAGGG CAGGC	XXXXX XXXXX XXXXX XXXX
WV-4658	fU * fC * fC * fA * fG * fG * fC * fA * mU * mC * mC * mC * mC * mA * mG * fG * fG * fG * fC * fC * fA * fG * fG	UCAGCAUCCCCCCAGG GCAGG	XXXXX XXXXX XXXXX XXXX
WV-4659	fU * fU * fC * fC * fA * fG * fC * fC * mA * mU * mC * mC * mC * mC * mC * mA * fG * fG * fG * fG * fC * fA * fG * fG	UUCAGCAUCCCCCCAG GGCAG	XXXXX XXXXX XXXXX XXXX
WV-4660	fU * fU * fU * fC * fC * fA * fG * mC * mA * mU * mC * mC * mC * mC * mC * mC * fA * fG * fG * fG * fG * fC * fC * fA	UUUCAGCAUCCCCCCA GGGCA	XXXXX XXXXX XXXXX XXXX
WV-4661	fA * fU * fU * fU * fC * fC * fA * mG * mC * mA * mU * mC * mC * mC * mC * fC * fC * fA * fG * fG * fG * fG * fC	AUUUCAGCAUCCCCC AGGGC	XXXXX XXXXX XXXXX XXXX
WV-4662	fG * fA * fU * fU * fU * fC * fC * mA * mG * mC * mA * mU * mC * mC * mC * fC * fC * fC * fC * fA * fG * fG * fG * fG	GAUUUCAGCAUCCCC CAGGG	XXXXX XXXXX XXXXX XXXX
WV-4663	fG * fG * fG * fA * fU * fU * fU * mC * mA * mG * mC * mA * mU * mC * mC * fC * fC * fC * fC * fA * fG * fG * fG	GGAUUUCAGCAUCCC CCAGG	XXXXX XXXXX XXXXX XXXX

WV-4664	fA * fG * fG * fA * fU * fU * mU * mC * mA * mG * mC * mA * mU * mC * fC * fC * fC * fC * fA * fG	AGGAUUUCAGCAUCC CCCAG	XXXXX XXXXX XXXXX XXXX
WV-4665	fC * fA * fG * fG * fA * fU * mU * mC * mA * mG * mC * mA * mU * fC * fC * fC * fC * fC * fA	CAGGAUUUCAGCAUC CCCCA	XXXXX XXXXX XXXXX XXXX
WV-4666	fU * fC * fA * fG * fG * fA * mU * mU * mC * mA * mG * mC * mA * fU * fC * fC * fC * fC * fC	UCAGGAUUUCAGCAU CCCCC	XXXXX XXXXX XXXXX XXXX
WV-4667	fU * fU * fC * fA * fG * fG * mA * mU * mU * mC * mA * mG * mC * fA * fU * fC * fC * fC * fC	UUCAGGAUUUCAGCA UCCCC	XXXXX XXXXX XXXXX XXXX
WV-4668	fU * fU * fU * fC * fA * fG * mG * mA * mU * mU * mC * mA * mG * fC * fC * fA * fU * fC * fC * fC	UUUCAGGAUUUCAGC AUCCC	XXXXX XXXXX XXXXX XXXX
WV-4669	fU * fU * fU * fU * fC * fA * mG * mG * mA * mU * mU * mC * mA * fG * fC * fC * fA * fU * fC * fC	UUUUCAGGAUUUCAG CAUCC	XXXXX XXXXX XXXXX XXXX
WV-4670	fU * fU * fU * fU * fU * fC * mA * mG * mA * mU * mU * mU * mC * fA * fG * fC * fA * fU * fC	UUUUUCAGGAUUUCA GCAUC	XXXXX XXXXX XXXXX XXXX
WV-4671	fU * fU * fU * fU * fU * fU * mC * mA * mG * mG * mA * mU * mU * mU * fC * fA * fG * fC * fA * fU	UUUUUUCAGGAUUUC AGCAU	XXXXX XXXXX XXXXX XXXX
WV-4672	fG * fU * fU * fU * fU * fU * mU * mC * mA * mG * mG * mA * mU * mU * fU * fC * fA * fG * fC * fA	GUUUUUUCAGGAUU UCAGCA	XXXXX XXXXX XXXXX XXXX
WV-4673	fU * fG * fU * fU * fU * fU * mU * mU * mC * mA * mG * mG * mA * mU * fU * fU * fC * fA * fG * fC	UGUUUUUUCAGGAU UUCAGC	XXXXX XXXXX XXXXX XXXX
WV-4674	fC * fU * fG * fU * fU * fU * mU * mU * mU * mC * mA * mG * mG * mA * fU * fU * fU * fU * fC * fA * fG	CUGUUUUUUCAGGAU UUCAG	XXXXX XXXXX XXXXX XXXX
WV-4675	fG * fC * fU * fG * fU * fU * mU * mU * mU * mC * mA * mG * mG * fA * fU * fU * fU * fU * fC * fA	GCUGUUUUUUCAGGA UUUCA	XXXXX XXXXX XXXXX XXXX
WV-4676	fA * fG * fC * fU * fG * fU * mU * mU * mU * mU * mC * mA * mG * fG * fA * fU * fU * fU * fU * fC	AGCUGUUUUUUCAGG AUUUC	XXXXX XXXXX XXXXX XXXX
WV-4677	fG * fA * fG * fC * fU * fG * mU * mU * mU * mU * mU * mC * mA * fG * fG * fA * fU * fU * fU * fU	GAGCUGUUUUUUCAG GAUUU	XXXXX XXXXX XXXXX XXXX
WV-4678	fU * fG * fA * fG * fC * fU * fG * mG * mU * mU * mU * mU * mU * mC * fA * fG * fG * fA * fU * fU	UGAGCUGUUUUUUCA GGAUU	XXXXX XXXXX XXXXX XXXX
WV-4679	fU * fU * fG * fA * fG * fC * mU * mG * mU * mU * mU * mU * mU * mU * fC * fA * fG * fG * fA * fU	UUGAGCUGUUUUUUC AGGAU	XXXXX XXXXX XXXXX XXXX
WV-4680	fU * fU * fU * fU * fG * fA * fG * mC * mU * mG * mU * mU * mU * mU * mU * fU * fC * fC * fA * fG * fG * fA	UUUGAGCUGUUUUUU UCAGGA	XXXXX XXXXX XXXXX XXXX
WV-4681	fG * fU * fU * fU * fU * fG * fA * mG * mC * mU * mG * mU * mU * mU * mU * fU * fU * fC * fA * fG * fG	GUUUGAGCUGUUUUU UUCAGG	XXXXX XXXXX XXXXX XXXX

WV-4682	fU * fU * fG * fU * fU * fU * mG * mA * mG * mC * mU * mG * mU * mU * fU * fU * fU * fU * fC * fA	UUGUUUGAGCUGUU UUUUCA	XXXXX XXXXX XXXXX XXXX
WV-4683	fC * fA * fU * fU * fG * fU * mU * mG * mA * mG * mC * mU * mG * fU * fU * fU * fU * fU * fU	CAUUGUUUGAGCUGU UUUUU	XXXXX XXXXX XXXXX XXXX
WV-4684	fG * fC * fA * fU * fU * fG * mU * mU * mG * mA * mG * mC * mU * fG * fU * fU * fU * fU * fU	GCAUUGUUUGAGCUG UUUUU	XXXXX XXXXX XXXXX XXXX
WV-4685	fU * fG * fC * fA * fU * fU * mG * mU * mU * mG * mA * mG * mC * fU * fG * fU * fU * fU * fU	UGCAUUGUUUGAGCU GUUUU	XXXXX XXXXX XXXXX XXXX
WV-4686	fC * fU * fG * fC * fA * fU * mU * mG * mU * mU * mG * mA * mG * fC * fU * fG * fU * fU * fU	CUGCAUUGUUUGAGC UGUUU	XXXXX XXXXX XXXXX XXXX
WV-4687	fU * fC * fU * fG * fC * fA * mU * mU * mG * mU * mU * mG * mA * fG * fC * fU * fG * fU * fU	UCUGCAUUGUUUGAG CUGUU	XXXXX XXXXX XXXXX XXXX
WV-4688	fC * fU * fC * fU * fG * fC * mA * mU * mU * mG * mU * mU * mG * fA * fG * fC * fU * fG * fU	CUCUGCAUUGUUUGA GCUGU	XXXXX XXXXX XXXXX XXXX
WV-4689	fA * fC * fU * fC * fU * fG * mC * mA * mU * mU * mG * mU * mU * fG * fA * fG * fC * fU * fG	ACUCUGCAUUGUUUG AGCUG	XXXXX XXXXX XXXXX XXXX
WV-4690	fU * fA * fC * fU * fC * fU * mG * mC * mA * mU * mU * mG * mU * mU * fU * fG * fA * fG * fC * fU	UACUCUGCAUUGUUU GAGCU	XXXXX XXXXX XXXXX XXXX
WV-4691	fU * fU * fA * fC * fU * fC * mU * mG * mC * mA * mU * mU * mG * mU * mU * fU * fU * fG * fA * fG * fC	UUACUCUGCAUUGUU UGAGC	XXXXX XXXXX XXXXX XXXX
WV-4692	fC * fU * fU * fA * fC * fU * mC * mU * mG * mC * mA * mU * mU * mG * fU * fU * fU * fU * fG * fA * fG	CUUACUCUGCAUUGU UUGAG	XXXXX XXXXX XXXXX XXXX
WV-4693	fU * fC * fU * fU * fA * fC * mU * mC * mU * mG * mC * mA * mU * mU * fG * fU * fU * fU * fG * fA	UCUUACUCUGCAUUG UUUGA	XXXXX XXXXX XXXXX XXXX
WV-4694	fA * fU * fC * fU * fU * fA * mC * mU * mC * mU * mG * mC * mA * mU * fU * fU * fU * fU * fG	AUCUUACUCUGCAUU GUUUG	XXXXX XXXXX XXXXX XXXX
WV-4695	fA * fA * fU * fC * fU * fU * mA * mC * mU * mC * mU * mG * mC * mA * fU * fU * fG * fU * fU * fU	AAUCUUACUCUGCAU UGUUU	XXXXX XXXXX XXXXX XXXX
WV-4696	fC * fA * fA * fA * fU * fC * mU * mU * mA * mC * mU * mC * mU * mG * fC * fA * fU * fU * fG * fU	CAAAUCUUACUCUGC AUUGU	XXXXX XXXXX XXXXX XXXX
WV-4697	fG * fA * fU * fU * fA * fC * fA * mA * mU * mC * mU * mU * mA * mC * fU * fC * fU * fG * fC * fA	GAUACAAAUCUUACU CUGCA	XXXXX XXXXX XXXXX XXXX
WV-4698	fA * fA * fU * fU * fC * fU * mU * mC * mA * mA * mC * mU * mA * fG * fA * fA * fU * fA * fA	AAUUCUUUCAAACUAG AAUAA	XXXXX XXXXX XXXXX XXXX
WV-4699	fU * fG * fA * fA * fU * fU * mC * mU * mU * mC * mA * mA * mC * fU * fA * fG * fA * fA * fU	UGAAUUCUUUCAACU AGAAU	XXXXX XXXXX XXXXX XXXX

WV-4700	fU * fC * fU * fG * fA * fA * mU * mU * mC * mU * mU * mU * mC * mA * fA * fC * fU * fA * fG * fA	UCUGAAUUCUUUCAA CUAGA	XXXXX XXXXX XXXXX XXXX
WV-4701	fA * fU * fU * fC * fU * fG * mA * mA * mU * mU * mC * mU * mU * mU * fC * fA * fA * fC * fU * fA	AUUCUGAAUUCUUUC AACUA	XXXXX XXXXX XXXXX XXXX
WV-4702	fU * fG * fA * fU * fU * fC * mU * mG * mA * mA * mU * mU * mC * mU * fU * fU * fC * fA * fA * fC	UGAUUCUGAAUUCUU UCAAC	XXXXX XXXXX XXXXX XXXX
WV-4703	fA * fC * fU * fG * fA * fU * mU * mC * mU * mG * mA * mA * mU * mU * fC * fU * fU * fU * fC * fA	ACUGAUUCUGAAUUC UUUCA	XXXXX XXXXX XXXXX XXXX
WV-4704	fC * fC * fA * fC * fU * fG * mA * mU * mU * mC * mU * mG * mA * mA * fU * fU * fC * fU * fU * fU	CCACUGAUUCUGAAU UCUUU	XXXXX XXXXX XXXXX XXXX
WV-4705	fU * fC * fC * fC * fA * fC * mU * mG * mA * mU * mU * mC * mU * mG * fA * fA * fU * fU * fC * fU	UCCCACUGAUUCUGA AUUCU	XXXXX XXXXX XXXXX XXXX
WV-4706	fC * fA * fU * fC * fC * fC * mA * mC * mU * mG * mA * mU * mU * mC * fU * fG * fA * fA * fU * fU	CAUCCCACUGAUUCU GAAUU	XXXXX XXXXX XXXXX XXXX
WV-4707	fU * fU * fC * fA * fU * fC * mC * mC * mA * mC * mU * mG * mA * mU * fU * fC * fU * fG * fA * fA	UUCAUCCCACUGAUU CUGAA	XXXXX XXXXX XXXXX XXXX
WV-4708	fA * fC * fU * fU * fU * fC * fA * mU * mC * mC * mC * mA * mC * mU * mG * fA * fU * fU * fC * fU * fG	ACUUCAUCCCACUGA UUCUG	XXXXX XXXXX XXXXX XXXX
WV-4709	fG * fU * fA * fC * fC * fU * fU * mC * mA * mU * mC * mC * mC * mA * mC * fU * fG * fA * fU * fU * fC	GUACUUCAUCCCACU GAUUC	XXXXX XXXXX XXXXX XXXX
WV-4710	fU * fU * fG * fU * fA * fC * mU * mC * mA * mU * mC * mC * mC * mC * fA * fC * fU * fG * fA * fU	UUGUACUUCAUCCCA CUGAU	XXXXX XXXXX XXXXX XXXX
WV-4711	fU * fC * fU * fU * fG * fU * mA * mC * mU * mU * mC * mA * mU * mC * fC * fC * fA * fC * fU * fG	UCUUGUACUUCAUCC CACUG	XXXXX XXXXX XXXXX XXXX
WV-4712	fG * fU * fU * fC * fU * fU * mG * mU * mA * mC * mU * mU * mC * mA * fU * fC * fC * fC * fA * fC	GUUCUUGUACUUCAU CCCAC	XXXXX XXXXX XXXXX XXXX
WV-4713	fG * fU * fG * fU * fU * fC * mU * mU * mG * mU * mA * mC * mU * mU * fC * fA * fU * fC * fC * fC	GUGUUCUUGUACUUC AUCCC	XXXXX XXXXX XXXXX XXXX
WV-4714	fA * fG * fG * fU * fG * fU * mU * mC * mU * mU * mG * mU * mA * mC * fU * fU * fC * fA * fU * fC	AGGUGUUCUUGUACU UCAUC	XXXXX XXXXX XXXXX XXXX
WV-4715	fG * fA * fA * fG * fG * fU * mG * mU * mU * mC * mU * mU * mG * mU * fA * fC * fU * fU * fC * fA	GAAGGUGUUCUUGU ACUUCA	XXXXX XXXXX XXXXX XXXX
WV-4716	fC * fU * fG * fA * fA * fG * mG * mU * mG * mU * mU * mC * mU * mU * fG * fU * fA * fC * fU * fU	CUGAAGGUGUUCUUG UACUU	XXXXX XXXXX XXXXX XXXX
WV-4717	fU * fU * fC * fU * fG * fA * mA * mG * mU * mG * mU * mU * mC * fU * fU * fG * fU * fA * fC	UUCUGAAGGUGUUCU UGUAC	XXXXX XXXXX XXXXX XXXX

WV-4718	fG * fG * fU * fU * fC * fU * mG * mA * mA * mG * mG * mU * mG * mU * fU * fC * fU * fU * fG * fU	GGUUCUGAAGGUGU UCUUGU	XXXXX XXXXX XXXXX XXXX
WV-4719	fC * fC * fG * fG * fU * fU * mC * mU * mG * mA * mA * mG * mG * mU * fG * fU * fU * fC * fU * fU	CCGGUUCUGAAGGUG UUCUU	XXXXX XXXXX XXXXX XXXX
WV-4720	fC * fU * fC * fC * fG * fG * mU * mU * mC * mU * mG * mA * mA * mG * fG * fU * fG * fU * fU * fC	CUCCGGUUCUGAAGG UGUUC	XXXXX XXXXX XXXXX XXXX
WV-4721	fG * fC * fC * fC * fU * fC * fC * mG * mG * mU * mU * mC * mU * mG * mA * fA * fG * fG * fU * fG * fU	GCCUCCGGUUCUGAA GGUGU	XXXXX XXXXX XXXXX XXXX
WV-4722	fU * fU * fG * fC * fC * fU * fU * mC * mC * mG * mG * mU * mU * mC * mU * fG * fA * fA * fG * fG * fU	UUGCCUCCGGUUCUG AAGGU	XXXXX XXXXX XXXXX XXXX
WV-4723	fU * fG * fU * fU * fU * fG * fC * mC * mU * mC * mC * mG * mG * mU * mU * fC * fU * fU * fG * fA * fA * fG	UGUUGCCUCCGGUUC UGAAG	XXXXX XXXXX XXXXX XXXX
WV-4724	fA * fC * fU * fU * fG * fU * fU * mG * mC * mC * mU * mC * mC * mC * mG * mG * fU * fU * fC * fU * fG * fG * fA	ACUGUUGCCUCCGGU UCUGA	XXXXX XXXXX XXXXX XXXX
WV-4725	fC * fA * fA * fC * fU * fG * fG * mU * mU * mG * mC * mC * mU * mC * mC * fG * fG * fU * fU * fC * fU	CAACUGUUGCCUCCG GUUCU	XXXXX XXXXX XXXXX XXXX
WV-4726	fU * fU * fC * fC * fA * fA * fC * fC * mU * mG * mU * mU * mG * mC * mC * mC * fU * fC * fC * fG * fG * fU * fU	UUCAACUGUUGCCUC CGGUU	XXXXX XXXXX XXXXX XXXX
WV-4727	fC * fA * fU * fU * fC * fU * fC * fA * mA * mC * mU * mG * mU * mU * mG * mC * fC * fU * fU * fC * fC * fG * fG	CAUUCAACUGUUGCC UCCGG	XXXXX XXXXX XXXXX XXXX
WV-4728	fU * fU * fC * fA * fU * fU * mC * mA * mA * mC * mU * mG * mU * mU * fU * fG * fC * fC * fC * fU * fC * fC	UUCAUUCAACUGUUG CCUCC	XXXXX XXXXX XXXXX XXXX
WV-4729	fA * fU * fU * fU * fC * fA * mU * mU * mC * mA * mA * mC * mC * mU * mG * fU * fU * fU * fG * fC * fC * fU	AUUUCAUUCAACUGU UGCCU	XXXXX XXXXX XXXXX XXXX
WV-4730	fA * fU * fC * fC * fU * fU * mU * mA * mA * mC * mA * mA * mU * mU * mU * fU * fC * fC * fA * fU * fU * fC * fA	AUCCUUUAACAUUUC AUUCA	XXXXX XXXXX XXXXX XXXX
WV-4731	fG * fA * fA * fU * fC * fC * mU * mU * mU * mA * mA * mC * mC * mA * mU * fU * fU * fC * fA * fU * fU	GAAUCCUUUAACAUU UCAUU	XXXXX XXXXX XXXXX XXXX
WV-4732	fU * fU * fG * fA * fA * fU * mC * mC * mU * mU * mU * mA * mA * mA * mC * fA * fU * fU * fU * fC * fA	UUGAAUCCUUUAACA UUUCA	XXXXX XXXXX XXXXX XXXX
WV-4733	fU * fG * fU * fU * fG * fA * mA * mU * mC * mC * mU * mU * mU * mA * fA * fC * fA * fU * fU * fU	UGUUGAAUCCUUUAA CAUUU	XXXXX XXXXX XXXXX XXXX
WV-4734	fU * fG * fU * fU * fG * fU * fU * mG * mA * mA * mU * mU * mC * mC * mC * mU * mU * fU * fA * fA * fC * fA * fU	UGUGUUGAAUCCUUU AACAU	XXXXX XXXXX XXXXX XXXX
WV-4735	fA * fU * fU * fG * fU * fG * mU * mG * mA * mA * mU * mU * mC * mC * fU * fU * fU * fU * fA * fA * fC	AUUGUGUUGAAUCCU UUAAC	XXXXX XXXXX XXXXX XXXX

WV-4736	fC * fC * fA * fU * fU * fG * mU * mG * mU * mG * mA * mA * mU * fC * fC * fU * fU * fU * fA	CCAUUGUGUUGAAUC CUUUA	XXXXX XXXXX XXXXX XXXX
WV-4737	fA * fG * fC * fC * fA * fU * mU * mG * mU * mG * mU * mU * mG * mA * fA * fU * fC * fC * fU * fU	AGCCAUUGUGUUGAA UCCUU	XXXXX XXXXX XXXXX XXXX
WV-4738	fC * fC * fA * fG * fC * fC * mA * mU * mU * mG * mU * mG * mU * mU * fG * fA * fA * fU * fC * fC	CCAGCCAUUGUGUUG AAUCC	XXXXX XXXXX XXXXX XXXX
WV-4739	fU * fU * fC * fC * fA * fG * mC * mC * mA * mU * mU * mG * mU * mG * fU * fU * fG * fA * fA * fU	UUCCAGCCAUUGUGU UGAAU	XXXXX XXXXX XXXXX XXXX
WV-4740	fG * fC * fU * fU * fC * fC * mA * mG * mC * mC * mA * mU * mU * mG * fU * fG * fU * fU * fG * fA	GCUUCCAGCCAUUGU GUUGA	XXXXX XXXXX XXXXX XXXX
WV-4741	fU * fA * fG * fC * fU * fU * mC * mC * mA * mG * mC * mC * mC * mA * mU * fU * fG * fU * fG * fU * fU	UAGCUUCCAGCCAUU GUGUU	XXXXX XXXXX XXXXX XXXX
WV-4742	fC * fU * fU * fU * fA * fG * fC * mU * mU * mC * mC * mA * mG * mC * mC * fA * fU * fU * fG * fU * fG	CUUAGCUUCCAGCCA UUGUG	XXXXX XXXXX XXXXX XXXX
WV-4743	fU * fC * fC * fC * fU * fU * fU * fA * mG * mC * mU * mU * mC * mC * mC * mA * mG * fC * fC * fC * fA * fU * fU * fU * fG	UCCUUAGCUUCCAGC CAUUG	XXXXX XXXXX XXXXX XXXX
WV-4744	fC * fU * fU * fU * fC * fC * fU * mU * mA * mG * mC * mU * mU * mC * mC * fA * fG * fC * fC * fC * fA * fU	CUUCCUUAGCUUCCA GCCAU	XXXXX XXXXX XXXXX XXXX
WV-4745	fU * fU * fC * fU * fU * fC * fC * mC * mU * mU * mA * mG * mC * mC * mU * mU * fC * fC * fC * fA * fG * fC * fC * fC	UUCUUCCUUAGCUUC CAGCC	XXXXX XXXXX XXXXX XXXX
WV-4746	fG * fC * fU * fU * fC * fC * fU * mU * mC * mC * mU * mU * mA * mA * mG * mC * fU * fU * fU * fC * fC * fC * fA * fG	GCUUCUUCCUUAGCU UCCAG	XXXXX XXXXX XXXXX XXXX
WV-4747	fC * fA * fG * fC * fC * fU * fU * mC * mU * mU * mC * mC * mU * mU * mA * fG * fC * fC * fU * fU * fU * fC * fC	CAGCUUCUUCCUUAG CUUCC	XXXXX XXXXX XXXXX XXXX
WV-4748	fC * fU * fC * fC * fA * fG * fC * mU * mU * mC * mU * mU * mC * mC * mC * mU * fU * fU * fA * fG * fC * fC * fU * fU	CUCAGCUUCUUCCUU AGCUU	XXXXX XXXXX XXXXX XXXX
WV-4749	fC * fU * fG * fC * fC * fU * fC * mA * mG * mC * mU * mU * mC * mC * mU * mU * fC * fC * fC * fU * fU * fU * fA * fG	CUGCUCAGCUUCUUC CUUAG	XXXXX XXXXX XXXXX XXXX
WV-4750	fA * fC * fC * fC * fU * fG * fC * mU * mC * mA * mG * mC * mC * mU * mU * mC * fU * fU * fC * fC * fC * fU * fU	ACCUGCUCAGCUUCU UCCUU	XXXXX XXXXX XXXXX XXXX
WV-4751	fA * fG * fA * fC * fC * fU * mG * mC * mU * mC * mA * mG * mC * mC * mU * fU * fC * fC * fU * fU * fC * fC	AGACCUGCUCAGCUU CUUCC	XXXXX XXXXX XXXXX XXXX
WV-4752	fU * fA * fA * fG * fA * fC * mC * mU * mG * mC * mU * mC * mC * mA * mG * fC * fC * fU * fU * fC * fU * fU	UAAGACCUGCUCAGC UUCUU	XXXXX XXXXX XXXXX XXXX
WV-4753	fC * fC * fC * fU * fA * fA * fG * mA * mC * mC * mU * mG * mC * mU * mC * fA * fG * fC * fC * fU * fU * fC	CCUAAGACCUGCUCA GCUUC	XXXXX XXXXX XXXXX XXXX

WV-4754	fG * fU * fC * fC * fU * fA * mA * mG * mA * mC * mC * mU * mG * mC * fU * fC * fA * fG * fC * fU	GUCCUAAGACCUGCU CAGCU	XXXXX XXXXX XXXXX XXXX
WV-4755	fC * fU * fG * fU * fC * fC * mU * mA * mA * mG * mA * mC * mC * mU * fG * fC * fU * fC * fA * fG	CUGUCCUAAGACCUG CUCAG	XXXXX XXXXX XXXXX XXXX
WV-4756	fG * fG * fC * fC * fU * fG * mU * mC * mC * mU * mA * mA * mG * mA * fC * fC * fU * fG * fC * fU	GGCCUGUCCUAAGAC CUGCU	XXXXX XXXXX XXXXX XXXX
WV-4757	fC * fU * fG * fG * fC * fC * mU * mG * mU * mC * mC * mU * mA * mA * fG * fA * fC * fC * fU * fG	CUGGCCUGUCCUAAG ACCUG	XXXXX XXXXX XXXXX XXXX
WV-4758	fC * fU * fC * fU * fG * fG * mC * mC * mU * mG * mU * mC * mC * mU * fA * fA * fG * fA * fC * fC	CUCUGGCCUGUCCUA AGACC	XXXXX XXXXX XXXXX XXXX
WV-4759	fG * fG * fC * fC * fU * fC * fU * mG * mC * mC * mU * mG * mU * mC * fC * fU * fA * fG * fA	GGCUCUGGCCUGUCC UAAGA	XXXXX XXXXX XXXXX XXXX
WV-4760	fU * fU * fG * fG * fC * fU * mC * mU * mG * mG * mC * mC * mU * mG * fU * fC * fC * fU * fA * fA	UUGGCUCUGGCCUGU CCUAA	XXXXX XXXXX XXXXX XXXX
WV-4761	fG * fC * fU * fU * fG * fG * mC * mU * mC * mU * mG * mG * mC * mC * fU * fG * fU * fC * fC * fU	GCUUGGCUCUGGCCU GUCCU	XXXXX XXXXX XXXXX XXXX
WV-4762	fA * fA * fG * fC * fU * fU * mG * mG * mC * mU * mC * mU * mG * mG * fC * fC * fU * fG * fU * fC	AAGCUUGGCUCUGGC CUGUC	XXXXX XXXXX XXXXX XXXX
WV-4763	fU * fC * fA * fA * fG * fC * mU * mU * mG * mG * mC * mU * mC * mU * fG * fG * fC * fC * fU * fG	UCAAGCUUGGCUCUG GCCUG	XXXXX XXXXX XXXXX XXXX
WV-4764	fU * fC * fC * fU * fU * fC * mC * mA * mU * mG * mA * mC * mU * mC * fA * fA * fG * fG * fC * fU * fU	UCCUUCCAUGACUCA AGCUU	XXXXX XXXXX XXXXX XXXX
WV-4765	fC * fC * fU * fC * fC * fU * mU * mC * mC * mA * mU * mG * mA * mC * fU * fC * fA * fA * fG * fC	CCUCCUUCCAUGACU CAAGC	XXXXX XXXXX XXXXX XXXX
WV-4766	fA * fC * fC * fC * fC * fU * fC * mC * mU * mC * mC * mA * mU * mG * fA * fC * fU * fC * fA * fA	ACCCUCCUUCCAUGA CUCAA	XXXXX XXXXX XXXXX XXXX
WV-4767	fG * fG * fA * fC * fC * fC * mU * mC * mC * mU * mU * mC * mC * mA * fU * fG * fG * fA * fC * fU * fC	GGACCCUCCUUCCAU GACUC	XXXXX XXXXX XXXXX XXXX
WV-4768	fA * fG * fG * fG * fA * fC * mC * mU * mC * mC * mC * mU * mU * mC * fC * fA * fU * fG * fA * fC	AGGGACCCUCCUUCC AUGAC	XXXXX XXXXX XXXXX XXXX
WV-4769	fA * fU * fA * fG * fG * fG * mA * mC * mC * mU * mC * mC * mC * mU * fU * fC * fC * fA * fU * fG	AUAGGGACCCUCCUU CCAUG	XXXXX XXXXX XXXXX XXXX
WV-4770	fG * fU * fA * fU * fA * fG * mG * mA * mC * mC * mC * mU * mC * fC * fU * fU * fC * fC * fA	GUAUAGGGACCCUCC UUCCA	XXXXX XXXXX XXXXX XXXX
WV-4771	fC * fU * fG * fU * fA * fU * mA * mG * mG * mA * mC * mC * mC * fU * fU * fC * fC * fU * fU * fC	CUGUAUAGGGACCCU CCUUC	XXXXX XXXXX XXXXX XXXX

WV-4772	fU * fA * fC * fU * fG * fU * mA * mU * mA * mG * mG * mA * mC * fC * fC * fU * fC * fU * fC * fU	UACUGUAUAGGGACC CUCCU	XXXXX XXXXX XXXXX XXXX
WV-4773	fU * fC * fU * fA * fC * fU * mG * mU * mA * mU * mA * mG * mG * mG * fA * fC * fC * fC * fU * fC	UCUACUGUAUAGGGA CCCUC	XXXXX XXXXX XXXXX XXXX
WV-4774	fC * fA * fU * fC * fU * fA * mC * mU * mG * mU * mA * mU * mA * mG * fG * fG * fA * fC * fC * fC	CAUCUACUGUAUAGG GACCC	XXXXX XXXXX XXXXX XXXX
WV-4775	fU * fG * fC * fA * fU * fC * mU * mA * mC * mU * mG * mU * mA * mU * fA * fG * fG * fG * fA * fC	UGCAUCUACUGUAUA GGGAC	XXXXX XXXXX XXXXX XXXX
WV-4776	fA * fU * fU * fG * fC * fA * mU * mC * mU * mA * mC * mU * mG * mU * fA * fU * fA * fG * fG * fG	AUUGCAUCUACUGUA UAGGG	XXXXX XXXXX XXXXX XXXX
WV-4777	fG * fG * fA * fU * fU * fG * mC * mA * mU * mC * mU * mA * mC * mU * fG * fU * fA * fU * fA * fG	GGAUUGCAUCUACUG UAUAG	XXXXX XXXXX XXXXX XXXX
WV-4778	fU * fU * fG * fG * fA * fU * mU * mG * mC * mA * mU * mC * mU * mA * fC * fU * fG * fU * fA * fU	UUGGAUUGCAUCUAC UGUAU	XXXXX XXXXX XXXXX XXXX
WV-4779	fU * fU * fU * fU * fG * fG * mA * mU * mU * mG * mC * mA * mU * mC * fU * fA * fC * fU * fG * fU	UUUUGGAUUGCAUCU ACUGU	XXXXX XXXXX XXXXX XXXX
WV-4780	fU * fC * fU * fU * fU * fU * mG * mG * mA * mU * mU * mG * mC * mA * fU * fC * fU * fA * fC * fU	UCUUUUGGAUUGCAU CUACU	XXXXX XXXXX XXXXX XXXX
WV-4781	fU * fU * fU * fC * fU * fU * mU * mU * mG * mG * mA * mU * mU * mG * fC * fC * fA * fU * fC * fU * fA	UUUCUUUUGGAUUGC AUCUA	XXXXX XXXXX XXXXX XXXX
WV-4782	fA * fU * fU * fU * fU * fC * mU * mU * mU * mU * mG * mG * mA * mU * fU * fG * fC * fA * fU * fC	AUUUUCUUUUGGAU UGCAUC	XXXXX XXXXX XXXXX XXXX
WV-4783	fU * fG * fA * fU * fU * fU * mU * mC * mU * mU * mU * mU * mG * mG * fA * fU * fU * fG * fC * fA	UGAUUUUCUUUUGG AUUGCA	XXXXX XXXXX XXXXX XXXX
WV-4784	fU * fG * fU * fG * fA * fU * mU * mU * mC * mU * mU * mU * mU * mU * fG * fA * fU * fU * fG	UGUGAUUUUCUUUU GGAUUG	XXXXX XXXXX XXXXX XXXX
WV-4785	fU * fC * fU * fG * fU * fG * mA * mU * mU * mU * mU * mC * mU * mU * fU * fU * fG * fG * fA * fU	UCUGUGAUUUUCUUU UGGAU	XXXXX XXXXX XXXXX XXXX
WV-4786	fU * fU * fU * fC * fU * fG * mU * mG * mA * mU * mU * mU * mU * mC * fU * fU * fU * fU * fG * fG	UUUCUGUGAUUUUCU UUUGG	XXXXX XXXXX XXXXX XXXX
WV-4787	fG * fG * fU * fU * fU * fC * mU * mG * mU * mG * mA * mU * mU * mU * fU * fU * fC * fU * fU * fU	GGUUUCUGUGAUUU UCUUU	XXXXX XXXXX XXXXX XXXX
WV-4788	fU * fU * fG * fG * fU * fU * mU * mC * mU * mG * mU * mG * mA * mU * fU * fU * fU * fC * fU * fU	UUGGUUUCUGUGAU UUUCUU	XXXXX XXXXX XXXXX XXXX
WV-4789	fC * fC * fU * fU * fG * fG * mU * mU * mU * mC * mU * mG * mU * mG * fA * fU * fU * fU * fU * fC	CCUUGGUUUCUGUGA UUUUC	XXXXX XXXXX XXXXX XXXX

WV-4790	fA * fA * fC * fC * fU * fU * mG * mG * mU * mU * mC * mC * mU * mG * fU * fG * fG * fA * fU * fU * fU	AACCUUGGUUUCUGU GAUUU	XXXXX XXXXX XXXX XXX
WV-4791	fC * fU * fA * fA * fC * fC * mU * mU * mG * mG * mU * mU * mU * mC * fU * fG * fU * fG * fA * fU	CUAACCUUGGUUUCU GUGAU	XXXXX XXXXX XXXX XXX
WV-4792	fU * fA * fC * fU * fA * fA * mC * mC * mU * mU * mG * mG * mU * mU * fU * fC * fU * fG * fU * fG	UACUAACCUUGGUUU CUGUG	XXXXX XXXXX XXXX XXX
WV-4793	fG * fA * fU * fA * fC * fU * mA * mA * mC * mC * mU * mU * mG * mG * fU * fU * fU * fC * fU * fG	GAUACUAACCUUGGU UUCUG	XXXXX XXXXX XXXX XXX
WV-4890	ChTEGfU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSSOO SSSSS
WV-6010	L001 mG * mG * mC * mC * mA * mA * mC * mC * mU * mU * mC * mG * mG * mC * mU * mU * mA * mC * mC * mU	GGCCAAACCUCGGCU UACCU	OXXXX XXXXX XXXX XXX
WV-6137	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXOXOXXO OXXXXX
WV-6409	Mod012L001fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * S mUfG * S mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSOSO SSSSS
WV-6410	Mod012L001fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXXXXXOXOXO XOXXXXX
WV-6560	L001fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * S mUfG * S mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSOSO SSSSS
WV-6826	Mod012L001 mU * S mC * S mA * S mA * S mG * S mG * S mA mA * S mG mA * S mU mG * S mG mC * S mA * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSOSO SSSSS
WV-6827	Mod012L001 mU * mC * mA * mA * mG * mG * mA mA * mG mA * mU mG * mG mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	OXXXXXXOXOXO XOXXXXX
WV-6828	Mod012L001 mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	OXXXXX XXXXX XXXX XXX
WV-6829	Mod012L001fC * fC * fU * fU * fC * fC * mCfU * mGfA * mAfG * mGfU * fU * fC * fC * fU * fC * fC	CCUUCCCUGAAGGUU CCUCC	OXXXXXXOXOXO XOXXXXX
WV-6830	Mod012L001 mC * mC * mU * mU * mC * mC * mC mU * mG mA * mA mG * mG mU * mU * mC * mC * mU * mC * mC	CCUUCCCUGAAGGUU CCUCC	OXXXXXXOXOXO XOXXXXX
WV-7109	L001 mU * S mC * S mA * S mA * S mG * S mG * S mA mA * S mG mA * S mU mG * S mG mC * S mA * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSOSO SSSSS
WV-7110	L001 mU * mC * mA * mA * mG * mG * mA mA * mG mA * mU mG * mG mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	OXXXXXXOXOXO XOXXXXX
WV-7111	L001fC * fC * fU * fU * fC * fC * mCfU * mGfA * mAfG * mGfU * fU * fC * fC * fU * fC * fC	CCUUCCCUGAAGGUU CCUCC	OXXXXXXOXOXO XOXXXXX

WV-7112	L001 mC * mC * mU * mU * mC * mC * mC mU * mG mA * mA mG * mG mU * mU * mC * mC * mU * mC * mC	CCUUCCCUGAAGGUU CCUCC	OXXXXXXOXOXO XOXXXXXX
WV-7333	fU * fC * fAfAfGfG mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXOOOOOXOXXO OXXXXXX
WV-7334	fU * fC * fAfA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXOXXXOXOXXO OXXXXXX
WV-7335	fU * fC * fA * fAfG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXOXXOXOXXO OXXXXXX
WV-7336	fU * fC * fA * fA * fGfG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXOXOXOXXO OXXXXXX
WV-7337	fU * fC * fA * fA * fG * fG mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXOOXOXXO OXXXXXX
WV-7338	Mod020L001fU * fC * fAfAfGfG mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXOOOOOXOXX OOXXXXX
WV-7339	Mod020L001fU * fC * fAfA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXOXXXOXOXX OOXXXXX
WV-7340	Mod020L001fU * fC * fA * fAfG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXXOXXOXOXX OOXXXXX
WV-7341	Mod020L001fU * fC * fA * fA * fGfG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXXXOXOXOXX OOXXXXX
WV-7342	Mod020L001fU * fC * fA * fA * fG * fG mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXXXXOOXOXX OOXXXXX
WV-7343	T * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	TCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7344	fU * C * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7345	fU * fC * A * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7346	fU * fC * fA * A * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7347	fU * fC * fA * fA * G * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7348	fU * fC * fA * fA * fG * G * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7349	fU * fC * fA * fA * fG * fG * mAA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX

WV-7350	fU * fC * fA * fA * fG * fG * mAfA * mG mA * T * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7351	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7352	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * A * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7353	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * T * fU * fU * fC * fU	UCAAGGAAGAUGGCA TUUCU	XXXXXXOXOXXO OXXXXXX
WV-7354	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * T * fU * fC * fU	UCAAGGAAGAUGGCA UTUCU	XXXXXXOXOXXO OXXXXXX
WV-7355	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * T * fC * fU	UCAAGGAAGAUGGCA UUTCU	XXXXXXOXOXXO OXXXXXX
WV-7356	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * C * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7357	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * T	UCAAGGAAGAUGGCA UUUCT	XXXXXXOXOXXO OXXXXXX
WV-7358	fU * fC * A * fA * fG * G * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7359	fU * C * fA * fA * G * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7360	T * fC * fA * A * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	TCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7361	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * T * fU * fU * T * fU	UCAAGGAAGAUGGCA TUUTU	XXXXXXOXOXXO OXXXXXX
WV-7362	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * A * fU * fU * fU * T * fC * fU	UCAAGGAAGAUGGCA UUTCU	XXXXXXOXOXXO OXXXXXX
WV-7363	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGC * fA * fU * T * fU * fC * T	UCAAGGAAGAUGGCA UTUCT	XXXXXXOXOXXO OXXXXXX
WV-7364	fU * fC * A * fA * fG * G * mAfA * mG mA * fU * mG mGfC * fA * T * fU * fU * T * fU	UCAAGGAAGAUGGCA TUUTU	XXXXXXOXOXXO OXXXXXX
WV-7365	fU * fC * A * fA * fG * G * mAfA * mG mA * fU * mG mGfC * A * fU * fU * T * fC * fU	UCAAGGAAGAUGGCA UUTCU	XXXXXXOXOXXO OXXXXXX
WV-7366	fU * fC * A * fA * fG * G * mAfA * mG mA * fU * mG mGC * fA * fU * T * fU * fC * T	UCAAGGAAGAUGGCA UTUCT	XXXXXXOXOXXO OXXXXXX
WV-7367	fU * C * fA * fA * G * fG * mAfA * mG mA * fU * mG mGfC * fA * T * fU * fU * T * fU	UCAAGGAAGAUGGCA TUUTU	XXXXXXOXOXXO OXXXXXX

WV-7368	fU * C * fA * fA * G * fG * mAfA * mG mA * fU * mG mGfC * A * fU * fU * T * fC * fU	UCAAGGAAGAUGGCA UUTCU	XXXXXXOXOXXO OXXXXXX
WV-7369	fU * C * fA * fA * G * fG * mAfA * mG mA * fU * mG mGC * fA * fU * T * fU * fC * T	UCAAGGAAGAUGGCA UTUCT	XXXXXXOXOXXO OXXXXXX
WV-7370	T * fC * fA * A * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * T * fU * fU * T * fU	TCAAGGAAGAUGGCA TUUTU	XXXXXXOXOXXO OXXXXXX
WV-7371	T * fC * fA * A * fG * fG * mAfA * mG mA * fU * mG mGfC * A * fU * fU * T * fC * fU	TCAAGGAAGAUGGCA UUTCU	XXXXXXOXOXXO OXXXXXX
WV-7372	T * fC * fA * A * fG * fG * mAfA * mG mA * fU * mG mGC * fA * fU * T * fU * fC * T	TCAAGGAAGAUGGCA UTUCT	XXXXXXOXOXXO OXXXXXX
WV-7373	Teo * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fC * fU	TCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7374	fU * m5Ceo * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7375	fU * fC * Aeo * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7376	fU * fC * fA * Aeo * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7377	fU * fC * fA * fA * Geo * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7378	fU * fC * fA * fA * fG * Geo * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7379	fU * fC * fA * fA * fG * fG * mAAeo * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7380	fU * fC * fA * fA * fG * fG * mAfA * mG mA * Teo * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7381	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mG m5Ceo * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7382	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * Aeo * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7383	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * Teo * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA TUUCU	XXXXXXOXOXXO OXXXXXX
WV-7384	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * Teo * fU * fC * fU	UCAAGGAAGAUGGCA UTUCU	XXXXXXOXOXXO OXXXXXX
WV-7385	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * Teo * fC * fU	UCAAGGAAGAUGGCA UUTCU	XXXXXXOXOXXO OXXXXXX

WV-7386	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * m5Ceo * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7387	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * Teo	UCAAGGAAGAUGGCA UUUCT	XXXXXXOXOXXO OXXXXXX
WV-7388	fU * fC * Aeo * fA * fG * Geo * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7389	fU * m5Ceo * fA * fA * Geo * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7390	Teo * fC * fA * Aeo * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	TCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXXO OXXXXXX
WV-7391	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * Teo * fU * fU * Teo * fU	UCAAGGAAGAUGGCA TUUTU	XXXXXXOXOXXO OXXXXXX
WV-7392	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mGfC * Aeo * fU * fU * Teo * fC * fU	UCAAGGAAGAUGGCA UUTCU	XXXXXXOXOXXO OXXXXXX
WV-7393	fU * fC * fA * fA * fG * fG * mAfA * mG mA * fU * mG mG m5Ceo * fA * fU * Teo * fU * fC * Teo	UCAAGGAAGAUGGCA UTUCT	XXXXXXOXOXXO OXXXXXX
WV-7394	fU * fC * Aeo * fA * fG * Geo * mAfA * mG mA * fU * mG mGfC * fA * Teo * fU * fU * Teo * fU	UCAAGGAAGAUGGCA TUUTU	XXXXXXOXOXXO OXXXXXX
WV-7395	fU * fC * Aeo * fA * fG * Geo * mAfA * mG mA * fU * mG mGfC * Aeo * fU * fU * Teo * fC * fU	UCAAGGAAGAUGGCA UUTCU	XXXXXXOXOXXO OXXXXXX
WV-7396	fU * fC * Aeo * fA * fG * Geo * mAfA * mG mA * fU * mG mG m5Ceo * fA * fU * Teo * fU * fC * Teo	UCAAGGAAGAUGGCA UTUCT	XXXXXXOXOXXO OXXXXXX
WV-7397	fU * m5Ceo * fA * fA * Geo * fG * mAfA * mG mA * fU * mG mGfC * fA * Teo * fU * fU * fU * Teo * fU	UCAAGGAAGAUGGCA TUUTU	XXXXXXOXOXXO OXXXXXX
WV-7398	fU * m5Ceo * fA * fA * Geo * fG * mAfA * mG mA * fU * mG mGfC * Aeo * fU * fU * fU * Teo * fC * fU	UCAAGGAAGAUGGCA UUTCU	XXXXXXOXOXXO OXXXXXX
WV-7399	fU * m5Ceo * fA * fA * Geo * fG * mAfA * mG mA * fU * mG mG m5Ceo * fA * fU * Teo * fU * fC * Teo	UCAAGGAAGAUGGCA UTUCT	XXXXXXOXOXXO OXXXXXX
WV-7400	Teo * fC * fA * Aeo * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * Teo * fU * fU * fU * Teo * fU	TCAAGGAAGAUGGCA TUUTU	XXXXXXOXOXXO OXXXXXX
WV-7401	Teo * fC * fA * Aeo * fG * fG * mAfA * mG mA * fU * mG mGfC * Aeo * fU * fU * Teo * fC * fU	TCAAGGAAGAUGGCA UUTCU	XXXXXXOXOXXO OXXXXXX
WV-7402	Teo * fC * fA * Aeo * fG * fG * mAfA * mG mA * fU * mG mG m5Ceo * fA * fU * Teo * fU * fC * Teo	TCAAGGAAGAUGGCA UTUCT	XXXXXXOXOXXO OXXXXXX
WV-7410	BrfU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * S mUfG * S mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSOSOS SSSSS

WV-7411	Acet5fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * S mUfG * S mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSOSOS SSSSS
WV-7412	BrfU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXOX OXXXXXX
WV-7413	Acet5fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXOX OXXXXXX
WV-7414	BrmU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-7415	Acet5 mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-7436	fC * fU * fU * fU * fU * fA * fA * mC * mA * mU * mU * mU * mC * mC * mA * mU * fU * fC * fC * fA * fC * fU	CUUUAACAUUUCAUU CAACU	XXXXX XXXXX XXXXX XXXX
WV-7437	fU * fU * fA * fA * fC * fA * mU * mU * mU * mC * mA * mU * mU * mC * fA * fA * fC * fU * fG * fU	UUAACAUUUCAUUCA ACUGU	XXXXX XXXXX XXXXX XXXX
WV-7438	fA * fA * fC * fA * fU * fU * mU * mC * mA * mU * mU * mC * mC * mA * mA * fC * fU * fG * fU * fU * fG	AACAUUUCAUUCAAC UGUUG	XXXXX XXXXX XXXXX XXXX
WV-7439	fC * fA * fU * fU * fU * fU * fC * mA * mU * mU * mC * mA * mA * mC * mU * fG * fU * fU * fG * fU * fC	CAUUUCAUUCAACUG UUGUC	XXXXX XXXXX XXXXX XXXX
WV-7440	fU * fU * fU * fC * fA * fU * mU * mC * mA * mA * mC * mU * mG * mU * fU * fG * fU * fU * fC * fU * fC	UUUCAUUCAACUGUU GUCUC	XXXXX XXXXX XXXXX XXXX
WV-7441	fU * fC * fA * fU * fU * fC * mA * mA * mC * mU * mG * mU * mU * mG * fU * fC * fU * fC * fC * fC * fU	UCAUUCAACUGUUGU CUCCU	XXXXX XXXXX XXXXX XXXX
WV-7442	fA * fU * fU * fC * fC * fA * fA * mC * mU * mG * mU * mU * mG * mU * mC * fU * fC * fC * fC * fU * fG * fU	AUUCAACUGUUGUCU CCUGU	XXXXX XXXXX XXXXX XXXX
WV-7443	fU * fC * fC * fA * fA * fC * fU * mG * mU * mU * mG * mU * mC * mU * mC * fC * fU * fG * fU * fU * fU * fC	UCAACUGUUGUCUCC UGUUC	XXXXX XXXXX XXXXX XXXX
WV-7444	fA * fA * fC * fC * fU * fG * fU * mU * mG * mU * mC * mU * mC * mC * mU * fG * fU * fU * fC * fU * fU * fG	AACUGUUGUCUCCUG UUCUG	XXXXX XXXXX XXXXX XXXX
WV-7445	fC * fU * fG * fU * fU * fG * mU * mC * mU * mC * mC * mU * mG * mU * fU * fC * fU * fG * fC * fA	CUGUUGUCUCCUGUU CUGCA	XXXXX XXXXX XXXXX XXXX
WV-7446	fG * fU * fU * fG * fU * fC * mU * mC * mC * mU * mG * mU * mU * mC * fU * fG * fC * fA * fG * fC	GUUGUCUCCUGUUCU GCAGC	XXXXX XXXXX XXXXX XXXX
WV-7447	fU * fG * fU * fC * fU * fC * mC * mU * mG * mU * mU * mC * mU * mG * fC * fA * fG * fC * fU * fG	UGUCUCCUGUUCUGC AGCUG	XXXXX XXXXX XXXXX XXXX
WV-7448	fU * fC * fU * fC * fC * fU * mG * mU * mU * mC * mU * mG * mC * mA * fG * fC * fU * fG * fU * fU	UCUCCUGUUCUGCAG CUGUU	XXXXX XXXXX XXXXX XXXX

WV-7449	fU * fC * fC * fU * fG * fU * mU * mC * mU * mG * mC * mA * mG * mC * fU * fG * fU * fU * fC * fU	UCCUGUUCUGCAGCU GUUCU	XXXXX XXXXX XXXXX XXXX
WV-7450	fC * fU * fG * fU * fU * fC * mU * mG * mC * mA * mG * mC * mC * mU * mG * fU * fU * fC * fU * fU * fG	CUGUUCUGCAGCUGU UCUUG	XXXXX XXXXX XXXXX XXXX
WV-7451	fG * fU * fU * fC * fU * fG * mC * mA * mG * mC * mU * mG * mU * mU * fC * fU * fU * fG * fA * fA	GUUCUGCAGCUGUUC UUGAA	XXXXX XXXXX XXXXX XXXX
WV-7452	fU * fC * fU * fG * fC * fA * mG * mC * mU * mG * mU * mU * mC * mU * fU * fG * fA * fA * fC * fC	UCUGCAGCUGUUCUU GAACC	XXXXX XXXXX XXXXX XXXX
WV-7453	fU * fG * fC * fA * fG * fC * mU * mG * mU * mU * mC * mU * mU * mG * fA * fA * fC * fC * fU * fC	UGCAGCUGUUCUUGA ACCUC	XXXXX XXXXX XXXXX XXXX
WV-7454	fU * fG * fU * fU * fC * fU * mU * mG * mA * mA * mC * mC * mU * mC * fA * fU * fC * fC * fC * fA	UGUUCUUGAACCUCA UCCCA	XXXXX XXXXX XXXXX XXXX
WV-7455	fC * fA * fG * fC * fU * fG * mU * mU * mC * mU * mU * mG * mA * mA * fC * fC * fU * fC * fA * fU	CAGCUGUUCUUGAAC CUCAU	XXXXX XXXXX XXXXX XXXX
WV-7456	fG * fC * fU * fU * fG * fU * fU * mC * mU * mU * mG * mA * mA * mC * mC * fU * fC * fA * fU * fC * fC	GCUGUUCUUGAACCU CAUCC	XXXXX XXXXX XXXXX XXXX
WV-7457	L001fU * fC * fAfAfGfG mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXOOOOOXOXX OOXXXXX
WV-7458	L001fU * fC * fAfA * fG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXOXXXOXOXX OOXXXXX
WV-7459	L001fU * fC * fA * fAfG * fG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXXOXXOXOXX OOXXXXX
WV-7460	L001fU * fC * fA * fA * fGfG * mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXXXOXOXOXX OOXXXXX
WV-7461	L001fU * fC * fA * fA * fG * fG mAfA * mG mA * fU * mG mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	OXXXXXOOXOXX OOXXXXX
WV-7506	mU * mC * mA * mA * mG * mG * mA mA * mG mA * mU mG * mG mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXXXOXOXOX OXXXXX
WV-7507	fC * fC * fU * fU * fC * fC * mCfU * mGfA * mAfG * mGfU * fU * fC * fC * fU * fC * fC	CCUUCCCUGAAGGUU CCUCC	XXXXXXOXOXOX OXXXXX
WV-7508	mC * mC * mU * mU * mC * mC * mC mU * mG mA * mA mG * mG mU * mU * mC * mC * mU * mC * mC	CCUUCCCUGAAGGUU CCUCC	XXXXXXOXOXOX OXXXXX
WV-7596	fU * RfC * RfA * RfA * RfG * RfG * R mAfA * R mGfA * R mUfG * R mGfC * RfA * RfU * RfU * RfU * RfC * RfU	UCAAGGAAGAUGGCA UUUCU	RRRRRROROROR ORRRRR
WV-7677	fG * fC * fC * fC * fA * fU * fU * mU * mG * mU * mU * mG * mC * mU * fC * fU * fU * fU * fC * fA	GCCAUUUUGUUGCUC UUUCA	XXXXX XXXXX XXXXX XXXX

WV-7678	fA * fG * fC * fC * fA * fU * mU * mU * mU * mG * mU * mU * mG * mC * fU * fC * fU * fU * fU * fC	AGCCAUUUUGUUGCU CUUUC	XXXXX XXXXX XXXXX XXXX
WV-7679	fA * fA * fG * fC * fC * fA * mU * mU * mU * mU * mG * mU * mU * mG * fC * fU * fC * fU * fU * fU	AAGCCAUUUUGUUGC UCUUU	XXXXX XXXXX XXXXX XXXX
WV-7680	fU * fU * fG * fA * fA * fG * mC * mC * mA * mU * mU * mU * mU * mG * fU * fU * fG * fC * fU * fC	UUGAAGCCAUUUUGU UGCUC	XXXXX XXXXX XXXXX XXXX
WV-7681	fU * fA * fG * fU * fU * fG * mA * mA * mG * mC * mC * mA * mU * mU * fU * fU * fG * fU * fU * fG	UAGUUGAAGCCAUUU UGUUG	XXXXX XXXXX XXXXX XXXX
WV-7682	fA * fG * fA * fU * fA * fG * mU * mU * mG * mA * mA * mG * mC * mC * fA * fU * fU * fU * fU * fG	AGAUAGUUGAAGCCA UUUUG	XXXXX XXXXX XXXXX XXXX
WV-7683	fC * fU * fC * fC * fA * fG * fA * mU * mA * mG * mU * mU * mG * mA * mA * fG * fC * fC * fA * fU * fU	CUCAGAUAGUUGAAG CCAUU	XXXXX XXXXX XXXXX XXXX
WV-7684	fU * fC * fA * fC * fU * fC * mA * mG * mA * mU * mA * mG * mU * mU * fG * fA * fA * fG * fC * fC	UCACUCAGAUAGUUG AAGCC	XXXXX XXXXX XXXXX XXXX
WV-7685	fG * fU * fG * fU * fC * fA * mC * mU * mC * mA * mG * mA * mU * mA * fG * fU * fU * fG * fA * fA	GUGUCACUCAGAUAG UUGAA	XXXXX XXXXX XXXXX XXXX
WV-7686	fA * fC * fA * fG * fU * fG * mU * mC * mA * mC * mU * mC * mA * mG * fA * fU * fA * fG * fU * fU	ACAGUGUCACUCAGA UAGUU	XXXXX XXXXX XXXXX XXXX
WV-7687	fC * fA * fC * fA * fG * fU * mG * mU * mC * mA * mC * mU * mC * mA * fG * fA * fU * fA * fG * fU	CACAGUGUCACUCAG AUAGU	XXXXX XXXXX XXXXX XXXX
WV-7688	fC * fU * fU * fC * fA * fC * mA * mG * mU * mG * mU * mC * mA * mC * fU * fC * fA * fG * fA * fU	CUUCACAGUGUCACU CAGAU	XXXXX XXXXX XXXXX XXXX
WV-7689	fC * fC * fU * fU * fC * fA * mC * mA * mG * mU * mG * mU * mC * mA * fC * fU * fC * fA * fG * fA	CCUUCACAGUGUCAC UCAGA	XXXXX XXXXX XXXXX XXXX
WV-7690	fC * fU * fC * fC * fU * fU * mC * mA * mC * mG * mA * mG * mU * mG * mU * fC * fA * fC * fU * fC * fA	CUCCUUCACAGUGUC ACUCA	XXXXX XXXXX XXXXX XXXX
WV-7691	fA * fU * fC * fU * fC * fC * mU * mU * mC * mA * mC * mA * mG * mG * mU * fG * fU * fC * fA * fC * fU	AUCUCCUUCACAGUG UCACU	XXXXX XXXXX XXXXX XXXX
WV-7692	fC * fC * fA * fU * fC * fC * fU * mC * mC * mU * mU * mC * mA * mC * mC * mA * fG * fU * fG * fU * fC * fA	CCAUCUCCUUCACAG UGUCA	XXXXX XXXXX XXXXX XXXX
WV-7693	fG * fG * fC * fC * fC * fA * fU * mC * mU * mC * mC * mU * mU * mC * mA * fC * fA * fG * fU * fG * fU	GGCCAUCUCCUUCAC AGUGU	XXXXX XXXXX XXXXX XXXX
WV-7694	fU * fU * fG * fG * fC * fC * fC * mA * mU * mC * mU * mC * mC * mC * mU * mU * fC * fA * fC * fA * fG * fU	UUGGCCAUCUCCUUC ACAGU	XXXXX XXXXX XXXXX XXXX
WV-7695	fU * fC * fC * fU * fU * fG * fG * mC * mC * mA * mU * mC * mU * mU * mC * mC * fU * fU * fC * fA * fC * fA	UCUUGGCCAUCUCCU UCACA	XXXXX XXXXX XXXXX XXXX

WV-7696	fU * fU * fU * fC * fU * fU * mG * mG * mC * mC * mA * mU * mC * mU * fC * fC * fU * fU * fC * fA	UUUCUUGGCCAUCUC CUUCA	XXXXX XXXXX XXXXX XXXX
WV-7697	fG * fC * fU * fU * fC * mU * mG * mG * mC * mC * mA * mU * fC * fU * fC * fC * fU * fU	GCUUUCUUGGCCAUC UCCUU	XXXXX XXXXX XXXXX XXXX
WV-7698	fG * fU * fG * fC * fU * fU * mU * mC * mU * mG * mG * mC * mC * fA * fU * fC * fU * fC * fC	GUGCUUUCUUGGCCA UCUCC	XXXXX XXXXX XXXXX XXXX
WV-7699	fA * fG * fG * fU * fG * fC * mU * mU * mU * mC * mU * mU * mG * mG * fC * fC * fA * fU * fC * fU	AGGUGCUUUCUUGGC CAUCU	XXXXX XXXXX XXXXX XXXX
WV-7700	fG * fA * fA * fG * fG * fU * mG * mC * mU * mU * mC * mU * mU * fG * fG * fC * fC * fA * fU	GAAGGUGCUUUCUUG GCCAU	XXXXX XXXXX XXXXX XXXX
WV-7701	fC * fU * fG * fA * fA * fG * mG * mU * mG * mC * mU * mU * mU * mC * fU * fU * fG * fG * fC * fC	CUGAAGGUGCUUUCU UGGCC	XXXXX XXXXX XXXXX XXXX
WV-7702	fU * fU * fC * fU * fG * fA * mA * mG * mG * mU * mG * mC * mC * mU * mU * fU * fC * fU * fU * fG * fG	UUCUGAAGGUGCUUU CUUGG	XXXXX XXXXX XXXXX XXXX
WV-7703	fU * fA * fU * fU * fU * fC * mU * mG * mA * mA * mG * mG * mU * mG * fC * fU * fU * fC * fU	UAUUUCUGAAGGUGC UUUCU	XXXXX XXXXX XXXXX XXXX
WV-7704	fA * fU * fA * fU * fU * fU * mC * mU * mG * mA * mA * mG * mG * mU * fG * fC * fU * fU * fU * fC	AUAUUUCUGAAGGU GCUUUC	XXXXX XXXXX XXXXX XXXX
WV-7705	fG * fG * fC * fA * fU * fA * mU * mU * mC * mU * mG * mA * mA * fG * fG * fU * fG * fC * fC * fU	GGCAUAUUUCUGAAG GUGCU	XXXXX XXXXX XXXXX XXXX
WV-7706	fU * fG * fG * fC * fA * fU * mA * mU * mU * mC * mU * mG * mA * fA * fG * fG * fU * fG * fC	UGGCAUAUUUCUGAA GGUGC	XXXXX XXXXX XXXXX XXXX
WV-7707	fU * fC * fU * fG * fC * mA * mU * mA * mU * mU * mC * mU * fG * fA * fA * fG * fG * fU	UCUGGCAUAUUUCUG AAGGU	XXXXX XXXXX XXXXX XXXX
WV-7708	fU * fC * fU * fG * fA * fC * mA * mG * mA * mU * mA * mU * mU * mU * fC * fU * fG * fG * fC * fA	UCUGACAGAUAUUUC UGGCA	XXXXX XXXXX XXXXX XXXX
WV-7709	fA * fU * fU * fC * fU * fG * mA * mC * mA * mG * mA * mU * mA * mU * fU * fU * fC * fU * fG * fG	AUUCUGACAGAUAUU UCUGG	XXXXX XXXXX XXXXX XXXX
WV-7710	fC * fA * fA * fA * fU * fU * mC * mU * mG * mA * mC * mA * mG * mA * fU * fA * fU * fU * fU * fC	CAAAUUCUGACAGAU AUUUC	XXXXX XXXXX XXXXX XXXX
WV-7711	fU * fC * fU * fU * fC * fU * mU * mC * mA * mA * mA * mU * mU * mC * mU * fG * fA * fC * fA * fG * fA	UCUCUUCAAAUUCUG ACAGA	XXXXX XXXXX XXXXX XXXX
WV-7712	fC * fC * fU * fC * fA * fA * mU * mC * mU * mC * mU * mU * mC * mA * fA * fA * fA * fU * fU * fC * fU	CCUCAAUCUCUUCAA AUUCU	XXXXX XXXXX XXXXX XXXX
WV-7713	fG * fC * fC * fC * fC * fU * mC * mA * mA * mU * mC * mU * mC * mU * fU * fC * fA * fA * fA * fU	GCCCCUCAAUCUCUU CAAAU	XXXXX XXXXX XXXXX XXXX

WV-7714	fU * fG * fC * fC * fC * fC * mU * mC * mA * mA * mU * mC * mU * mC * fU * fU * fC * fA * fA * fA	UGCCCCUCAAUCUCU UCAAA	XXXXX XXXXX XXXXX XXXX
WV-7715	fG * fU * fG * fC * fC * fC * mC * mU * mC * mA * mA * mU * mC * mU * fC * fU * fU * fC * fA * fA	GUGCCCCUCAAUCUC UUCAA	XXXXX XXXXX XXXXX XXXX
WV-7716	fA * fG * fU * fG * fC * fC * mC * mC * mU * mC * mA * mA * mU * mC * fU * fC * fU * fU * fC * fA	AGUGCCCCUCAAUCU CUUCA	XXXXX XXXXX XXXXX XXXX
WV-7717	fC * fC * fA * fG * fU * fG * mC * mC * mC * mC * mU * mC * mA * mA * fU * fC * fU * fC * fU * fU	CCAGUGCCCCUCAAU CUCUU	XXXXX XXXXX XXXXX XXXX
WV-7718	fU * fU * fC * fC * fA * fG * mU * mG * mC * mC * mC * mC * mU * mC * fA * fA * fU * fC * fU * fC	UUCCAGUGCCCCUCA AUCUC	XXXXX XXXXX XXXXX XXXX
WV-7719	fU * fC * fU * fU * fC * fC * mA * mG * mU * mG * mC * mC * mC * mC * fU * fC * fA * fA * fU * fC	UCUUCCAGUGCCCCU CAAUC	XXXXX XXXXX XXXXX XXXX
WV-7720	fU * fU * fU * fC * fU * fU * mC * mC * mA * mG * mU * mG * mC * mC * fC * fC * fC * fU * fC * fA * fA	UUUCUUCCAGUGCCC CUCAA	XXXXX XXXXX XXXXX XXXX
WV-7721	fA * fG * fU * fU * fU * fC * mU * mU * mC * mC * mA * mG * mU * mG * fC * fC * fC * fC * fU * fC	AGUUUCUUCCAGUGC CCCUC	XXXXX XXXXX XXXXX XXXX
WV-7722	fA * fA * fA * fG * fU * fU * mU * mC * mU * mU * mC * mC * mA * mG * fU * fG * fC * fC * fC * fC	AAAGUUUCUUCCAGU GCCCC	XXXXX XXXXX XXXXX XXXX
WV-7723	fA * fG * fG * fA * fA * fA * mG * mU * mU * mU * mC * mU * mU * mC * fC * fC * fA * fG * fU * fG * fC	AGGAAAGUUUCUUCC AGUGC	XXXXX XXXXX XXXXX XXXX
WV-7724	fG * fG * fA * fG * fG * fA * mA * mG * mU * mU * mU * mC * mU * fU * fC * fC * fC * fA * fG * fU	GGAGGAAAGUUUCU UCCAGU	XXXXX XXXXX XXXXX XXXX
WV-7725	fC * fU * fG * fG * fG * fA * mG * mA * mA * mA * mG * mU * mU * fC * fU * fU * fU * fC * fC	CUGGGAGGAAAGUU UCUUCC	XXXXX XXXXX XXXXX XXXX
WV-7726	fA * fC * fU * fG * fG * fC * mA * mG * mG * mA * mA * mA * mG * mU * fU * fC * fC * fU * fU * fC	ACUGGGAGGAAAGU UUCUUC	XXXXX XXXXX XXXXX XXXX
WV-7727	fC * fC * fA * fC * fC * fA * fA * mG * mG * mA * mG * mG * mA * mA * fA * fG * fU * fU * fU * fC	CCAACUGGGAGGAAA GUUUC	XXXXX XXXXX XXXXX XXXX
WV-7728	fC * fC * fA * fC * fC * fC * fA * mA * mC * mU * mG * mG * mG * mA * mG * fG * fA * fA * fA * fG * fU	CCACCAACUGGGAGG AAAGU	XXXXX XXXXX XXXXX XXXX
WV-7729	fU * fU * fU * fU * fC * fC * fA * mC * mC * mA * mA * mC * mU * mG * mG * fG * fA * fG * fG * fA * fA	UUUCCACCAACUGGG AGGAA	XXXXX XXXXX XXXXX XXXX
WV-7730	fC * fU * fU * fU * fC * fC * fC * mA * mC * mC * mA * mA * mC * mU * mG * fG * fG * fA * fG * fG * fA	CUUUCCACCAACUGG GAGGA	XXXXX XXXXX XXXXX XXXX
WV-7731	fG * fC * fC * fU * fU * fU * fC * mC * mA * mC * mC * mA * mA * mC * mU * fG * fG * fG * fA * fG * fG	GCUUUCCACCAACUG GGAGG	XXXXX XXXXX XXXXX XXXX

WV-7732	fC * fA * fG * fC * fU * fU * mU * mC * mC * mA * mC * mC * mA * mA * fC * fU * fU * fG * fG * fG * fA	CAGCUUUCCACCAAC UGGGA	XXXXX XXXXX XXXXX XXXX
WV-7733	fG * fG * fC * fA * fG * fC * mU * mU * mC * mC * mA * mC * mC * fA * fA * fC * fU * fG * fG	GGCAGCUUUCCACCA ACUGG	XXXXX XXXXX XXXXX XXXX
WV-7734	fU * fU * fG * fG * fC * fA * mG * mC * mU * mU * mU * mC * mC * mA * fC * fC * fA * fA * fC * fU	UUGGCAGCUUUCCAC CAACU	XXXXX XXXXX XXXXX XXXX
WV-7735	fU * fU * fU * fU * fG * fG * mC * mA * mG * mC * mU * mU * mU * mC * fC * fA * fC * fC * fA * fA	UUUUGGCAGCUUUCC ACCAA	XXXXX XXXXX XXXXX XXXX
WV-7736	fG * fC * fU * fU * fU * fU * mG * mG * mC * mA * mG * mC * mC * mU * mU * fU * fC * fC * fA * fC * fC	GCUUUUGGCAGCUUU CCACC	XXXXX XXXXX XXXXX XXXX
WV-7737	fU * fA * fG * fC * fU * fU * mU * mU * mG * mG * mC * mA * mG * mC * fU * fU * fU * fC * fC * fA	UAGCUUUUGGCAGCU UUCCA	XXXXX XXXXX XXXXX XXXX
WV-7738	fU * fC * fU * fU * fA * fG * fC * mU * mU * mU * mU * mG * mG * mC * mA * fG * fC * fU * fU * fU * fC	UCUAGCUUUUGGCAG CUUUC	XXXXX XXXXX XXXXX XXXX
WV-7739	fC * fU * fU * fC * fU * fU * fA * mG * mC * mU * mU * mU * mU * mG * mG * fC * fA * fG * fC * fU * fU	CUUCUAGCUUUUGGC AGCUU	XXXXX XXXXX XXXXX XXXX
WV-7740	fU * fU * fC * fU * fU * fC * mU * mA * mG * mC * mU * mU * mU * mU * fG * fC * fA * fG * fC	UUCUUCUAGCUUUUG GCAGC	XXXXX XXXXX XXXXX XXXX
WV-7741	fU * fG * fU * fU * fC * fU * mU * mC * mU * mA * mG * mC * mU * mU * fU * fU * fU * fG * fG * fC * fA	UGUUCUUCUAGCUUU UGGCA	XXXXX XXXXX XXXXX XXXX
WV-7742	fU * fA * fU * fG * fU * fU * mC * mU * mC * mU * mA * mG * mC * fU * fU * fU * fU * fG * fG	UAUGUUCUUCUAGCU UUUGG	XXXXX XXXXX XXXXX XXXX
WV-7743	fC * fA * fU * fA * fU * fG * mU * mU * mC * mU * mU * mC * mU * mA * fG * fC * fU * fU * fU * fU	CAUAUGUUCUUCUAG CUUUU	XXXXX XXXXX XXXXX XXXX
WV-7744	fU * fU * fC * fA * fU * fA * mU * mG * mU * mC * mU * mU * mC * fU * fA * fG * fC * fU * fU	UUCAUAUGUUCUUCU AGCUU	XXXXX XXXXX XXXXX XXXX
WV-7745	fA * fU * fU * fC * fA * fU * mA * mU * mG * mU * mU * mC * mU * mU * fC * fU * fA * fG * fC * fU	AUUCAUAUGUUCUUC UAGCU	XXXXX XXXXX XXXXX XXXX
WV-7746	fU * fA * fU * fU * fC * fA * mU * mA * mU * mG * mU * mU * mU * mC * mU * fU * fC * fU * fA * fG * fC	UAUUCAUAUGUUCUU CUAGC	XXXXX XXXXX XXXXX XXXX
WV-7747	fG * fU * fU * fA * fU * mU * mC * mA * mU * mA * mU * mG * mU * fU * fC * fU * fU * fC * fU	GUUUAUUCAUAUGU UCUUCU	XXXXX XXXXX XXXXX XXXX
WV-7748	fA * fG * fU * fU * fU * fA * mU * mU * mC * mA * mU * mU * mA * mG * fU * fU * fU * fC * fU * fU * fC	AGUUUAUUCAUAUG UUCUUC	XXXXX XXXXX XXXXX XXXX
WV-7749	fG * fA * fA * fG * fU * fU * mA * mU * mU * mC * mA * mU * mA * fU * fG * fU * fU * fC * fU	GAAGUUUAUUCAUA UGUUCU	XXXXX XXXXX XXXXX XXXX

WV-7750	fU * fC * fG * fA * fA * fG * mU * mU * mU * mA * mU * mU * mC * mA * fU * fA * fU * fG * fU * fU	UCGAAGUUUAUUCAU AUGUU	XXXXX XXXXX XXXXX XXXX
WV-7751	fU * fU * fC * fG * fA * fA * mG * mU * mU * mU * mA * mU * mU * mC * fA * fU * fA * fU * fG * fU	UUCGAAGUUUAUUCA UAUGU	XXXXX XXXXX XXXXX XXXX
WV-7752	fU * fU * fU * fC * fG * fA * mA * mG * mU * mU * mU * mA * mU * mU * fC * fA * fU * fA * fU * fG	UUUCGAAGUUUAUUC AUAUG	XXXXX XXXXX XXXXX XXXX
WV-7753	fA * fA * fU * fU * fU * fU * mC * mG * mA * mA * mG * mU * mU * mU * fA * fU * fU * fC * fA * fU	AAUUUUCGAAGUUU AUUCAU	XXXXX XXXXX XXXXX XXXX
WV-7754	fU * fG * fA * fA * fU * mU * mU * mC * mG * mA * mA * mG * fU * fU * fU * fA * fU * fU	UGAAAUUUUCGAAG UUUAUU	XXXXX XXXXX XXXXX XXXX
WV-7755	fA * fC * fC * fU * fG * fA * mA * mU * mU * mU * mU * mC * mG * fA * fA * fG * fU * fU	ACCUGAAAUUUUCGA AGUUU	XXXXX XXXXX XXXXX XXXX
WV-7756	fU * fU * fA * fC * fC * fU * mG * mA * mA * mA * mU * mU * mU * mU * fC * fC * fG * fA * fA * fG * fU	UUACCUGAAAUUUUC GAAGU	XXXXX XXXXX XXXXX XXXX
WV-7757	fG * fC * fU * fU * fA * fC * mC * mU * mG * mA * mA * mA * mU * mU * fU * fU * fC * fG * fA * fA	GCUUACCUGAAAUUU UCGAA	XXXXX XXXXX XXXXX XXXX
WV-7758	fC * fG * fG * fC * fU * fU * mA * mC * mC * mU * mG * mA * mA * mA * mA * fU * fU * fU * fU * fC * fG	CGGCUUACCUGAAAU UUUCG	XXXXX XXXXX XXXXX XXXX
WV-7759	fC * fU * fC * fG * fG * fC * mU * mU * mA * mC * mC * mU * mG * mA * fA * fA * fU * fU * fU * fU	CUCGGCUUACCUGAA AUUUU	XXXXX XXXXX XXXXX XXXX
WV-7760	fA * fC * fC * fU * fC * fG * mG * mC * mU * mU * mA * mC * mC * mC * mU * fG * fA * fA * fA * fU * fU	ACCUCGGCUUACCUG AAAUU	XXXXX XXXXX XXXXX XXXX
WV-7761	fA * fA * fA * fC * fC * fC * fU * mC * mG * mG * mC * mU * mU * mU * mA * mC * fC * fU * fG * fA * fA * fA	AAACCUCGGCUUACC UGAAA	XXXXX XXXXX XXXXX XXXX
WV-7762	fC * fC * fC * fA * fA * fA * fC * mC * mU * mC * mG * mG * mC * mC * mU * mU * fA * fC * fC * fC * fU * fG * fA	CCAAACCUCGGCUUA CCUGA	XXXXX XXXXX XXXXX XXXX
WV-7763	fG * fC * fC * fC * fA * fA * fA * mC * mC * mU * mC * mG * mG * mG * mC * mU * fU * fA * fC * fC * fC * fU * fG	GCCAAACCUCGGCUU ACCUG	XXXXX XXXXX XXXXX XXXX
WV-7764	fA * fG * fG * fC * fC * fC * fA * mA * mA * mC * mC * mU * mC * mC * mG * mG * fC * fU * fU * fU * fA * fC * fC	AGGCCAAACCUCGGC UUACC	XXXXX XXXXX XXXXX XXXX
WV-7765	fA * fA * fA * fG * fG * fC * mC * mA * mA * mA * mC * mC * mC * mU * mC * fG * fG * fG * fC * fC * fU * fU * fA	AAAGGCCAAACCUCG GCUUA	XXXXX XXXXX XXXXX XXXX
WV-7766	fU * fU * fA * fA * fA * fG * mG * mC * mC * mA * mA * mA * mC * mC * fU * fC * fG * fG * fC * fC * fU	UUAAAGGCCAAACCU CGGCU	XXXXX XXXXX XXXXX XXXX
WV-7767	fG * fU * fU * fU * fU * fA * fA * mA * mG * mG * mC * mC * mA * mA * mA * mA * fC * fC * fC * fU * fC * fG * fG	GUUUAAAGGCCAAAC CUCGG	XXXXX XXXXX XXXXX XXXX

WV-7768	fU * fA * fG * fU * fU * fU * mA * mA * mA * mG * mG * mC * mC * mA * fA * fA * fC * fC * fU * fC	UAGUUUAAAGGCCAA ACCUC	XXXXX XXXXX XXXXX XXXX
WV-7769	fU * fA * fU * fA * fG * fU * mU * mU * mA * mA * mA * mG * mG * mC * fC * fA * fA * fA * fC * fC	UAUAGUUUAAAGGCC AAACC	XXXXX XXXXX XXXXX XXXX
WV-7770	fA * fA * fU * fA * fU * fA * mG * mU * mU * mU * mA * mA * mA * mG * fG * fC * fC * fA * fA * fA	AAUAUAGUUUAAAG GCCAAA	XXXXX XXXXX XXXXX XXXX
WV-7771	fA * fA * fA * fA * fU * fA * mU * mA * mG * mU * mU * mU * mA * mA * fA * fG * fG * fC * fC * fC * fA	AAAAUAUAGUUUAA AGGCCA	XXXXX XXXXX XXXXX XXXX
WV-8130	Mod028L001 * fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	XSSSSSSOSOSSOO SSSSS
WV-8131	Mod028L001fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSSSSOSOSSOO SSSSS
WV-8230	fU * SfC * SfA * SfA * SfG * SfG * SAeofA * SGeoAeo * SfU * SGeoGeofC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSSOOS SSSSS
WV-8231	fU * SfC * SfA * SfA * SfG * SfG * SAeofA * SGeoAeofU * SGeoGeofC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOOSOOS SSSSS
WV-8232	fU * SfC * SfA * SfG * SfG * SAeoAeoGeoAeoTeoGeoGeofC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGATGGCA UUUCU	SSSSSSOOOOOOO SSSSSS
WV-8449	fU * RfC * RfA * RfA * RfG * RfG * R mAfA * R mG mA * RfU * R mG mGfC * RfA * RfU * RfU * RfU * RfC * RfU	UCAAGGAAGAUGGCA UUUCU	RRRRRRORORRO ORRRRR
WV-8478	fU * fC * fA * fA * fG * fG * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * Aeo * Teo * Teo * Teo * m5Ceo * Teo	UCAAGGAAGATGGCA TTTCT	XXXXX XXXXX XXXXX XXXX
WV-8479	fU * fC * fA * fA * fG * fG * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * Aeo * Teo * Teo * Teo * m5Ceo * mU	UCAAGGAAGATGGCA TTTCU	XXXXX XXXXX XXXXX XXXX
WV-8480	fU * fC * fA * fA * fG * fG * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * Aeo * Teo * Teo * Teo * mC * mU	UCAAGGAAGATGGCA TTTCU	XXXXX XXXXX XXXXX XXXX
WV-8481	fU * fC * fA * fA * fG * fG * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * Aeo * Teo * Teo * mU * mC * mU	UCAAGGAAGATGGCA TTUCU	XXXXX XXXXX XXXXX XXXX
WV-8482	fU * fC * fA * fA * fG * fG * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * Aeo * Teo * mU * mU * mC * mU	UCAAGGAAGATGGCA TUUCU	XXXXX XXXXX XXXXX XXXX
WV-8483	fU * fC * fA * fA * fG * fG * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * Aeo * mU * mU * mU * mC * mU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8484	fU * fC * fA * fA * fG * fG * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * mA * mU * mU * mU * mC * mU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8485	fU * fC * fA * fA * fG * fG * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX

WV-8486	fU * fC * fA * fA * fG * fG * Aeo * Aeo * Geo * Aeo * Teo * Geo * mG * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8487	fU * fC * fA * fA * fG * fG * Aeo * Aeo * Geo * Aeo * Teo * mG * mG * mC * mA * mU * mU * mU * mU * mC * mU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8488	fU * fC * fA * fA * fG * fG * Aeo * Aeo * Geo * Aeo * mU * mG * mG * mC * mA * mU * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8489	fU * fC * fA * fA * fG * fG * Aeo * Aeo * Geo * mA * mU * mG * mG * mC * mA * mU * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8490	fU * fC * fA * fA * fG * fG * Aeo * Aeo * mG * mA * mU * mG * mG * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8491	fU * fC * fA * fA * fG * fG * Aeo * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8492	Teo * m5Ceo * Aeo * Aeo * Geo * Geo * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * fA * fU * fU * fU * fC * fU	TCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8493	mU * m5Ceo * Aeo * Aeo * Geo * Geo * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * fA * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8494	mU * mC * Aeo * Aeo * Geo * Geo * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * fA * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8495	mU * mC * mA * Aeo * Geo * Geo * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * fA * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8496	mU * mC * mA * mA * Geo * Geo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * fA * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8497	mU * mC * mA * mA * mG * Geo * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * fA * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8498	mU * mC * mA * mA * mG * mG * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * fA * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8499	mU * mC * mA * mA * mG * mG * mA * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * fA * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8500	mU * mC * mA * mA * mG * mG * mA * mA * Geo * Aeo * Teo * Geo * Geo * m5Ceo * fA * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8501	mU * mC * mA * mA * mG * mG * mA * mA * mG * Aeo * Teo * Geo * Geo * m5Ceo * fA * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8502	mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * Teo * Geo * Geo * m5Ceo * fA * fU * fU * fU * fC * fU	UCAAGGAAGATGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-8503	mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * Geo * Geo * m5Ceo * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX

WV-8504	mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * Geo * m5Ceo * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX XXX
WV-8505	mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * m5Ceo * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXX XXX
WV-8506	Teo * m5Ceo * Aeo * Aeo * Geo * Geo * Geo * Aeo * Aeo * Geo * Aeo * Teo * Geo * Geo * m5Ceo * Aeo * Teo * Teo * Teo * m5Ceo * Teo	TCAAGGAAGATGGCA TTTCT	XXXXX XXXXX XXXX XXX
WV-8806	CTCCAACATCAAGGAAGATGGCATTTCTAG [all PMO]	CTCCAACATCAAGGA AGATGG CATTTCTAG	XXXXX XXXXX XXXX XXX
WV-884	mU * R mC * R mA * R mA * R mG * R mG * R mA * R mA * R mG * R mA * R mU * R mG * R mG * R mC * R mA * R mU * R mU * R mU * R mC * R mU	UCAAGGAAGAUGGCA UUUCU	RRRRRRRRRRRRR RRRRRR
WV-885	mU * S mC * R mA * S mA * R mG * S mG * R mA * S mA * R mG * S mA * R mU * S mG * R mG * S mC * R mA * S mU * R mU * S mU * R mC * S mU	UCAAGGAAGAUGGCA UUUCU	SRSRSRSRSRSR SRSRS
WV-886	mU * R mC * R mA * R mA * S mG * S mG * S mA * S mA * S mG * S mA * S mU * S mG * S mC * S mA * S mU * S mU * R mU * R mC * R mU	UCAAGGAAGAUGGCA UUUCU	RRRSSSSSSSSSS SRRR
WV-887	mU * S mC * S mA * S mA * R mG * R mG * R mA * R mA * R mG * R mA * R mU * R mG * R mC * R mA * R mU * R mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSRRRRRRRRR RRRSSS	
WV-888	mU * R mC * R mA * R mA * R mG * R mG * S mA * S mA * R mG * S mA * S mU * R mG * S mG * S mC * R mA * R mU * R mU * R mU * R mC * R mU	UCAAGGAAGAUGGCA UUUCU	RRRRRSSRSSRSSR RRRRR	
WV-889	mU * S mC * S mA * S mA * S mG * S mG * R mA * R mA * S mG * R mA * R mU * S mG * R mG * R mC * S mA * S mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSRRSRRSRRS SSSSS	
WV-890	mU * R mC * R mA * R mA * S mG * S mG * R mA * R mA * S mG * R mA * R mU * R mG * S mG * R mC * R mA * S mU * S mU * R mU * R mC * R mU	UCAAGGAAGAUGGCA UUUCU	RRRSSRRSRRRSR RSSRRR	
WV-891	mU * S mC * S mA * S mA * R mG * R mG * S mA * S mA * R mG * S mA * S mU * S mG * R mG * S mC * S mA * R mU * R mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSRRSSRSSSRSS RRSSS	
WV-892	mU * S mC * R mA * R mA * R mG * R mG * R mA * R mA * R mG * R mA * R mU * R mG * R mG * R mC * R mA * R mU * R mU * R mU * R mC * S mU	UCAAGGAAGAUGGCA UUUCU	SRRRRRRRRRRRR RRRRRS	
WV-	mU * R mC * S mA * S mA * S mG * S mG * S mA * S mG * S mA *	UCAAGGAAGAUGGCA	RSSSSSSSSSSSS

893	S mU * S mG * S mG * S mC * S mA * S mU * S mU * S mC * R mU	UUUCU	SSSR
WV-8937	fA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	AAGGAAGAUGGCAU UUCU	SSSSOSOSSOOSSS SSS
WV-894	mU * S mC * R mA * S mA * S mG * R mG * R mA * S mA * S mG * R mA * S mU * S mG * R mC * R mA * S mU * S mU * S mC * R mU	UCAAGGAAGAUGGCA UUUCU	SRSSRRSSRSSRRR SSSSR
WV-895	mU * R mC * S mA * R mA * R mG * S mG * S mA * R mA * R mG * S mA * R mU * R mG * S mG * S mC * S mA * R mU * R mU * R mU * R mC * S mU	UCAAGGAAGAUGGCA UUUCU	RSRRSSRRSRRSSS RRRRS
WV-896	mU * S mC * S mA * R mA * R mG * R mG * R mA * R mA * R mG * R mA * R mU * S mG * R mG * R mC * S mA * R mU * S mU * S mU * S mC * S mU	UCAAGGAAGAUGGCA UUUCU	SSRRRRRRRRSRR SRSSSS
WV-897	mU * R mC * R mA * S mA * S mG * S mG * S mA * S mA * S mG * S mA * S mU * R mG * S mG * S mC * R mA * S mU * R mU * R mU * R mC * R mU	UCAAGGAAGAUGGCA UUUCU	RRSSSSSSSSRSSR SRRRR
WV-9067	fG * fU * fA * fC * fU * fU * mU * m5Ceo * Aeo * Teo * m5Ceo * m5Ceo * m5Ceo * Aeo * m5Ceo * fU * fG * fA * fU * fU * fC	GUACUUCATCCCACU GAUUC	XXXX XXXX XXXX XXXX
WV-9068	fG * fU * fA * fC * fU * fU * mU * m5Ceo * AeoTeo * m5Ceo m5Ceo * m5CeoAeo * m5CeofU * fG * fA * fU * fU * fC	GUACUUCATCCCACU GAUUC	XXXXXXXOXOXO XOXXXXX	
WV-9069	fG * fU * fA * fC * fU * fU * mU * m5CeoAeo * Teo m5Ceo * m5Ceo m5Ceo * Aeo m5Ceo * fU * fG * fA * fU * fU * fC	GUACUUCATCCCACU GAUUC	XXXXXXOXOXOX OXXXXXX	
WV-9070	fG * fU * fA * fC * fU * fU * mU * m5Ceo * mA * Teo * mC * m5Ceo * mC * Aeo * mC * fU * fG * fA * fU * fU * fC	GUACUUCATCCCACU GAUUC	XXXX XXXX XXXX XXXX	
WV-9071	fG * fU * fA * fC * fU * fU * mU * m5Ceo * mC m5Ceo * mCAeo * mCfU * fG * fA * fU * fU * fC	GUACUUCATCCCACU GAUUC	XXXXXXXOXOXO XOXXXXX	
WV-9072	fG * fU * fA * fC * fU * fU * mU * m5Ceo mA * Teo mC * m5Ceo mC * Aeo mC * fU * fG * fA * fU * fU * fC	GUACUUCATCCCACU GAUUC	XXXXXXOXOXOX OXXXXXX	
WV-9073	fG * fU * fA * fC * fU * fU * mU * mC * Aeo * mU * m5Ceo * mC * m5Ceo * mA * m5Ceo * fU * fG * fA * fU * fU * fC	GUACUUCAUCCCACU GAUUC	XXXX XXXX XXXX XXXX	
WV-9074	fG * fU * fA * fC * fU * fU * mU * mC * Aeo mU * m5Ceo mC * m5Ceo mA * m5CeofU * fG * fA * fU * fU * fC	GUACUUCAUCCCACU GAUUC	XXXXXXXOXOXO XOXXXXX	
WV-9075	fG * fU * fA * fC * fU * fU * mU * mCAeo * mU m5Ceo * mC m5Ceo * mA m5Ceo * fU * fG * fA * fU * fU * fC	GUACUUCAUCCCACU GAUUC	XXXXXXOXOXOX OXXXXXX	
WV-9076	fG * fU * fA * fC * fU * fU * m5Ceo * fA * Teo * fC * m5Ceo * fC * Aeo * fC * fU * fG * fA * fU * fU * fC	GUACUUCATCCCACU GAUUC	XXXXX XXXXX XXXXX XXXX	
WV-	fG * fU * fA * fC * fU * fU * m5Ceo * fATeo * fC m5Ceo * fCAeo * fCfU * fG	GUACUUCATCCCACU	XXXXXXXOXOXO	

9077	* fA * fU * fU * fC	GAUUC	XOXXXXX
WV-9078	fG * fU * fA * fC * fU * fU * m5CeofA * TeofC * m5CeofC * AeofC * fU * fG * fA * fU * fU * fC	GUACUUCATCCCACU GAUUC	XXXXXXOXOXOX OXXXXXX
WV-9079	fG * fU * fA * fC * fU * fU * fC * Aeo * fU * m5Ceo * fC * m5Ceo * fA * m5Ceo * fU * fG * fA * fU * fU * fC	GUACUUCAUCCCACU GAUUC	XXXXX XXXXX XXXXX XXXX
WV-9080	fG * fU * fA * fC * fU * fU * fC * AeofU * m5CeofC * m5CeofA * m5CeofU * fG * fA * fU * fU * fC	GUACUUCAUCCCACU GAUUC	XXXXXXXOXOXO XOXXXXX
WV-9081	fG * fU * fA * fC * fU * fU * fCAeo * fU m5Ceo * fC m5Ceo * fA m5Ceo * fU * fG * fA * fU * fU * fC	GUACUUCAUCCCACU GAUUC	XXXXXXOXOXOX OXXXXXX
WV-9082	fG * fU * fA * fC * fU * fU * mC * fA * mU * fC * mC * fC * mA * fC * fU * fG * fA * fU * fU * fC	GUACUUCAUCCCACU GAUUC	XXXXX XXXXX XXXXX XXXX
WV-9083	fG * fU * fA * fC * fU * fU * mC * fA mU * fC mC * fC mA * fCfU * fG * fA * fU * fU * fC	GUACUUCAUCCCACU GAUUC	XXXXXXXOXOXO XOXXXXX
WV-9084	fG * fU * fA * fC * fU * fU * mCfA * mUfC * mCfC * mAfC * fU * fG * fA * fU * fU * fC	GUACUUCAUCCCACU GAUUC	XXXXXXOXOXOX OXXXXXX
WV-9085	fG * fU * fA * fC * fU * fU * fC * mA * fU * mC * fC * mC * fA * mC * fU * fG * fA * fU * fU * fC	GUACUUCAUCCCACU GAUUC	XXXXX XXXXX XXXXX XXXX
WV-9086	fG * fU * fA * fC * fU * fU * fC * mAfU * mCfC * mCfA * mCfU * fG * fA * fU * fU * fC	GUACUUCAUCCCACU GAUUC	XXXXXXXOXOXO XOXXXXX
WV-9087	fG * fU * fA * fC * fU * fU * fC mA * fU mC * fC mC * fA mC * fU * fG * fA * fU * fU * fC	GUACUUCAUCCCACU GAUUC	XXXXXXOXOXOX OXXXXXX
WV-9088	Geo * Teo * Aeo * m5Ceo * Teo * Teo * m5Ceo * Aeo * Teo * m5Ceo * m5Ceo * m5Ceo * Aeo * m5Ceo * fU * fG * fA * fU * fU * fC	GTACTTCATCCCACU GAUUC	XXXXX XXXXX XXXXX XXXX
WV-9089	mG * mU * mA * mC * mU * Teo * m5Ceo * Aeo * Teo * m5Ceo * m5Ceo * m5Ceo * Aeo * m5Ceo * fU * fG * fA * fU * fU * fC	GUACUTCATCCCACU GAUUC	XXXXX XXXXX XXXXX XXXX
WV-9090	mG * mU * mA * mC * mU * m5Ceo * Aeo * Teo * m5Ceo * m5Ceo * m5Ceo * Aeo * m5Ceo * fU * fG * fA * fU * fU * fC	GUACUUCATCCCACU GAUUC	XXXXX XXXXX XXXXX XXXX
WV-9091	fG * fU * fG * fU * fU * fC * Teo * Teo * Geo * Teo * Aeo * m5Ceo * Teo * Teo * fC * fA * fU * fC * fC * fC	GUGUUCTTGTACTTC AUCCC	XXXXX XXXXX XXXXX XXXX
WV-9092	fG * fU * fG * fU * fU * fC * Teo * TeoGeo * TeoAeo * m5CeoTeo * TeofC * fA * fU * fC * fC * fC	GUGUUCTTGTACTTC AUCCC	XXXXXXXOXOXO XOXXXXX
WV-9093	fG * fU * fG * fU * fU * fC * TeoTeo * GeoTeo * Aeo m5Ceo * TeoTeo * fC * fA * fU * fC * fC * fC	GUGUUCTTGTACTTC AUCCC	XXXXXXOXOXOX OXXXXXX
WV-9094	fG * fU * fG * fU * fU * fC * Teo * mU * Geo * mU * Aeo * mC * Teo * mU * fC * fA * fU * fC * fC * fC	GUGUUCTUGUACTUC AUCCC	XXXXX XXXXX XXXXX XXXX
WV-	fG * fU * fG * fU * fU * fC * Teo * mUGeo * mUAeo * mCTeo * mUfC * fA	GUGUUCTUGUACTUC	XXXXXXOXOXO

9095	* fU * fC * fC * fC	AUCCC	XOXXXXX
WV-9096	fG * fU * fG * fU * fU * fC * Teo mU * Geo mU * Aeo mC * Teo mU * fC * fA * fU * fC * fC * fC	GUGUUCTUGUACTUC AUCCC	XXXXXXOXOXOX OXXXXXX
WV-9097	fG * fU * fG * fU * fU * fC * mU * Teo * mG * Teo * mA * m5Ceo * mU * Teo * fC * fA * fU * fC * fC * fC	GUGUUCUTGTACUTC AUCCC	XXXXX XXXXX XXXXX XXXX
WV-9098	fG * fU * fG * fU * fU * fC * mU * Teo mG * Teo mA * m5Ceo mU * TeofC * fA * fU * fC * fC * fC	GUGUUCUTGTACUTC AUCCC	XXXXXXXOXOXO XOXXXXX
WV-9099	fG * fU * fG * fU * fU * fC * mUTeo * mGTeo * mA m5Ceo * mUTeo * fC * fA * fU * fC * fC * fC	GUGUUCUTGTACUTC AUCCC	XXXXXXOXOXOX OXXXXXX
WV-9100	fG * fU * fG * fU * fU * fC * Teo * fU * Geo * fU * Aeo * fC * Teo * fU * fC * fA * fU * fC * fC * fC	GUGUUCTUGUACTUC AUCCC	XXXX XXXX XXXX XXXX
WV-9101	fG * fU * fG * fU * fU * fC * Teo * fUGeo * fUAeo * fCTeo * fUfC * fA * fU * fC * fC * fC	GUGUUCTUGUACTUC AUCCC	XXXXXXXOXOXO XOXXXXX
WV-9102	fG * fU * fG * fU * fU * fC * TeofU * GeofU * AeofC * TeofU * fC * fA * fU * fC * fC * fC	GUGUUCTUGUACTUC AUCCC	XXXXXXOXOXOX OXXXXXX
WV-9103	fG * fU * fG * fU * fU * fC * fU * Teo * fG * Teo * fA * m5Ceo * fU * Teo * fC * fA * fU * fC * fC * fC	GUGUUCUTGTACUTC AUCCC	XXXXX XXXXX XXXXX XXXX
WV-9104	fG * fU * fG * fU * fU * fC * fU * TeofG * TeofA * m5CeofU * TeofC * fA * fU * fC * fC * fC	GUGUUCUTGTACUTC AUCCC	XXXXXXXOXOXO XOXXXXX
WV-9105	fG * fU * fG * fU * fU * fC * fUTeo * fGTeo * fA m5Ceo * fUTeo * fC * fA * fU * fC * fC * fC	GUGUUCUTGTACUTC AUCCC	XXXXXXOXOXOX OXXXXXX
WV-9106	fG * fU * fG * fU * fU * fC * mU * fU * mG * fU * mA * fC * mU * fU * fC * fA * fU * fC * fC * fC	GUGUUCUUGUACUUC AUCCC	XXXXX XXXXX XXXXX XXXX
WV-9107	fG * fU * fG * fU * fU * fC * mU * fU mG * fU mA * fC mU * fUfC * fA * fU * fC * fC * fC	GUGUUCUUGUACUUC AUCCC	XXXXXXXOXOXO XOXXXXX
WV-9108	fG * fU * fG * fU * fU * fC * mUfU * mGfU * mAfC * mUfU * fC * fA * fU * fC * fC * fC	GUGUUCUUGUACUUC AUCCC	XXXXXXOXOXOX OXXXXXX
WV-9109	fG * fU * fG * fU * fU * fC * fU * mU * fG * mU * fA * mC * fU * mU * fC * fA * fU * fC * fC * fC	GUGUUCUUGUACUUC AUCCC	XXXXX XXXXX XXXXX XXXX
WV-9110	fG * fU * fG * fU * fU * fC * fU * mUfG * mUfA * mCfU * mUfC * fA * fU * fC * fC * fC	GUGUUCUUGUACUUC AUCCC	XXXXXXXOXOXO XOXXXXX
WV-9111	fG * fU * fG * fU * fU * fC * fU mU * fG mU * fA mC * fU mU * fC * fA * fU * fC * fC * fC	GUGUUCUUGUACUUC AUCCC	XXXXXXOXOXOX OXXXXXX
WV-9112	Geo * Teo * Geo * Teo * Teo * m5Ceo * Teo * Teo * Geo * Teo * Aeo * m5Ceo * Teo * Teo * fC * fA * fU * fC * fC * fC	GTGTTCTTGTACTTCA UCCC	XXXXX XXXXX XXXX XXXX
WV-	mG * mU * mG * mU * mU * m5Ceo * Teo * Teo * Geo * Teo * Aeo *	GUGUUCTTGTACTTC	XXXXX XXXXX

9113	m5Ceo * Teo * Teo * fC * fA * fU * fC * fC * fC	AUCCC	XXXXX XXXX
WV-9114	mG * mU * mG * mU * mU * mC * Teo * Teo * Geo * Teo * Aeo * m5Ceo * Teo * Teo * fC * fA * fU * fC * fC * fC	GUGUUCTTGTACTTC AUCCC	XXXXX XXXXX XXXXX XXXX
WV-9115	fU * fU * fC * fU * fU * fG * fA * Aeo * Geo * Geo * Teo * Geo * Teo * Teo * m5Ceo * fU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXX XXXXX XXXXX XXXX
WV-9116	fU * fU * fC * fU * fU * fG * fA * Aeo * GeoGeo * TeoGeo * TeoTeo * m5CeofU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXXXXOXOXO XOXXXXX
WV-9117	fU * fU * fC * fU * fU * fG * fA * AeoGeo * GeoTeo * GeoTeo * Teo m5Ceo * fU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXXXOXOXOX OXXXXXX
WV-9118	fU * fU * fC * fU * fU * fG * fA * Aeo * mG * Geo * mU * Geo * mU * Teo * mC * fU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXX XXXXX XXXXX XXXX
WV-9119	fU * fU * fC * fU * fU * fG * fA * Aeo * mGGeo * mUGeo * mUTeo * mCfU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXXXXOXOXO XOXXXXX
WV-9120	fU * fU * fC * fU * fU * fG * fA * Aeo mG * Geo mU * Geo mU * Teo mC * fU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXXXOXOXOX OXXXXXX
WV-9121	fU * fU * fC * fU * fU * fG * fA * mA * Geo * mG * Teo * mG * Teo * mU * m5Ceo * fU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXX XXXXX XXXXX XXXX
WV-9122	fU * fU * fC * fU * fU * fG * fA * mA * Geo mG * Teo mG * Teo mU * m5CeofU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXXXXOXOXO XOXXXXX
WV-9123	fU * fU * fC * fU * fU * fG * fA * mAGeo * mGTeo * mGTeo * mU m5Ceo * fU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXXXOXOXOX OXXXXXX
WV-9124	fU * fU * fC * fU * fU * fG * fA * Aeo * fG * Geo * fU * Geo * fU * Teo * fC * fU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXX XXXXX XXXXX XXXX
WV-9125	fU * fU * fC * fU * fU * fG * fA * Aeo * fGGeo * fUGeo * fUTeo * fCfU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXXXXOXOXO XOXXXXX
WV-9126	fU * fU * fC * fU * fU * fG * fA * AeofG * GeofU * GeofU * TeofC * fU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXXOXOXOX OXXXXXX
WV-9127	fU * fU * fC * fU * fU * fG * fA * fA * Geo * fG * Teo * fG * Teo * fU * m5Ceo * fU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXX XXXXX XXXXX XXXX
WV-9128	fU * fU * fC * fU * fU * fG * fA * fA * GeofG * TeofG * TeofU * m5CeofU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXXXXOXOXO XOXXXXX
WV-9129	fU * fU * fC * fU * fU * fG * fA * fAGeo * fGTeo * fGTeo * fU m5Ceo * fU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXXXOXOXOX OXXXXXX
WV-9130	fU * fU * fC * fU * fU * fG * fA * mA * fG * mG * fU * mG * fU * mU * fC * fU * fU * fG * fU * fA * fC	UUCUGAAGGTGUUCU UGUAC	XXXXX XXXXX XXXX XXX
WV-	fU * fU * fC * fU * fU * fG * fA * mA * fG mG * fU mU * fCfU * fU * fG	UUCUGAAGGTGUUCU	XXXXXXXOXOXO

9131	* fU * fA * fC	UGUAC	XOXXXXX
WV-9132	fU * fU * fC * fU * fG * fA * mAfG * mGfU * mUfC * fU * fU * fG * fU * fA * fC	UUCUGAAGGUGUUCU UGUAC	XXXXXOXOXOX OXXXXXX
WV-9133	fU * fU * fC * fU * fG * fA * fA * mG * fG * mU * fG * mU * fU * mC * fU * fU * fG * fU * fA * fC	UUCUGAAGGUGUUCU UGUAC	XXXXX XXXXX XXXXX XXXX
WV-9134	fU * fU * fC * fU * fG * fA * fA * mGfG * mUfU * mUfU * mCfU * fU * fG * fU * fA * fC	UUCUGAAGGUGUUCU UGUAC	XXXXXXXOXOXO XOXXXXX
WV-9135	fU * fU * fC * fU * fG * fA * fA mG * fG mU * fG mU * fU mC * fU * fU * fG * fU * fA * fC	UUCUGAAGGUGUUCU UGUAC	XXXXXOXOXOX OXXXXXX
WV-9136	Teo * Teo * m5Ceo * Teo * Geo * Aeo * Aeo * Geo * Geo * Teo * Geo * Teo * Teo * m5Ceo * fU * fU * fG * fU * fA * fC	TTCTGAAGGTGTTCU UGUAC	XXXXX XXXXX XXXXX XXXX
WV-9137	mU * mU * mC * mU * mG * Aeo * Aeo * Geo * Geo * Teo * Geo * Teo * Teo * m5Ceo * fU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXX XXXXX XXXX XXX
WV-9138	mU * mU * mC * mU * mG * mA * Aeo * Geo * Geo * Teo * Geo * Teo * Teo * m5Ceo * fU * fU * fG * fU * fA * fC	UUCUGAAGGTGTTCU UGUAC	XXXXX XXXXX XXXXX XXX
WV-9139	fC * fU * fC * fC * fG * fG * Teo * Teo * m5Ceo * Teo * Geo * Aeo * Aeo * Geo * fG * fU * fG * fU * fU * fC	CUCCGGTTCTGAAGG UGUUC	XXXXX XXXXX XXXX XXX
WV-9140	fC * fU * fC * fC * fG * fG * Teo * Teo m5Ceo * TeoGeo * AeoAeo * GeofG * fU * fG * fU * fU * fC	CUCCGGTTCTGAAGG UGUUC	XXXXXXXOXOXO XOXXXXX
WV-9141	fC * fU * fC * fC * fG * fG * TeoTeo * m5CeoTeo * GeoAeo * AeoGeo * fG * fU * fG * fU * fU * fU * fC	CUCCGGTTCTGAAGG UGUUC	XXXXXXOXOXOX OXXXXXX
WV-9142	fC * fU * fC * fC * fC * fG * fG * Teo * mU * m5Ceo * mU * Geo * mA * Aeo * mG * fG * fU * fG * fU * fU * fC	CUCCGGTUCUGAAGG UGUUC	XXXXX XXXXX XXXX XXX
WV-9143	fC * fU * fC * fC * fC * fG * fG * Teo * mU m5Ceo * mUGeo * mAAeo * mGfG * fU * fG * fU * fU * fC	CUCCGGTUCUGAAGG UGUUC	XXXXXXXOXOXO XOXXXXX
WV-9144	fC * fU * fC * fC * fC * fG * fG * Teo mU * m5Ceo mU * Geo mA * Aeo mG * fG * fU * fG * fU * fU * fC	CUCCGGTUCUGAAGG UGUUC	XXXXXXOXOXOX OXXXXXX
WV-9145	fC * fU * fC * fC * fC * fG * fG * mU * Teo * mC * Teo * mG * Aeo * mA * Geo * fG * fU * fG * fU * fU * fC	CUCCGGUTCTGAAGG UGUUC	XXXXX XXXXX XXXXX XXX
WV-9146	fC * fU * fC * fC * fG * fG * mU * Teo mC * Teo mG * Aeo mA * GeofG * fU * fG * fU * fU * fU * fC	CUCCGGUTCTGAAGG UGUUC	XXXXXXXOXOXO XOXXXXX
WV-9147	fC * fU * fC * fC * fG * fG * mUTeo * mCTeo * mGAeo * mAGeo * fG * fU * fG * fU * fU * fU * fC	CUCCGGUTCTGAAGG UGUUC	XXXXXXOXOXOX OXXXXXX
WV-9148	fC * fU * fC * fC * fG * fG * Teo * fU * m5Ceo * fU * Geo * fA * Aeo * fG * fG * fU * fG * fU * fU * fC	CUCCGGTUCUGAAGG UGUUC	XXXXX XXXXX XXXX XXX
WV-	fC * fU * fC * fC * fG * fG * Teo * fU m5Ceo * fUGeo * fAAeo * fGfG * fU *	CUCCGGTUCUGAAGG	XXXXXXXOXOXO

9149	fG * fU * fU * fC	UGUUC	XOXXXXX
WV-9150	fC * fU * fC * fC * fG * fG * TeofU * m5CeofU * GeofA * AeofG * fG * fU * fG * fU * fU * fC	CUCCGGTUCUGAAGG UGUUC	XXXXXXOXOXOX OXXXXXX
WV-9151	fC * fU * fC * fC * fC * fG * fG * fU * Teo * fC * Teo * fG * Aeo * fA * Geo * fG * fU * fG * fU * fU * fC	CUCCGGUTCTGAAGG UGUUC	XXXXX XXXXX XXXXX XXXX
WV-9152	fC * fU * fC * fC * fC * fG * fG * fU * TeofC * TeofG * AeofA * GeofG * fU * fG * fU * fU * fU * fC	CUCCGGUTCTGAAGG UGUUC	XXXXXXXOXOXO XOXXXXX
WV-9153	fC * fU * fC * fC * fC * fG * fG * fUTeo * fCTeo * fGAeo * fAGeo * fG * fU * fG * fU * fU * fU * fC	CUCCGGUTCTGAAGG UGUUC	XXXXXXOXOXOX OXXXXXX
WV-9154	fC * fU * fC * fC * fC * fG * fG * mU * fU * mC * fU * mG * fA * mA * fG * fG * fU * fG * fU * fU * fU * fC	CUCCGGUUCUGAAGG UGUUC	XXXXX XXXXX XXXXX XXXX
WV-9155	fC * fU * fC * fC * fC * fG * fG * mU * fU mC * fU mG * fA mA * fGfG * fU * fG * fU * fU * fU * fC	CUCCGGUUCUGAAGG UGUUC	XXXXXXXOXOXO XOXXXXX
WV-9156	fC * fU * fC * fC * fC * fG * fG * mUfU * mCfU * mGfA * mAfG * fG * fU * fU * fG * fU * fU * fU * fC	CUCCGGUUCUGAAGG UGUUC	XXXXXXOXOXOX OXXXXXX
WV-9157	fC * fU * fC * fC * fC * fG * fG * fU * mU * fC * mU * fG * mA * fA * mG * fG * fU * fG * fU * fU * fU * fC	CUCCGGUUCUGAAGG UGUUC	XXXXX XXXXX XXXXX XXXX
WV-9158	fC * fU * fC * fC * fC * fG * fG * fU * mUfC * mUfG * mAfA * mGfG * fU * fG * fU * fU * fU * fC	CUCCGGUUCUGAAGG UGUUC	XXXXXXXOXOXO XOXXXXX
WV-9159	fC * fU * fC * fC * fC * fG * fG * fU mU * fC mU * fG mA * fA mG * fG * fU * fG * fU * fU * fU * fC	CUCCGGUUCUGAAGG UGUUC	XXXXXXOXOXOX OXXXXXX
WV-9160	m5Ceo * Teo * m5Ceo * m5Ceo * Geo * Geo * Teo * Teo * m5Ceo * Teo * Geo * Aeo * Aeo * Geo * fG * fU * fG * fU * fU * fC	CTCCGGTTCTGAAGG UGUUC	XXXXX XXXXX XXXXX XXXX
WV-9161	mC * mU * mC * mC * mG * Geo * Teo * Teo * m5Ceo * Teo * Geo * Aeo * Aeo * Geo * fG * fU * fG * fU * fU * fC	CUCCGGTTCTGAAGG UGUUC	XXXXX XXXXX XXXXX XXXX
WV-9162	mC * mU * mC * mC * mG * Teo * Teo * m5Ceo * Teo * Geo * Aeo * Aeo * Geo * fG * fU * fG * fU * fU * fC	CUCCGGTTCTGAAGG UGUUC	XXXXX XXXXX XXXXX XXXX
WV-9163	fU * fC * fU * fU * fU * fG * fG * m5Ceo * m5Ceo * Aeo * Teo * m5Ceo * Teo * m5Ceo * m5Ceo * fU * fU * fC * fA * fC * fA	UCUUGGCCATCTCCU UCACA	XXXXX XXXXX XXXXX XXXX
WV-9164	fU * fC * fU * fU * fU * fG * fG * m5Ceo * m5CeoAeo * Teo m5Ceo * Teo m5Ceo * m5CeofU * fU * fC * fA * fC * fA	UCUUGGCCATCTCCU UCACA	XXXXXXXOXOXO XOXXXXX
WV-9165	fU * fC * fU * fU * fG * fG * m5Ceo m5Ceo * AeoTeo * m5CeoTeo * m5Ceo m5Ceo * fU * fU * fC * fA * fC * fA	UCUUGGCCATCTCCU UCACA	XXXXXXOXOXOX OXXXXXX
WV-9166	fU * fC * fU * fU * fU * fG * fG * m5Ceo * mC * Aeo * mU * m5Ceo * mU * m5Ceo * mC * fU * fU * fC * fA * fC * fA	UCUUGGCCAUCUCCU UCACA	XXXXX XXXXX XXXX XXXX
WV-	fU * fC * fU * fU * fG * fG * m5Ceo * mCAeo * mU m5Ceo * mU m5Ceo *	UCUUGGCCAUCUCCU	XXXXXXXOXOXO

9167	mCfU * fU * fC * fA * fC * fA	UCACA	XOXXXXX
WV-9168	fU * fC * fU * fU * fG * fG * m5Ceo mC * Aeo mU * m5Ceo mU * m5Ceo mC * fU * fU * fC * fA * fC * fA	UCUUGGCCAUCUCCU UCACA	XXXXXXOXOXOX OXXXXXX
WV-9169	fU * fC * fU * fU * fG * fG * mC * m5Ceo * mA * Teo * mC * Teo * mC * m5Ceo * fU * fU * fC * fA * fC * fA	UCUUGGCCATCTCCU UCACA	XXXXX XXXXX XXXXX XXXX
WV-9170	fU * fC * fU * fU * fG * fG * mC * m5Ceo mA * Teo mC * Teo mC * m5CeofU * fU * fC * fA * fC * fA	UCUUGGCCATCTCCU UCACA	XXXXXXXOXOXO XOXXXXX
WV-9171	fU * fC * fU * fU * fG * fG * mC m5Ceo * mATeo * mCTeo * mC m5Ceo * fU * fU * fC * fA * fC * fA	UCUUGGCCATCTCCU UCACA	XXXXXXOXOXOX OXXXXXX
WV-9172	fU * fC * fU * fU * fG * fG * m5Ceo * fC * Aeo * fU * m5Ceo * fU * m5Ceo * fC * fU * fU * fC * fA * fC * fA	UCUUGGCCAUCUCCU UCACA	XXXXX XXXXX XXXXX XXXX	
WV-9173	fU * fC * fU * fU * fG * fG * m5Ceo * fCAeo * fU m5Ceo * fU m5Ceo * fCfU * fU * fC * fA * fC * fA	UCUUGGCCAUCUCCU UCACA	XXXXXXXOXOXO XOXXXXX
WV-9174	fU * fC * fU * fU * fG * fG * m5CeofC * AeofU * m5CeofU * m5CeofC * fU * fU * fC * fA * fC * fA	UCUUGGCCAUCUCCU UCACA	XXXXXXOXOXOX OXXXXXX
WV-9175	fU * fC * fU * fU * fG * fG * fC * m5Ceo * fA * Teo * fC * Teo * fC * m5Ceo * fU * fU * fC * fA * fC * fA	UCUUGGCCATCTCCU UCACA	XXXXX XXXXX XXXXX XXXX
WV-9176	fU * fC * fU * fU * fG * fG * fC * m5CeofA * TeofC * TeofC * m5CeofU * fU * fC * fA * fC * fA	UCUUGGCCATCTCCU UCACA	XXXXXXXOXOXO XOXXXXX
WV-9177	fU * fC * fU * fU * fG * fG * fC m5Ceo * fATeo * fCTeo * fC m5Ceo * fU * fU * fC * fA * fC * fA	UCUUGGCCATCTCCU UCACA	XXXXXXOXOXOX OXXXXXX
WV-9178	fU * fC * fU * fU * fG * fG * mC * fC * mA * fU * mC * fU * mC * fC * fU * fU * fC * fA * fC * fA	UCUUGGCCAUCUCCU UCACA	XXXXX XXXXX XXXXX XXXX
WV-9179	fU * fC * fU * fU * fG * fG * mC * fC mA * fU mC * fU mC * fCfU * fU * fC * fA * fC * fA	UCUUGGCCAUCUCCU UCACA	XXXXXXXOXOXO XOXXXXX
WV-9180	fU * fC * fU * fU * fG * fG * mCfC * mAfU * mCfU * mCfC * fU * fU * fC * fA * fC * fA	UCUUGGCCAUCUCCU UCACA	XXXXXXOXOXOX OXXXXXX
WV-9181	fU * fC * fU * fU * fG * fG * fC * mC * fA * mU * fC * mU * fC * mC * fU * fU * fC * fA * fC * fA	UCUUGGCCAUCUCCU UCACA	XXXXX XXXXX XXXXX XXXX
WV-9182	fU * fC * fU * fU * fG * fG * fC * mCfA * mUfC * mUfC * mCfU * fU * fC * fA * fC * fA	UCUUGGCCAUCUCCU UCACA	XXXXXXXOXOXO XOXXXXX
WV-9183	fU * fC * fU * fU * fG * fG * fC mC * fA mU * fC mU * fC mC * fU * fU * fC * fA * fC * fA	UCUUGGCCAUCUCCU UCACA	XXXXXXOXOXOX OXXXXXX
WV-9184	Teo * m5Ceo * Teo * Teo * Geo * Geo * m5Ceo * m5Ceo * Aeo * Teo * m5Ceo * Teo * m5Ceo * m5Ceo * fU * fU * fC * fA * fC * fA	TCTTGGCCATCTCCUU CACA	XXXXX XXXXX XXXX XXXX
WV-	mU * mC * mU * mU * mG * Geo * m5Ceo * m5Ceo * Aeo * Teo *	UCUUGGCCATCTCCU	XXXXX XXXXX

9185	m5Ceo * Teo * m5Ceo * m5Ceo * fU * fU * fC * fA * fC * fA	UCACA	XXXXX XXXX
WV-9186	mU * mC * mU * mU * mG * m5Ceo * m5Ceo * Aeo * Teo * m5Ceo * Teo * m5Ceo * m5Ceo * fU * fU * fC * fA * fC * fA	UCUUGGCCATCTCCU UCACA	XXXXX XXXXX XXXXX XXXX
WV-9187	fU * fU * fU * fC * fU * fU * Geo * Geo * m5Ceo * m5Ceo * Aeo * Teo * m5Ceo * Teo * fC * fC * fU * fU * fC * fA	UUUCUUGGCCATCTC CUUCA	XXXXX XXXXX XXXXX XXXX
WV-9188	fU * fU * fU * fC * fU * fU * Geo * Geo m5Ceo * m5CeoAeo * Teo m5Ceo * TeofC * fC * fC * fU * fU * fC * fA	UUUCUUGGCCATCTC CUUCA	XXXXXXXOXOXO XOXXXXX
WV-9189	fU * fU * fU * fC * fU * fU * GeoGeo * m5Ceo m5Ceo * AeoTeo * m5CeoTeo * fC * fC * fU * fU * fC * fA	UUUCUUGGCCATCTC CUUCA	XXXXXXOXOXOX OXXXXXX
WV-9190	fU * fU * fU * fC * fU * fU * Geo * mG * m5Ceo * mC * Aeo * mU * m5Ceo * mU * fC * fC * fU * fU * fC * fA	UUUCUUGGCCAUCUC CUUCA	XXXXX XXXXX XXXXX XXXX
WV-9191	fU * fU * fU * fC * fU * fU * Geo * mG m5Ceo * mCAeo * mU m5Ceo * mUfC * fC * fU * fU * fC * fA	UUUCUUGGCCAUCUC CUUCA	XXXXXXXOXOXO XOXXXXX
WV-9192	fU * fU * fU * fC * fU * fU * Geo mG * m5Ceo mC * Aeo mU * m5Ceo mU * fC * fC * fU * fU * fC * fA	UUUCUUGGCCAUCUC CUUCA	XXXXXXOXOXOX OXXXXXX
WV-9193	fU * fU * fU * fC * fU * fU * mG * Geo * mC * m5Ceo * mA * Teo * mC * Teo * fC * fC * fU * fU * fC * fA	UUUCUUGGCCATCTC CUUCA	XXXXX XXXXX XXXXX XXXX
WV-9194	fU * fU * fU * fC * fU * fU * mG * Geo mC * m5Ceo mA * Teo mC * TeofC * fC * fU * fU * fC * fA	UUUCUUGGCCATCTC CUUCA	XXXXXXXOXOXO XOXXXXX
WV-9195	fU * fU * fU * fC * fU * fU * mGGeo * mC m5Ceo * mATeo * mCTeo * fC * fC * fU * fU * fC * fA	UUUCUUGGCCATCTC CUUCA	XXXXXXOXOXOX OXXXXXX
WV-9196	fU * fU * fU * fC * fU * fU * Geo * fG * m5Ceo * fC * Aeo * fU * m5Ceo * fU * fC * fC * fU * fU * fC * fA	UUUCUUGGCCAUCUC CUUCA	XXXXX XXXXX XXXXX XXXX
WV-9197	fU * fU * fU * fC * fU * fU * Geo * fG m5Ceo * fCAeo * fU m5Ceo * fUfC * fC * fU * fU * fC * fA	UUUCUUGGCCAUCUC CUUCA	XXXXXXXOXOXO XOXXXXX
WV-9198	fU * fU * fU * fC * fU * fU * GeofG * m5CeofC * AeofU * m5CeofU * fC * fC * fU * fU * fC * fA	UUUCUUGGCCAUCUC CUUCA	XXXXXXOXOXOX OXXXXXX
WV-9199	fU * fU * fU * fC * fU * fU * fG * Geo * fC * m5Ceo * fA * Teo * fC * Teo * fC * fC * fU * fU * fC * fA	UUUCUUGGCCATCTC CUUCA	XXXXX XXXXX XXXXX XXXX
WV-9200	fU * fU * fU * fC * fU * fU * fG * GeofC * m5CeofA * TeofC * TeofC * fC * fU * fU * fC * fA	UUUCUUGGCCATCTC CUUCA	XXXXXXXOXOXO XOXXXXX
WV-9201	fU * fU * fU * fC * fU * fU * fGGeo * fC m5Ceo * fATeo * fCTeo * fC * fC * fU * fU * fC * fA	UUUCUUGGCCATCTC CUUCA	XXXXXXOXOXOX OXXXXXX
WV-9202	fU * fU * fU * fC * fU * fU * mG * fG * mC * fC * mA * fU * mC * fU * fC * fC * fU * fU * fC * fA	UUUCUUGGCCAUCUC CUUCA	XXXXX XXXXX XXXXX XXXX
WV-	fU * fU * fU * fC * fU * fU * mG * fG mC * fC mA * fU mC * fUfC * fC * fU	UUUCUUGGCCAUCUC	XXXXXXXOXOXO

9203	* fU * fC * fA	CUUCA	XOXXXXX
WV-9204	fU * fU * fU * fC * fU * fU * mGfG * mCfC * mAfU * mCfU * fC * fC * fU * fU * fC * fA	UUUCUUGGCCAUCUC CUUCA	XXXXXOXOXOX OXXXXXX
WV-9205	fU * fU * fU * fC * fU * fU * fG * mG * fC * mC * fA * mU * fC * mU * fC * fC * fU * fU * fC * fA	UUUCUUGGCCAUCUC CUUCA	XXXXX XXXXX XXXXX XXXX
WV-9206	fU * fU * fU * fC * fU * fU * fG * mGfC * mCfA * mUfC * mUfC * fC * fU * fU * fC * fA	UUUCUUGGCCAUCUC CUUCA	XXXXXXXOXOXO XOXXXXX
WV-9207	fU * fU * fU * fC * fU * fU * fG mG * fC mC * fA mU * fC mU * fC * fC * fU * fU * fC * fA	UUUCUUGGCCAUCUC CUUCA	XXXXXOXOXOX OXXXXXX
WV-9208	Teo * Teo * Teo * m5Ceo * Teo * Teo * Geo * Geo * m5Ceo * m5Ceo * Aeo * Teo * m5Ceo * Teo * fC * fC * fU * fU * fC * fA	TTTCTTGGCCATCTCC UUCA	XXXXX XXXXX XXXXX XXXX
WV-9209	mU * mU * mU * mC * mU * Teo * Geo * Geo * m5Ceo * m5Ceo * Aeo * Teo * m5Ceo * Teo * fC * fC * fU * fU * fC * fA	UUUCUTGGCCATCTC CUUCA	XXXXX XXXXX XXXXX XXXX
WV-9210	mU * mU * mU * mC * mU * mU * Geo * Geo * m5Ceo * m5Ceo * Aeo * Teo * m5Ceo * Teo * fC * fC * fU * fU * fC * fA	UUUCUUGGCCATCTC CUUCA	XXXXX XXXXX XXXXX XXXX
WV-9222	Teo * S m5Ceo * SAeo * SAeo * SGeo * SGeo * SAeofA * SGeoAeo * SfU * SGeoGeofC * SfA * SfU * SfU * SfU * SfC * SfU	TCAAGGAAGAUGGCA UUUCU	SSSSSOSOSSOOS SSSSS
WV-9223	Teo * S m5Ceo * SAeo * SAeo * SGeo * SGeo * SAeoAeo * SGeoAeo * STeo * SGeoGeo m5Ceo * SfA * SfU * SfU * SfU * SfC * SfU	TCAAGGAAGATGGCA UUUCU	SSSSSOSOSSOOS SSSSS	
WV-9224	Teo * S m5Ceo * SAeo * SAeo * SGeo * SGeo * SAeo * SAeo * SGeo * SAeo * STeo * SGeo * SGeo * S m5Ceo * SfA * SfU * SfU * SfU * SfC * SfU	TCAAGGAAGATGGCA UUUCU	SSSSSSSSSSSSS SSSS	
WV-9225	Teo * m5Ceo * Aeo * Aeo * Geo * Geo * AeofA * GeoAeo * fU * GeoGeofC * fA * fU * fU * fU * fC * fU	TCAAGGAAGAUGGCA UUUCU	XXXXXOXOXOXXO OXXXXXX	
WV-9226	Teo * m5Ceo * Aeo * Aeo * Geo * Geo * AeoAeo * GeoAeo * Teo * GeoGeo m5Ceo * fA * fU * fU * fU * fC * fU	TCAAGGAAGATGGCA UUUCU	XXXXXOXOXOXXO OXXXXXX	
WV-9227	fU * fC * fA * fA * fG * fG * AeofA * GeoAeo * fU * GeoGeofC * fA * fU * fU * fU * fC * fU	UCAAGGAAGAUGGCA UUUCU	XXXXXOXOXOXXO OXXXXXX	
WV-9408	fU * SfU * SfU * SfU * SfG * SfG * S mC * S mA * S mG * S mC * S mU * S mU * S mU * S mC * SfC * SfA * SfC * SfC * SfA * SfA	UUUUGGCAGCUUUCC ACCAA	SSSSSSSSSSSSS SSSS	
WV-9409	fU * SfU * SfU * SfU * SfG * SfG * S mC * SfA * S mG * S mC * SfU * S mU * S mU * SfC * SfC * SfA * SfC * SfC * SfA * SfA	UUUUGGCAGCUUUCC ACCAA	SSSSSSSSSSSSS SSSS	
WV-9410	fU * SfU * SfU * SfU * SfG * SfG * S m5Ceo * SfA * SGeo * S m5Ceo * SfU * STeo * STeo * SfC * SfC * SfC * SfA * SfC * SfC * SfA * SfA	UUUUGGCAGCUTTCC ACCAA	SSSSSSSSSSSSS SSSS	
WV-9411	fU * SfU * SfU * SfU * SfG * SfG * S mCfA * S mG mC * SfU * S mU mUfC * SfC * SfA * SfC * SfC * SfA * SfA	UUUUGGCAGCUUUCC ACCAA	SSSSSOSOSOSSOOS SSSSS	
WV-	fU * SfU * SfU * SfU * SfG * SfG * S m5CeofA * SGeo m5Ceo * SfU *	UUUUGGCAGCUTTCC	SSSSSOSOSSOOS	

9412	STeoTeofC * SfC * SfA * SfC * SfC * SfA * SfA	ACCAA	SSSSS
WV-9413	fU * SfU * SfU * SfU * SfG * S m5CeofA * S mG m5Ceo * SfU * STeoTeofC * SfC * SfA * SfC * SfC * SfA * SfA	UUUUGGCAGCUTTCC ACCAA	SSSSSSOSOSSOOS SSSSS
WV-9414	fU * SfU * SfU * SfU * SfG * SfG * S m5CeofA * S mG mC * SfU * STeoTeofC * SfC * SfA * SfC * SfC * SfA * SfA	UUUUGGCAGCUTTCC ACCAA	SSSSSSOSOSSOOS SSSSS
WV-9415	fU * fU * fU * fU * fU * fG * fG * mC * fA * mG * mC * fU * mU * mU * fC * fC * fA * fC * fC * fA * fA	UUUUGGCAGCUUUCC ACCAA	XXXXX XXXXX XXXXX XXXX
WV-9416	fU * fU * fU * fU * fU * fG * fG * m5Ceo * fA * Geo * m5Ceo * fU * Teo * Teo * fC * fC * fC * fA * fC * fC * fA * fA	UUUUGGCAGCUTTCC ACCAA	XXXXX XXXXX XXXXX XXXX
WV-9417	fU * fU * fU * fU * fU * fG * fG * mG mC * fU * mU mUfC * fC * fA * fC * fC * fC * fA * fA	UUUUGGCAGCUUUCC ACCAA	XXXXXXOXOXXO OXXXXXX
WV-9418	fU * fU * fU * fU * fU * fG * fG * m5CeofA * Geo m5Ceo * fU * TeoTeofC * fC * fA * fC * fC * fC * fA * fA	UUUUGGCAGCUTTCC ACCAA	XXXXXXOXOXXO OXXXXXX
WV-9419	fU * fU * fU * fU * fU * fG * fG * m5CeofA * mG m5Ceo * fU * TeoTeofC * fC * fA * fC * fC * fC * fA * fA	UUUUGGCAGCUTTCC ACCAA	XXXXXXOXOXXO OXXXXXX
WV-942	mU * mC * mA * mA * mG * mG * mA * mA * mG * mA * mU * mG * mG * mC * mA * mU * mU * mC * mU	UCAAGGAAGAUGGCA UUUCU	XXXXX XXXXX XXXXX XXXX
WV-9420	fU * fU * fU * fU * fU * fG * fG * m5CeofA * mG mC * fU * TeoTeofC * fC * fA * fC * fC * fC * fA * fA	UUUUGGCAGCUTTCC ACCAA	XXXXXXOXOXXO OXXXXXX
WV-9422	fC * SfU * SfC * SfC * SfG * SfG * S mUfU * S mC mU * SfG * S mA mAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSOSOSSOOS SSSSS
WV-9423	fC * SfU * SfC * SfC * SfG * SfG * STeofU * S m5CeoTeo * SfG * SAeoAeofG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGTUCTGAAGG UGUUC	SSSSSSOSOSSOOS SSSSS
WV-9424	fC * SfU * SfC * SfC * SfG * SfG * STeofU * S m5CeoTeo * SfG * S mA mAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGTUCTGAAGG UGUUC	SSSSSSOSOSSOOS SSSSS
WV-9425	fC * SfU * SfC * SfC * SfG * SfG * STeofU * S m5Ceo mU * SfG * S mA mAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGTUCTGAAGG UGUUC	SSSSSSOSOSSOOS SSSSS
WV-9426	fC * fU * fC * fC * fC * fG * fG * mU * fG * mA mAfG * fG * fU * fG * fU * fU * fC	CUCCGGUUCUGAAGG UGUUC	XXXXXXOXOXXO OXXXXXX
WV-9427	fC * fU * fC * fC * fG * fG * TeofU * m5CeoTeo * fG * AeoAeofG * fG * fU * fG * fU * fU * fC	CUCCGGTUCTGAAGG UGUUC	XXXXXXOXOXXO OXXXXXX
WV-9428	fC * fU * fC * fC * fC * fG * fG * TeofU * m5CeoTeo * fG * mA mAfG * fG * fU * fG * fU * fU * fC	CUCCGGTUCTGAAGG UGUUC	XXXXXXOXOXXO OXXXXXX
WV-9429	fC * fU * fC * fC * fC * fG * fG * TeofU * m5Ceo mU * fG * mA mAfG * fG * fU * fG * fU * fU * fC	CUCCGGTUCUGAAGG UGUUC	XXXXXXOXOXXO OXXXXXX
WV-	mG * mG * mC * mC * mA * mA * mA * mC * mC * mU * mC * mG *	GGCCAAACCUCGGCU	XXXXX XXXXX

943	mG * mC * mU * mU * mA * mC * mC * mU	UACCU	XXXXX XXXX
WV-9511	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfC * SfU * S mG mA mA mGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSSSOOOO SSSSS
WV-9512	fC * SfU * SfC * SfC * SfG * SfG * SfU * S mCfU * S mGfA * S mA mG mGfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSOSOO OSSSS
WV-9513	fC * SfU * SfC * SfC * SfG * SfG * SfU * S mCfU * S mGfA * S mA mGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSOSOO SSSSS
WV-9514	fC * SfU * SfC * SfC * SfG * SfG * SfU * S mCfU * S mGfA * S mAfG * S mGfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSOSOS OSSSS
WV-9515	fC * SfU * SfC * SfC * SfG * SfG * SfU * S mCfU * S mGfA * SfA * S mG mGfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSOSSO OSSSS
WV-9516	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * S mCfU * S mG * SfA * S mA mG mGfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSSSOO OSSSS
WV-9517	fC * SfU * SfC * SfC * SfG * SfG * SfU * S mCfU * S mG * SfA * S mA mGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSSSOO SSSSS
WV-9518	fC * SfU * SfC * SfC * SfG * SfG * SfU * S mCfU * S mG * SfA * S mAfG * S mGfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSSSOS OSSSS
WV-9519	fC * SfU * SfC * SfC * SfG * SfG * SfU * S mCfU * S mG * SfA * S mG mGfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSSSSO OSSSS
WV-9520	fC * SfU * SfC * SfC * SfG * SfG * SfU * S mCfU * SfG * SfA * S mA mG mGfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSSSOO OSSSS
WV-9521	fC * SfU * SfC * SfC * SfG * SfG * SfU * S mCfU * SfG * SfA * S mA mGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSSSOO SSSSS
WV-9522	fC * SfU * SfC * SfC * SfG * SfG * SfU * S mCfU * SfG * SfA * S mAfG * S mGfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSSSOS OSSSS
WV-9523	fC * SfU * SfC * SfC * SfG * SfG * SfU * S mCfU * SfG * SfA * SfA * S mG mGfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSSSSO OSSSS
WV-9524	fC * SfU * SfC * SfC * SfG * SfG * S mUfU * S mCfU * S mGfA * S mAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSOSOSOSOS SSSSS
WV-9525	fC * SfU * SfC * SfC * SfG * SfG * SfU * mUfC * mUfG * mAfA * mGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSXOXOXOX OSSSSS
WV-9534	fC * SfU * SfC * SfC * SfG * SfG * SfU * S mUfC * S mUfG * S mAfA * S mGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSOSOSOSO SSSSS
WV-9535	fC * SfU * SfC * SfC * SfG * S mG * SfU * SfU * S mCfU * SfG * SfA * S mA mG mGfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSOSSSOO OSSSS
WV-	fC * SfU * SfC * SfC * SfG * S mG * SfU * SfU * S mCfU * SfG * SfA * S mA	CUCCGGUUCUGAAGG	SSSSSSSOSSSOO

9536	mGfG * SfU * SfG * SfU * SfU * SfC	UGUUC	SSSSS
WV-9537	fC * SfU * SfC * SfC * SfG * S mG * SfU * SfU * S mCfU * SfG * SfA * S mAfG * S mGfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSSSSOS OSSSS
WV-9538	fC * SfU * SfC * SfC * SfG * S mG * SfU * SfU * S mCfU * SfG * SfA * SfA * S mG mGfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSSOSSSSO OSSSS
WV-9539	fC * SfU * SfC * SfC * SfG * S mG * SfU * SfU * SfC * SfU * S mG mA mA mGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSSSOOOO SSSSS
WV-9540	Teo * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	TCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSSOOS SSSSS	
WV-9541	Teo * RfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	TCAAGGAAGAUGGCA UUUCU	RSSSSSOSOSSOOS SSSSS

WV-9594	fA * fA * fU * fA * fU * fU * mC * mU * mU * mC * mU * mA * mA * mA * mG * mA * mA * mG * fC * fU * fU * fA * fA * fA	AAUAUUCUUCUAAA GAAAGCUUAAA	XXXXX XXXXX XXXXX XXXX
WV-9595	fU * fC * fU * fU * fC * fU * mA * mA * mA * mG * mA * mA * mA * mG * mC * mU * mU * mA * mA * fA * fA * fA * fG * fU * fC	UCUUCUAAAGAAAG CUUAAAAAGUC	XXXXX XXXXX XXXXX XXXX
WV-9596	fU * fA * fA * fA * fG * fA * mA * mA * mG * mC * mU * mU * mA * mA * mA * mA * mG * mU * fC * fU * fG * fC * fU * fA	UAAAGAAAGCUUAA AAAGUCUGCUA	XXXXX XXXXX XXXXX XXXX
WV-9597	fA * fA * fA * fG * fC * fU * mU * mA * mA * mA * mA * mA * mG * mU * mC * mU * mG * mC * mU * fA * fA * fA * fA * fU * fG	AAAGCUUAAAAAGUC UGCUAAAAUG	XXXXX XXXXX XXXXX XXXX
WV-9598	fU * fU * fA * fA * fA * fA * mA * mG * mU * mC * mU * mG * mC * mU * mA * mA * mA * mA * mU * fG * fU * fU * fU * fU * fU * fC	UUAAAAAGUCUGCUA AAAUGUUUUC	XXXXX XXXXX XXXXX XXXX
WV-9599	fA * fA * fA * fG * fU * fC * fU * mG * mC * mU * mA * mA * mA * mA * mU * mG * mU * mU * mU * mU * fC * fA * fU * fU * fC * fU * fC	AAGUCUGCUAAAAAUG UUUUCAUUCC	XXXXX XXXXX XXXXX XXXX
WV-9600	fU * fG * fC * fU * fA * fA * mA * mA * mU * mG * mU * mU * mU * mU * mC * mA * mU * mU * mC * fC * fU * fA * fU * fU * fA	UGCUAAAAAUGUUUUC AUUCCUAUUA	XXXXX XXXXX XXXXX XXXX
WV-9601	fA * fA * fA * fA * fU * fG * fU * mU * mU * mU * mC * mA * mU * mU * mC * mC * mU * mA * mU * mU * fA * fG * fA * fU * fC * fU	AAAUGUUUUCAUUCC UAUUAGAUCU	XXXXX XXXXX XXXXX XXXX

WV-9602	fU * fU * fU * fU * fC * fA * mU * mU * mC * mC * mU * mA * mU * mU * mA * mG * mA * mU * mC * fU * fG * fU * fC * fG * fC	UUUUCAUUCCUAUUA GAUCUGUCCGC	XXXXX XXXXX XXXXX XXXX
WV-9603	fA * fU * fU * fC * fC * fU * mA * mU * mU * mA * mG * mA * mU * mC * mU * mG * mU * mC * mG * fC * fC * fC * fU * fA * fC	AUUCCUAUUAGAUCU GUCGCCCUAC	XXXXX XXXXX XXXXX XXXX
WV-9604	fU * fA * fU * fU * fA * fG * mA * mU * mC * mU * mG * mU * mC * mG * mC * mC * mU * mA * fC * fC * fU * fC * fU * fU	UAUUAGAUCUGUCGC CCUACCUCUU	XXXXX XXXXX XXXXX XXXX
WV-9605	fG * fA * fU * fC * fU * fG * mU * mC * mG * mC * mC * mC * mU * mA * mC * mC * mU * mC * mU * fU * fU * fU * fU * fC	GAUCUGUCGCCCUAC CUCUUUUUUC	XXXXX XXXXX XXXXX XXXX
WV-9606	fG * fU * fC * fG * fC * fC * mC * mU * mA * mC * mC * mU * mC * mU * mU * mU * mU * mU * fC * fU * fG * fU * fC * fU	GUCGCCCUACCUCUU UUUUCUGUCU	XXXXX XXXXX XXXXX XXXX
WV-9607	fC * fC * fU * fA * fC * fC * mC * mU * mC * mU * mU * mU * mU * mU * mC * mU * mG * mU * mC * fU * fG * fA * fC * fA * fG	CCUACCUCUUUUUUC UGUCUGACAG	XXXXX XXXXX XXXXX XXXX
WV-9608	fC * fU * fC * fU * fU * fU * mU * mU * mU * mC * mU * mG * mU * mC * mU * mG * mA * mC * mA * fG * fC * fU * fG * fU * fU	CUCUUUUUUCUGUCU GACAGCUGUU	XXXXX XXXXX XXXXX XXXX
WV-9609	fU * fU * fU * fU * fC * fU * mG * mU * mC * mU * mG * mA * mC * mA * mG * mC * mU * mG * mU * fU * fU * fG * fC * fA * fG	UUUUCUGUCUGACAG CUGUUUGCAG	XXXXX XXXXX XXXXX XXXX
WV-9610	fU * fG * fU * fC * fU * fG * mA * mC * mA * mG * mC * mU * mG * mU * mU * mG * mC * mA * fG * fC * fC * fC * fU * fC	UGUCUGACAGCUGUU UGCAGACCUC	XXXXX XXXXX XXXXX XXXX
WV-9611	fG * fA * fC * fA * fG * fC * mU * mG * mU * mU * mU * mG * mC * mA * mG * mA * mC * mC * mU * fC * fC * fU * fG * fC * fC	GACAGCUGUUUGCAG ACCUCCUGCC	XXXXX XXXXX XXXXX XXXX
WV-9612	fC * fU * fG * fU * fU * fU * mG * mC * mA * mG * mA * mC * mC * mU * mC * mU * mG * mC * fC * fA * fC * fC * fG * fC	CUGUUUGCAGACCUC CUGCCACCGC	XXXXX XXXXX XXXXX XXXX
WV-9613	fU * fG * fC * fA * fG * fA * mC * mC * mU * mC * mC * mU * mG * mC * mC * mA * mC * mC * mG * fC * fA * fG * fA * fU * fU	UGCAGACCUCCUGCC ACCGCAGAUU	XXXXX XXXXX XXXXX XXXX

WV-9614	fA * fC * fC * fU * fC * fC * mU * mG * mC * mC * mA * mC * mC * mG * mC * mA * mG * mA * mU * fU * fC * fA * fG * fG * fC	ACCUCCUGCCACCGC AGAUUCAGGC	XXXXX XXXXX XXXX
WV-9615	fC * fU * fG * fC * fC * fA * mC * mC * mG * mC * mA * mG * mA * mU * mU * mC * mA * mG * fC * fU * fU * fC * fC * fC	CUGCCACCGCAGAUU CAGGCUUCCC	XXXXX XXXXX XXXX XXXX
WV-9616	fA * fC * fC * fC * fG * fC * fA * mG * mA * mU * mU * mC * mA * mG * mG * mC * mU * mU * mC * mC * fC * fA * fA * fU * fU * fU	ACCGCAGAUUCAGGC UUCCCAAUUU	XXXXX XXXXX XXXX XXXX
WV-9617	fA * fG * fA * fU * fU * fC * mA * mG * mG * mC * mU * mU * mC * mC * mC * mA * mA * mU * mU * fU * fU * fU * fC * fC * fC * fU	AGAUUCAGGCUUCCC AAUUUUUCCU	XXXXX XXXXX XXXX XXXX
WV-9618	fC * fA * fG * fG * fC * fU * mU * mC * mC * mC * mA * mA * mU * mU * mU * mU * mC * mC * fU * fG * fU * fA * fG * fA	CAGGCUUCCCAAUUU UUCCUGUAGA	XXXXX XXXXX XXXX XXXX
WV-9619	fU * fU * fC * fC * fC * fA * mA * mU * mU * mU * mU * mU * mC * mC * mU * mG * mU * mA * mG * fA * fA * fU * fA * fC * fU	UUCCCAAUUUUUCCU GUAGAAUACU	XXXXX XXXXX XXXX XXXX
WV-9620	fA * fA * fU * fU * fU * fU * mU * mC * mC * mU * mG * mU * mA * mG * mA * mA * mU * mU * mA * mC * fU * fG * fC * fA * fU	AAUUUUUCCUGUAGA AUACUGGCAU	XXXXX XXXXX XXXX XXXX
WV-9621	fU * fU * fC * fC * fU * fG * mU * mA * mG * mA * mA * mU * mA * mC * mU * mG * mC * mA * fU * fC * fU * fG * fU * fU	UUCCUGUAGAAUACU GGCAUCUGUU	XXXXX XXXXX XXXX XXXX
WV-9622	fG * fU * fA * fG * fA * fA * mU * mA * mC * mU * mG * mG * mC * mA * mU * mC * mU * mG * fU * fU * fU * fU * fU * fG * fA	GUAGAAUACUGGCAU CUGUUUUUGA	XXXXX XXXXX XXXX XXXX
WV-9623	fA * fU * fA * fC * fU * fG * mG * mC * mA * mU * mC * mU * mG * mU * mU * mU * mU * mG * fA * fU * fU * fU	AUACUGGCAUCUGUU UUUGAGGAUU	XXXXX XXXXX XXXX XXXX
WV-9624	fG * fG * fC * fA * fU * fC * mU * mG * mU * mU * mU * mU * mG * mA * mG * mA * mU * fU * fG * fC * fU * fG * fA	GGCAUCUGUUUUUGA GGAUUGCUGA	XXXXX XXXXX XXXX XXXX
WV-9625	fC * fU * fG * fU * fU * fU * mU * mU * mG * mA * mG * mG * mA * mU * mU * mG * mC * mU * mG * fA * fA * fU * fU * fA * fU	CUGUUUUUGAGGAU UGCUGAAUUAU	XXXXX XXXXX XXXX XXXX

WV-9626	fU * fU * fU * fG * fA * fG * mG * mA * mU * mU * mG * mC * mU * mG * mA * mA * mU * mU * mA * fU * fU * fC * fU * fU	UUUGAGGAUUGCUG AAUUAUUUCUU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9627	fG * fG * fA * fU * fU * fG * mC * mU * mG * mA * mA * mU * mU * mA * mU * mU * mC * mU * fU * fC * fC * fC * fA	GGAUUGCUGAAUUA UUUCUUCCCCA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9628	fG * fC * fU * fG * fA * fA * mU * mU * mA * mU * mU * mU * mC * mU * mU * mC * mC * mC * fA * fG * fU * fU * fG * fC	GCUGAAUUAUUUCUU CCCCAGUUGC	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9629	fA * fU * fU * fA * fU * fU * mU * mC * mU * mU * mC * mC * mC * mC * mA * mG * mU * mU * mG * fC * fA * fU * fU * fC * fA	AUUAUUUCUUCCCCA GUUGCAUUCA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9630	fU * fU * fC * fU * fU * fC * mC * mC * mA * mG * mU * mU * mG * mC * mA * mU * mC * fA * fA * fU * fG * fU * fU	UUCUUCCCCAGUUGC AUUCAAUGUU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9631	fC * fC * fC * fC * fA * fG * mU * mU * mG * mC * mA * mU * mU * mC * mA * mA * mU * mG * mU * fU * fC * fU * fG * fA * fC	CCCCAGUUGCAUUCA AUGUUCUGAC	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9632	fG * fU * fU * fG * fC * fA * mU * mU * mC * mA * mA * mU * mG * mU * mU * mC * mU * mG * mA * fC * fA * fA * fC * fA * fG	GUUGCAUUCAAUGUU CUGACAACAG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9633	fA * fU * fU * fC * fA * fA * mU * mG * mU * mU * mC * mU * mG * mA * mC * mA * mA * mC * mA * fG * fU * fU * fU * fG * fC	AUUCAAUGUUCUGAC AACAGUUUGC	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9634	fA * fU * fU * fG * fU * fU * fC * mU * mG * mA * mC * mC * mA * mA * mC * mG * mU * mU * mU * mG * fC * fC * fG * fC * fC * fU * fG	AUGUUCUGACAACAG UUUGCCGCUG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9635	fC * fU * fG * fG * fA * fC * fA * mA * mC * mA * mG * mU * mU * mU * mG * mC * mC * mG * mC * mU * fG * fC * fC * fA * fA	CUGACAACAGUUUGC CGCUGCCCAA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9636	fA * fA * fC * fC * fA * fG * fU * mU * mU * mG * mC * mC * mG * mC * mU * mG * mC * mC * mC * mA * fA * fU * fG * fC * fC * fA	AACAGUUUGCCGCUG CCCAAUGCCA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9637	fU * fU * fU * fG * fC * fC * fG * mG * mC * mU * mG * mC * mC * mA * mA * mU * mG * mC * mC * fA * fU * fC * fC * fU * fG	UUUGCCGCUGCCCAA UGCCAUCCUG	XXXXX XXXXX XXXXX XXXXX XXXX

WV-9638	fC * fG * fC * fU * fG * fC * mC * mC * mA * mA * mU * mG * mC * mC * mA * mU * mC * mC * mU * fG * fA * fG * fU * fU	CGCUGCCCAAUGCCA UCCUGGAGUU	XXXXX XXXXX XXXXX XXXX
WV-9639	fC * fC * fC * fA * fA * fU * mG * mC * mC * mA * mU * mC * mC * mU * mG * mG * mA * mG * mU * fU * fC * fC * fU * fG * fU	CCCAAUGCCAUCCUG GAGUUCCUGU	XXXXX XXXXX XXXXX XXXX
WV-9640	fU * fG * fC * fC * fA * fU * mC * mC * mU * mG * mG * mA * mG * mU * mU * mC * mC * mU * mG * fU * fA * fA * fG * fA * fU	UGCCAUCCUGGAGUU CCUGUAAGAU	XXXXX XXXXX XXXXX XXXX
WV-9641	fU * fC * fC * fU * fG * fG * mA * mG * mU * mU * mC * mC * mU * mG * mU * mA * mA * mG * mA * fU * fA * fC * fC * fA * fA	UCCUGGAGUUCCUGU AAGAUACCAA	XXXXX XXXXX XXXXX XXXX
WV-9642	fG * fA * fG * fU * fU * fC * mC * mU * mG * mU * mA * mA * mG * mA * mU * mA * mC * mC * mA * fA * fA * fA * fG * fG	GAGUUCCUGUAAGAU ACCAAAAAGG	XXXXX XXXXX XXXXX XXXX
WV-9643	fC * fC * fU * fG * fU * fA * mA * mG * mA * mU * mA * mC * mC * mA * mA * mA * mA * mG * fG * fC * fA * fA * fA * fA	CCUGUAAGAUACCAA AAAGGCAAAA	XXXXX XXXXX XXXXX XXXX
WV-9644	fA * fA * fG * fA * fU * fA * mC * mC * mA * mA * mA * mA * mG * mG * mC * mA * mA * fA * fC * fA * fA * fA * fA	AAGAUACCAAAAAGG CAAAACAAAA	XXXXX XXXXX XXXXX XXXX
WV-9645	fA * fC * fC * fA * fA * fA * mA * mA * mG * mG * mC * mA * mA * mA * mC * mA * mA * fA * fA * fA * fU * fG * fA * fA	ACCAAAAAGGCAAAA CAAAAAUGAA	XXXXX XXXXX XXXXX XXXX
WV-9646	fA * fA * fA * fG * fG * fC * mA * mA * mA * mC * mA * mA * mA * mU * mG * mC * mA * fA * fG * fC * fC * fC * fC	AAAGGCAAAACAAAA AUGAAGCCCC	XXXXX XXXXX XXXXX XXXX
WV-9647	fC * fA * fA * fA * fA * fC * mA * mA * mA * mA * mA * mU * mG * mA * mA * mG * mC * mC * fC * fA * fU * fG * fU * fC	CAAACAAAAAUGAA GCCCCAUGUC	XXXXX XXXXX XXXXX XXXX
WV-9648	fC * fA * fA * fA * fA * fA * mU * mG * mA * mA * mG * mC * mC * mC * mA * mU * mG * mU * fC * fU * fU * fU * fU * fU	CAAAAAUGAAGCCCC AUGUCUUUUU	XXXXX XXXXX XXXXX XXXX
WV-9649	fA * fU * fG * fA * fA * fG * mC * mC * mC * mA * mU * mG * mU * mC * mU * mU * mU * fU * fA * fU * fU * fU * fG	AUGAAGCCCCAUGUC UUUUUAUUUG	XXXXX XXXXX XXXXX XXXX

WV-9650	fG * fC * fC * fC * fC * fA * mU * mG * mU * mC * mU * mU * mU * mU * mU * mA * mU * mU * fG * fA * fG * fA * fA * fA	GCCCCAUGUCUUUUU AUUUGAGAAA	XXXXX XXXXX XXXXX XXXX
WV-9651	fA * fU * fG * fU * fC * fU * mU * mU * mU * mA * mU * mU * mU * mG * mA * mG * mA * fA * fA * fG * fA * fU * fU	AUGUCUUUUUAUUU GAGAAAAGAUU	XXXXX XXXXX XXXXX XXXX
WV-9652	fU * fU * fU * fU * fU * fA * mU * mU * mU * mG * mA * mG * mA * mA * mA * mA * mG * mA * mU * fU * fA * fA * fC * fA	UUUUUAUUUGAGAA AAGAUUAAACA	XXXXX XXXXX XXXXX XXXX
WV-9653	fA * fU * fU * fU * fG * fA * mG * mA * mA * mA * mA * mG * mA * mU * mU * mA * mA * mA * mC * fA * fG * fU * fG * fU * fG	AUUUGAGAAAAGAU UAAACAGUGUG	XXXXX XXXXX XXXXX XXXX
WV-9654	fA * fG * fA * fA * fA * fA * mG * mA * mU * mU * mA * mA * mA * mC * mA * mG * mU * mG * fC * fU * fA * fC * fC	AGAAAAGAUUAAAC AGUGUGCUACC	XXXXX XXXXX XXXXX XXXX
WV-9655	fA * fG * fA * fU * fU * fA * mA * mA * mC * mA * mG * mU * mG * mU * mC * mU * mA * mC * fC * fA * fC * fA * fU * fG	AGAUUAAACAGUGU GCUACCACAUG	XXXXX XXXXX XXXXX XXXX
WV-9656	fA * fA * fA * fC * fA * fG * mU * mG * mU * mG * mC * mU * mA * mC * mC * mA * mC * mA * fC * fA * fG * fC * fA * fG * fU * fU	AAACAGUGUGCUACC ACAUGCAGUU	XXXXX XXXXX XXXXX XXXX
WV-9657	fG * fU * fG * fU * fG * fC * mU * mA * mC * mC * mA * mC * mA * mU * mG * mC * mA * mG * mU * fU * fG * fU * fA * fC * fU	GUGUGCUACCACAUG CAGUUGUACU	XXXXX XXXXX XXXXX XXXX
WV-9658	fU * fU * fG * fC * fC * fG * mC * mU * mG * mC * mC * mC * mA * mA * mU * mG * mC * mC * fU * fC * fC * fU * fG * fG	UUGCCGCUGCCCAAU GCCAUCCUGG	XXXXX XXXXX XXXXX XXXX

WV-9659	fG * fC * fC * fC * fA * fA * mU * mG * mC * mC * mA * fU * fC * fC * fU * fG * fG	GCCCAAUGCCAUCCU GG	XXXXX XXXXX XXXXX
WV-9680	fU * SfU * SfC * SfU * SfG * SfA * S mA mG mGfU * S mGfU * SfU * SfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOOOSOSSS SSSSS
WV-9681	fU * SfU * SfC * SfU * SfG * SfA * S mA mG mGfU * S mG * SfU * SfU * SfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOOOSSSSS SSSSS
WV-9682	fU * SfU * SfC * SfU * SfG * SfA * S mA mG mG mU * SfG * SfU * SfU * SfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOOOSSSSS SSSSS

WV-9683	fU * SfU * SfC * SfU * SfG * SfA * SfA * S mG mGfU * S mG * SfU * SfU * S mCfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSSOOSSSSO SSSSS
WV-9684	fU * SfU * SfC * SfU * SfG * SfA * S mAfG * S mGfU * S mG * SfU * SfU * S mCfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOSOSSSSO SSSSS
WV-9685	fU * SfU * SfC * SfU * SfG * SfA * S mA mGfG * SfU * S mG * SfU * SfU * S mCfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOOSSSSSO SSSSS
WV-9686	fU * SfU * SfC * SfU * SfG * S mAfA * S mG mGfU * S mG * SfU * SfU * S mCfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSOSOOSSSSO SSSSS
WV-9687	fU * SfU * SfC * SfU * SfG * S mA mAfG * S mGfU * S mG * SfU * SfU * S mCfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSOOSOSSSSO SSSSS
WV-9688	fU * SfU * SfC * SfU * SfG * S mA mA mGfG * SfU * S mG * SfU * SfU * S mCfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSOOOSSSSSO SSSSS
WV-9689	fU * SfU * SfC * SfU * SfG * S mAfA * S mG mGfU * S mG * SfU * SfU * SfC * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSOSOOSSSSS SSSSS
WV-9690	fU * SfU * SfC * SfU * SfG * S mA mAfG * S mGfU * S mG * SfU * SfU * SfC * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSOOSOSSSSS SSSSS
WV-9691	fU * SfU * SfC * SfU * SfG * S mA mA mGfG * SfU * S mG * SfU * SfU * SfC * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSOOOSSSSSS SSSSS
WV-9699	fC * fU * fC * fC * fG * fG * fU * fU * mCfU * mG * fA * mA mGfG * fU * fG * fU * fU * fC	CUCCGGUUCUGAAGG UGUUC	XXXXXXXXOXXX OOXXXXX
WV-9700	fC * SfU * SfC * SfC * SfG * SfG * S mUfU * S mCfU * S mG * SfA mAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSOSOSSOOS SSSSS
WV-9701	fC * SfU * SfC * SfC * SfG * SfG * S mU * SfU * S mCfU * S mG * SfA mAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSOSSOOS SSSSS
WV-9702	fC * SfU * SfC * SfC * SfG * SfG * S mUfU * S mC * SfU * S mG * SfA mAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSOSSSSOOS SSSSS
WV-9703	fC * SfU * SfC * SfC * SfG * SfG * S mUfU * S mCfU * S mG * SfA * S mAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSOSOSSSOS SSSSS
WV-9704	fC * SfU * SfC * SfC * SfG * SfG * S mUfU * S mCfU * S mG * SfA mA * SfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSOSOSSOSS SSSSS
WV-9709	fC * SfU * SfC * SfC * SfG * SfG * S mG * S mUfU * S mCfU * S mG * SfA mAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSOSOSSOOS SSSSS
WV-9710	fC * SfU * SfC * SfC * SfG * SfG * SfUfU * S mCfU * S mG * SfA mAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSOSOSSOOS SSSSS
WV-9711	fC * SfU * SfC * SfC * SfG * SfG * S mUfU * SfCfU * S mG * SfA mAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSOSOSSOOS SSSSS

WV-9712	fC * SfU * SfC * SfC * SfG * SfG * S mUfU * S mCfU * SfG * SfA mAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSOSOSSOOS SSSSS
WV-9713	fC * SfU * SfC * SfC * SfG * SfG * S mUfU * S mCfU * S mG * SfAfAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSOSOSSOOS SSSSS
WV-9714	fC * SfU * SfC * SfC * SfG * SfG * S mU * S mU * S mC * S mU * S mG * S mA * S mA * S mG * SfG * SfU * SfG * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSSSSSSS SSSS
WV-9715	fC * SfU * SfC * SfC * SfG * SfG * S mU * SfU * S mC * SfU * S mG * SfA * S mA * SfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSSSSSSS SSSS
WV-9737	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * SBrmUfG * S mGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSOSOS SSSSS
WV-9738	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * S mUfG * S mGfC * SfA * S BrfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSOSOS SSSSS
WV-9739	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * S mUfG * S mGfC * SfA * SfU * S BrfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSOSOS SSSSS
WV-9740	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * S mUfG * S mGfC * SfA * SfU * SfU * S BrfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSOSOS SSSSS
WV-9741	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * S mUfG * S mGfC * SfA * SfU * SfU * SfU * SfC * S BrfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSOSOS SSSSS
WV-9742	BrfU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mGfA * SBrmUfG * S mGfC * SfA * S BrfU * S BrfU * S BrfU * SfC * S BrfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSOSOS SSSSS
WV-9743	5 MSfC * SfU * SfC * SfC * SfG * SfG * S mUfU * S mC mU * SfG * S mA mAfG * SfG * SfU * SfG * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSOSOSSOOS SSSSS
WV-9744	fC * SfU * SfC * SfC * SfG * SfG * S mUfU * S mC mU * SfG * S mA mAfG * SfG * SfU * SfG * SfU * SfU * S 5 MSfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSOSOSSOOS SSSSS
WV-9745	5 MSfC * SfU * SfC * SfC * SfG * SfG * S mUfU * S mC mU * SfG * S mA mAfG * SfG * SfU * SfG * SfU * SfU * S 5 MSfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSOSOSSOOS SSSSS
WV-9746	fU * SfU * SfC * SfU * SfG * SfA * S mAfG * S mGfU * S mG * SfU mUfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOSOSSOOS SSSSS
WV-9747	fU * SfU * SfC * SfU * SfG * SfA * S mA * SfG * S mGfU * S mG * SfU mUfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSSOSOOS SSSSS
WV-9748	fU * SfU * SfC * SfU * SfG * SfA * S mAfG * S mG * SfU * S mG * SfU mUfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOSSSSOOS SSSSS
WV-9749	fU * SfU * SfC * SfU * SfG * SfA * S mAfG * S mGfU * S mG * SfU * S mUfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOSOSSSOS SSSSS
WV-9750	fU * SfU * SfC * SfU * SfG * SfA * S mAfG * S mGfU * S mG * SfU mU * SfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOSOSSOSS SSSSS

WV-9751	fU * SfU * SfC * SfU * SfG * S mA * S mAfG * S mGfU * S mG * SfU mUfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSOSOSSOOS SSSSS
WV-9752	fU * SfU * SfC * SfU * SfG * SfA * SfA * SfG * S mGfU * S mG * SfU mUfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSSOSSOOS SSSSS
WV-9753	fU * SfU * SfC * SfU * SfG * SfA * S mAfG * SfG * SfU * S mG * SfU mUfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOSSSSOOS SSSSS
WV-9754	fU * SfU * SfC * SfU * SfG * SfA * S mAfG * S mGfU * SfG * SfU * S mUfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOSOSSSOS SSSSS
WV-9755	fU * SfU * SfC * SfU * SfG * SfA * S mAfG * S mGfU * S mG * SfUfU * SfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOSOSSOSS SSSSS
WV-9756	fU * SfU * SfC * SfU * SfG * SfA * S mA * S mG * S mG * S mU * S mG * S mU * S mU * S mC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSSSSSSSSS SSSS
WV-9757	fU * SfU * SfC * SfU * SfG * SfA * S mA * SfG * S mG * SfU * S mG * SfU * S mU * SfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSSSSSSSSS SSSS
WV-9758	fU * SfU * SfC * SfU * SfG * SfA * SfAfG * S mGfU * S mG * SfU mUfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOSOSSOOS SSSSS
WV-9759	fU * SfU * SfC * SfU * SfG * SfA * S mAfG * SfGfU * S mG * SfU mUfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOSOSSOOS SSSSS
WV-9760	fU * SfU * SfC * SfU * SfG * SfA * S mAfG * S mGfU * SfG * SfU mUfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOSOSSOOS SSSSS
WV-9761	fU * SfU * SfC * SfU * SfG * SfA * S mAfG * S mGfU * S mG * SfUfUfC * SfU * SfU * SfG * SfU * SfA * SfC	UUCUGAAGGUGUUCU UGUAC	SSSSSSOSOSSOOS SSSSS

WV-9762	fA * fA * fU * fA * fU * fU * fC * fU * mU * mC * mU * mA * mA * mA * mG * mA * fA * fA * fG * fC * fU * fU * fA * fA * fA	AAUAUUCUUCUAAAG AAAGCUUAAA	XXXXX XXXXX XXXXX XXXX
WV-9763	fU * fC * fU * fU * fC * fU * fA * fA * mA * mG * mA * mA * mA * mG * mC * mU * fU * fA * fA * fA * fA * fA * fG * fU * fC	UCUUCUAAAGAAAGC UUAAAAAAGUC	XXXXX XXXXX XXXXX XXXX
WV-9764	fU * fA * fA * fA * fG * fA * fA * fA * mG * mC * mU * mU * mA * mA * mA * fA * fA * fG * fU * fC * fU * fG * fC * fU * fA	UAAAGAAAGCUUAA AAAGUCUGCUA	XXXXX XXXXX XXXXX XXXX
WV-9765	fA * fA * fA * fG * fC * fU * fU * fA * mA * mA * mA * mG * mU * mC * mU * fG * fC * fU * fU * fA * fA * fA * fU * fG	AAAGCUUAAAAAAGUC UGCUAAAAUG	XXXXX XXXXX XXXXX XXXX
WV-	fU * fU * fA * fA * fA * fA * fG * mU * mC * mU * mG * mC * mU *	UUAAAAAGUCUGCUA	XXXXX XXXXX

9766	mA * mA * fA * fA * fU * fG * fU * fU * fU * fU * fC	AAAUGUUUUC	XXXXX XXXXX XXXX
WV-9767	fA * fA * fG * fU * fC * fU * fG * fC * mU * mA * mA * mA * mA * mU * mG * mU * fU * fU * fC * fA * fU * fU * fC * fC	AAGUCUGCUAAAAAUG UUUUCAUUCC	XXXXX XXXXX XXXX
WV-9768	fU * fG * fC * fU * fA * fA * fA * fA * mU * mG * mU * mU * mU * mU * mC * mA * fU * fU * fC * fC * fU * fA * fU * fU * fA	UGCUAAAAAUGUUUUC AUUCCUAUUA	XXXXX XXXXX XXXX
WV-9769	fA * fA * fA * fU * fG * fU * fU * fU * mU * mC * mA * mU * mU * mC * mC * mU * fA * fU * fU * fA * fG * fA * fU * fC * fU	AAAUGUUUUCAUUCC UAUUAGAUCU	XXXXX XXXXX XXXX
WV-9770	fU * fU * fU * fU * fC * fA * fU * fU * mC * mC * mU * mA * mU * mU * mA * mG * fA * fU * fC * fU * fG * fU * fC * fG * fC	UUUUCAUUCCUAUUA GAUCUGUCGC	XXXXX XXXXX XXXX
WV-9771	fA * fU * fU * fC * fC * fU * fA * fU * mU * mA * mG * mA * mU * mC * mU * mG * fU * fC * fG * fC * fC * fC * fU * fA * fC	AUUCCUAUUAGAUCU GUCGCCCUAC	XXXXX XXXXX XXXX
WV-9772	fU * fA * fU * fU * fU * fA * fG * fA * fU * mC * mU * mG * mU * mC * mG * mC * mC * fC * fU * fA * fC * fC * fU * fC * fU * fU	UAUUAGAUCUGUCGC CCUACCUCUU	XXXXX XXXXX XXXX
WV-9773	fG * fA * fU * fC * fU * fG * fU * fC * mG * mC * mC * mC * mU * mA * mC * mC * fU * fC * fU * fU * fU * fU * fU * fU * fC	GAUCUGUCGCCCUAC CUCUUUUUUC	XXXXX XXXXX XXXX
WV-9774	fG * fU * fC * fG * fC * fC * fC * fU * mA * mC * mC * mU * mC * mU * mU * fU * fU * fU * fC * fU * fG * fU * fC * fU	GUCGCCCUACCUCUU UUUUCUGUCU	XXXXX XXXXX XXXX
WV-9775	fC * fC * fU * fA * fC * fC * fC * fU * fC * mU * mU * mU * mU * mU * mU * mC * mU * fG * fU * fC * fU * fG * fA * fC * fC * fA * fG	CCUACCUCUUUUUUC UGUCUGACAG	XXXXX XXXXX XXXX
WV-9776	fC * fU * fC * fC * fU * fU * fU * fU * fU * mU * mC * mU * mG * mU * mC * mU * mG * fA * fC * fA * fG * fC * fU * fG * fU * fU	CUCUUUUUUCUGUCU GACAGCUGUU	XXXXX XXXXX XXXX
WV-9777	fU * fU * fU * fU * fC * fU * fG * fU * mC * mU * mG * mA * mC * mA * mG * mC * fU * fG * fU * fU * fU * fG * fC * fA * fG	UUUUCUGUCUGACAG CUGUUUGCAG	XXXXX XXXXX XXXX
WV-	fU * fG * fU * fC * fU * fG * fA * fC * mA * mG * mC * mU * mG * mU *	UGUCUGACAGCUGUU	XXXXX XXXXX

9778	mU * mU * fG * fC * fA * fG * fA * fC * fC * fU * fC	UGCAGACCUC	XXXXX XXXXX XXXX
WV-9779	fG * fA * fC * fA * fG * fC * fU * fG * mU * mU * mG * mC * mA * mG * mA * fC * fC * fU * fC * fC * fU * fG * fC * fC	GACAGCUGUUUGCAG ACCUCCUGCC	XXXXX XXXXX XXXX XXXX XXXX
WV-9780	fC * fU * fG * fU * fU * fU * fG * fC * mA * mG * mA * mC * mC * mU * mC * mC * fU * fG * fC * fC * fC * fA * fC * fC * fG * fC	CUGUUUGCAGACCUC CUGCCACCGC	XXXXX XXXXX XXXX XXXX XXXX
WV-9781	fU * fG * fC * fA * fG * fA * fC * fC * mU * mC * mC * mU * mG * mC * mC * mA * fC * fC * fG * fC * fA * fG * fA * fU * fU	UGCAGACCUCCUGCC ACCGCAGAUU	XXXXX XXXXX XXXX XXXX XXXX
WV-9782	fA * fC * fC * fU * fC * fC * fU * fG * mC * mC * mA * mC * mC * mG * mC * mA * fG * fA * fU * fU * fC * fA * fG * fG * fC	ACCUCCUGCCACCGC AGAUUCAGGC	XXXXX XXXXX XXXX XXXX XXXX
WV-9783	fC * fU * fG * fC * fC * fA * fC * fC * mG * mC * mA * mG * mA * mU * mU * mC * fA * fG * fG * fC * fU * fU * fC * fC * fC	CUGCCACCGCAGAUU CAGGCUUCCC	XXXXX XXXXX XXXX XXXX XXXX
WV-9784	fA * fC * fC * fG * fC * fA * fG * fA * mU * mU * mC * mA * mG * mG * mC * mU * fU * fC * fC * fC * fA * fA * fU * fU * fU	ACCGCAGAUUCAGGC UUCCCAAUUU	XXXXX XXXXX XXXX XXXX XXXX
WV-9785	fA * fG * fA * fU * fU * fC * fC * fA * fG * mG * mC * mU * mU * mC * mC * mC * mA * fA * fU * fU * fU * fU * fU * fC * fC * fU	AGAUUCAGGCUUCCC AAUUUUCCU	XXXXX XXXXX XXXX XXXX XXXX
WV-9786	fC * fA * fG * fG * fC * fU * fU * fC * mC * mC * mA * mA * mU * mU * mU * mU * fC * fC * fC * fU * fG * fU * fA * fG * fA	CAGGCUUCCCAAUUU UUCCUGUAGA	XXXXX XXXXX XXXX XXXX XXXX
WV-9787	fU * fU * fC * fC * fC * fC * fA * fA * fU * mU * mU * mU * mU * mC * mC * mU * mG * fU * fA * fG * fG * fA * fA * fU * fA * fC * fU	UUCCCAAUUUUUCCU GUAGAAUACU	XXXXX XXXXX XXXX XXXX XXXX
WV-9788	fA * fA * fU * fU * fU * fU * fU * fU * fC * mC * mU * mG * mU * mA * mG * mA * mA * fU * fA * fC * fU * fU * fG * fC * fA * fU	AAUUUUUCCUGUAGA AUACUGGCAU	XXXXX XXXXX XXXX XXXX XXXX
WV-9789	fU * fU * fC * fC * fC * fU * fG * fU * fA * mG * mA * mA * mU * mA * mC * mU * mG * fG * fC * fA * fA * fU * fC * fU * fG * fU * fU	UUCCUGUAGAAUACU GGCAUCUGUU	XXXXX XXXXX XXXX XXXX XXXX
WV-	fG * fU * fA * fG * fA * fA * fU * fA * mC * mU * mG * mG * mC * mA *	GUAGAAUACUGGCAU	XXXXX XXXXX

9790	mU * mC * fU * fG * fU * fU * fU * fU * fG * fA	CUGUUUUUGA	XXXXX XXXXX XXXX
WV-9791	fA * fU * fA * fC * fU * fG * fG * fC * mA * mU * mC * mU * mG * mU * mU * mU * fU * fG * fA * fG * fA * fU * fU	AUACUGGCAUCUGUU UUUGAGGAUU	XXXXX XXXXX XXXX
WV-9792	fG * fG * fC * fA * fU * fC * fU * fG * mU * mU * mU * mU * mU * mG * mA * mG * fG * fA * fU * fU * fG * fC * fU * fG * fA	GGCAUCUGUUUUUGA GGAUUGCUGA	XXXXX XXXXX XXXX
WV-9793	fC * fU * fG * fU * fU * fU * fU * fU * mG * mA * mG * mG * mA * mU * mU * mG * fC * fU * fG * fA * fA * fU * fU * fA * fU	CUGUUUUUGAGGAU UGCUGAAUUAU	XXXXX XXXXX XXXX
WV-9794	fU * fU * fU * fG * fA * fG * fG * fA * mU * mU * mG * mC * mU * mG * mA * mA * fU * fU * fA * fU * fU * fC * fU * fU	UUUGAGGAUUGCUG AAUUAUUUCUU	XXXXX XXXXX XXXX
WV-9795	fG * fG * fA * fU * fU * fG * fC * fU * mG * mA * mA * mU * mU * mA * mU * mU * fC * fU * fU * fC * fC * fC * fC * fA	GGAUUGCUGAAUUA UUUCUUCCCCA	XXXXX XXXXX XXXX
WV-9796	fG * fC * fU * fG * fA * fA * fU * fU * mA * mU * mU * mU * mC * mU * mU * mC * fC * fC * fC * fA * fG * fU * fU * fG * fC	GCUGAAUUAUUUCUU CCCCAGUUGC	XXXXX XXXXX XXXX
WV-9797	fA * fU * fU * fA * fU * fU * fU * fC * mU * mU * mC * mC * mC * mC * mA * mG * fU * fU * fG * fC * fC * fA * fU * fU * fC * fA	AUUAUUUCUUCCCCA GUUGCAUUCA	XXXXX XXXXX XXXX
WV-9798	fU * fU * fU * fC * fU * fU * fC * fC * fC * mC * mA * mG * mU * mU * mG * mC * mA * fU * fU * fC * fA * fA * fU * fG * fU * fU	UUCUUCCCCAGUUGC AUUCAAUGUU	XXXXX XXXXX XXXX
WV-9799	fC * fC * fC * fC * fC * fA * fG * fU * fU * mG * mC * mA * mU * mU * mC * mA * mA * fU * fG * fU * fU * fC * fU * fG * fA * fC	CCCCAGUUGCAUUCA AUGUUCUGAC	XXXXX XXXXX XXXX
WV-9800	fG * fU * fU * fG * fC * fC * fA * fU * fU * mC * mA * mA * mU * mG * mU * mU * mC * fU * fG * fA * fC * fA * fA * fC * fA * fG	GUUGCAUUCAAUGUU CUGACAACAG	XXXXX XXXXX XXXX
WV-9801	fA * fU * fU * fC * fA * fA * fU * fG * mU * mU * mC * mU * mG * mA * mC * mA * fA * fC * fA * fG * fU * fU * fU * fG * fC	AUUCAAUGUUCUGAC AACAGUUUGC	XXXXX XXXXX XXXX
WV-	fA * fU * fG * fU * fU * fC * fU * fG * mA * mA * mC * mA * mA *	AUGUUCUGACAACAG	XXXXX XXXXX

9802	mG * mU * fU * fU * fG * fC * fC * fG * fC * fU * fG	UUUGCCGCUG	XXXXX XXXXX XXXX
WV-9803	fC * fU * fG * fA * fC * fA * fA * fC * mA * mG * mU * mU * mU * mG * mC * mC * fG * fC * fU * fG * fC * fC * fC * fA * fA	CUGACAACAGUUUGC CGCUGCCCAA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9804	fA * fA * fC * fA * fG * fU * fU * fU * mG * mC * mC * mG * mC * mU * mG * mC * fC * fC * fA * fA * fU * fG * fC * fC * fA	AACAGUUUGCCGCUG CCCAAUGCCA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9805	fU * fU * fU * fU * fG * fC * fC * fG * fC * mU * mG * mC * mC * mC * mA * mA * mU * fG * fC * fC * fA * fU * fC * fC * fU * fG	UUUGCCGCUGCCCAA UGCCAUCCUG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9806	fC * fG * fC * fU * fU * fG * fC * fC * fC * fC * mA * mA * mU * mG * mC * mC * mC * mA * mU * fC * fC * fU * fG * fG * fA * fG * fU * fU	CGCUGCCCAAUGCCA UCCUGGAGUU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9807	fC * fC * fC * fC * fA * fA * fU * fG * fC * mC * mA * mU * mC * mC * mC * mU * mG * mG * fA * fG * fU * fU * fC * fC * fU * fG * fU	CCCAAUGCCAUCCUG GAGUUCCUGU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9808	fU * fG * fC * fC * fC * fA * fU * fC * fC * mU * mG * mG * mA * mG * mU * mU * mC * fC * fU * fG * fU * fU * fA * fA * fG * fA * fU	UGCCAUCCUGGAGUU CCUGUAAGAU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9809	fU * fC * fC * fC * fU * fG * fG * fA * fG * mU * mU * mC * mC * mU * mG * mU * mA * fA * fG * fA * fU * fA * fC * fC * fC * fA * fA	UCCUGGAGUUCCUGU AAGAUACCAA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9810	fG * fA * fG * fU * fU * fC * fC * fU * mG * mU * mA * mA * mG * mA * mU * mA * fC * fC * fC * fA * fA * fA * fA * fA * fG * fG	GAGUUCCUGUAAGAU ACCAAAAAGG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9811	fC * fC * fC * fU * fG * fU * fU * fA * fG * mA * mU * mA * mC * mC * mC * mA * mA * mA * fA * fA * fG * fG * fC * fA * fA * fA * fA	CCUGUAAGAUACCAA AAAGGCAAAA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9812	fA * fA * fG * fA * fU * fA * fC * fC * mA * mA * mA * mA * mA * mG * mG * mC * fA * fA * fA * fA * fA * fC * fA * fA * fA * fA	AAGAUACCAAAAAGG CAAAACAAAA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9813	fA * fC * fC * fC * fA * fA * fA * fA * mG * mG * mC * mA * mA * mA * mA * mC * fA * fA * fA * fA * fU * fG * fA * fA	ACCAAAAAGGCAAAA CAAAAAUGAA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-	fA * fA * fA * fG * fG * fC * fA * fA * mA * mC * mA * mA * mA * mA *	AAAGGCAAAACAAAA	XXXXX XXXXX

9814	mA * mA * fU * fG * fA * fA * fG * fC * fC * fC * fC	AUGAAGCCCC	XXXXX XXXXX XXXX
WV-9815	fC * fA * fA * fA * fA * fC * fA * fA * mA * mA * mA * mU * mG * mA * mA * mG * fC * fC * fC * fC * fA * fU * fG * fU * fC	CAAAACAAAAAUGAA GCCCCAUGUC	XXXXX XXXXX XXXX XXXX
WV-9816	fC * fA * fA * fA * fA * fA * fU * fG * mA * mA * mG * mC * mC * mC * mC * mA * fU * fG * fU * fC * fU * fU * fA * fU * fU	CAAAAAUGAAGCCCC AUGUCUUUUU	XXXXX XXXXX XXXX XXXX
WV-9817	fA * fU * fG * fA * fA * fG * fC * fC * mC * mA * mU * mG * mU * mC * mU * fU * fU * fA * fU * fU * fU * fG	AUGAAGCCCCAUGUC UUUUUAUUUG	XXXXX XXXXX XXXX XXXX
WV-9818	fG * fC * fC * fC * fC * fA * fU * fG * mU * mC * mU * mU * mU * mU * mA * fU * fU * fU * fG * fA * fG * fA * fA * fA	GCCCCAUGUCUUUUU AUUUGAGAAA	XXXXX XXXXX XXXX XXXX
WV-9819	fA * fU * fG * fU * fC * fU * fU * fU * mU * mU * mA * mU * mU * mU * mG * mA * fG * fA * fA * fA * fA * fG * fA * fU * fU	AUGUCUUUUUAUUU GA GAAAAGAUU	XXXXX XXXXX XXXX XXXX
WV-9820	fU * fU * fU * fU * fU * fA * fU * fU * mU * mG * mA * mG * mA * mA * mA * fG * fA * fU * fU * fA * fA * fA * fC * fA	UUUUUAUUUGAGAA AA GAUUAAACA	XXXXX XXXXX XXXX XXXX
WV-9821	fA * fU * fU * fU * fU * fG * fA * fG * fA * mA * mA * mG * mA * mU * mU * mA * fA * fA * fC * fA * fG * fU * fU * fG	AUUUGAGAAAAGAU UAA ACAGUGUG	XXXXX XXXXX XXXX XXXX
WV-9822	fA * fG * fA * fA * fA * fA * fG * fA * mU * mU * mA * mA * mA * mC * mA * mG * fU * fU * fG * fC * fU * fA * fC * fC	AGAAAAGAUUAAAC AGU GUGCUACC	XXXXX XXXXX XXXX XXXX
WV-9823	fA * fG * fA * fU * fU * fA * fA * fC * mA * mG * mU * mG * mU * mG * mC * fU * fA * fC * fC * fA * fA * fU * fG	AGAUUAAACAGUGU GCU ACCACAUG	XXXXX XXXXX XXXX XXXX
WV-9824	fA * fA * fA * fC * fA * fG * fU * fG * mU * mG * mC * mU * mA * mC * mC * mA * fC * fA * fU * fG * fC * fA * fG * fU * fU	AAACAGUGUGCUACC ACA UGCAGUU	XXXXX XXXXX XXXX XXXX
WV-9825	fG * fU * fG * fU * fG * fC * fU * fA * mC * mC * mA * mC * mA * mU * mG * mC * fA * fG * fU * fU * fG * fA * fC * fC * fU	GUGUGCUACCACAUG CAG UUGUACU	XXXXX XXXXX XXXX XXXX

WV-9826	fG * fC * fC * fC * fA * fA * fU * fG * fC * fC * fC * fA * fU * fC * fC * fU * fG * fG	GCCCAAUGCCAUCCU GG	XXXXX XXXXX XXXXXX
WV-9827	fC * fC * fA * fC * fA * fG * mG * mU * mU * mG * mU * mC * mA * mC * mC * mA * mG * mA * mG * mU * mA * mA * fC * fA * fG * fU * fC * fU	CCACAGGUUGUGUCA CC AGAGUAACAGUCU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9828	fG * fU * fG * fU * fC * fA * mC * mC * mA * mG * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU * mC * mG * mA * mG * fU * fA * fG * fG * fA * fG	GUGUCACCAGAGUAA CA GUCUGAGUAGGAG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9829	fA * fG * fG * fU * fU * fG * mU * mG * mU * mC * mA * mC * mC * mA * mG * mA * mU * mA * mA * mC * mA * mG * mU * fC * fU * fG * fA * fG * fU	AGGUUGUGUCACCAG AG UAACAGUCUGAGU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9830	fG * fG * fC * fA * fG * fU * mU * mU * mC * mC * mU * mU * mA * mG * mU * mA * mA * mC * mC * mA * mC * mA * mG * mG * fU * fU * fG * fU * fG * fU	GGCAGUUUCCUUAGU AACCACAGGUUGUGU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9831	fA * fG * fA * fU * fG * fG * mC * mA * mG * mU * mU * mU * mC * mC * mU * mA * mG * mU * mA * mA * mC * mC * mA * fC * fA * fG * fG * fU * fU	AGAUGGCAGUUUCCU U AGUAACCACACAGGUU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9832	fA * fU * fG * fG * fC * fA * mU * mU * mU * mC * mU * mA * mG * mU * mU * mU * mG * mA * mG * mA * mU * mG * mG * fC * fA * fG * fU * fU * fU	AUGGCAUUUCUAGUU UG GAGAUGGCAGUUU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9833	fU * fU * fA * fU * fA * fA * mC * mU * mU * mG * mA * mU * mC * mA * mA * mG * mC * mA * mG * mA * mA * mA * fG * fC * fC * fA * fG * fU	UUAUAACUUGAUCAA GCA GAGAAAGCCAGU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9834	fA * fU * fA * fC * fC * fU * fU * mC * mU * mG * mC * mU * mU * mG * mA * mA * mU * mG * mA * mU * mC * mA * mU * mC * fC * fG * fU * fU * fG * fA	AUACCUUCUGCUUGA UGA UCAUCUCGUUGA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9835	fU * fG * fU * fC * fA * fC * mC * mA * mG * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU * mG * mA * mG * fU * fA * fG * fG * fA * fG	UGUCACCAGAGUAAC AGU CUGAGUAGGAG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9836	fG * fU * fC * fA * fC * fC * mA * mG * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU * mG * mA * mG * fU * fA * fG * fG * fA * fG	GUCACCAGAGUAACA GUC UGAGUAGGAG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9837	fU * fC * fA * fC * fC * fA * mG * mA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU * mG * mA * mG * fU * fA * fG * fG * fA * fG	UCACCAGAGUAACAG UCU GAGUAGGAG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-	fC * fA * fC * fC * fA * fG * fA * mG * mU * mA * mA * mC * mA * mG	CACCAGAGUAACAGU	XXXXX XXXXX

9838	* mU * mC * mU * mG * mA * mG * fU * fA * fG * fG * fA * fG	CUG AGUAGGAG	XXXXX XXXXX XXXXX
WV-9839	fA * fC * fC * fA * fG * fA * mG * mU * mA * mA * mC * mA * mG * mU * mC * mU * mG * mA * mG * fU * fA * fG * fG * fA * fG	ACCAGAGUAACAGUC UGA GUAGGAG	XXXXX XXXXX XXXXX XXXX
WV-9840	fC * fC * fA * fC * fA * fG * fG * fU * fU * fG * fU * mG * mU * mC * mA * mC * mC * mA * mG * fA * fG * fU * fA * fA * fC * fA * fG * fU * fC * fU	CCACAGGUUGUGUCA CCAGAGUAACAGUCU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9841	fG * fU * fG * fU * fC * fA * fC * fC * fA * fG * fA * mG * mU * mA * mA * mC * mA * mG * mU * fC * fU * fG * fA * fG * fU * fA * fG * fG * fA * fG	GUGUCACCAGAGUAA C AGUCUGAGUAGGAG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-9842	fA * fG * fG * fU * fU * fG * fG * fU * fC * fC * fA * mC * mC * mA * mG * mA * mG * mU * mA * fA * fC * fA * fG * fU * fC * fU * fG * fA * fG * fU	AGGUUGUGUCACCAG A GUAACAGUCUGAGU	XXXXX XXXXX XXXXX XXXX XXX
WV-9843	fG * fG * fC * fA * fG * fU * fU * fU * fC * fC * fC * fU * mU * mA * mG * mU * mA * mA * mC * mC * fA * fC * fA * fG * fG * fA * fU * fG * fU * fG * fG * fU	GGCAGUUUCCUUAGU A ACCACAGGUUGUGU	XXXXX XXXXX XXXXX XXXX XXXX
WV-9844	fA * fG * fA * fU * fG * fG * fC * fA * fG * fU * fU * fU * mU * mC * mC * mU * mA * mG * mU * fA * fA * fC * fC * fC * fA * fC * fA * fG * fG * fU * fU	AGAUGGCAGUUUCCU UA GUAACCACAGGUU	XXXXX XXXXX XXXXX XXXX XXX
WV-9845	fA * fU * fG * fG * fC * fC * fA * fU * fU * fU * fC * fC * fU * mA * mG * mU * mU * mU * mG * mA * fG * fA * fU * fU * fG * fG * fC * fA * fG * fG * fU * fU * fU * fU	AUGGCAUUUCUAG UUUGGAGAUGGCAG UUU	XXXXX XXXXX XXXXX XXXX XXX
WV-9846	fU * fU * fA * fU * fA * fA * fC * fC * fU * fU * fG * fG * fA * mU * mC * mC * mA * mA * mG * mC * mA * mG * fA * fG * fA * fA * fA * fG * fC * fC * fC * fA * fG * fG * fU	UUAUAACUUGAUCA AGCAGAGAAAGCCAG U	XXXXX XXXXX XXXXX XXXX XXXX
WV-9847	fA * fU * fA * fA * fC * fC * fU * fU * fC * fU * fG * fG * fC * mU * mU * mU * mG * mA * mU * mG * mA * mU * fC * fC * fA * fU * fC * fC * fC * fG * fU * fU * fU * fG * fA	AUACCUUCUGCUUGA UGAUCAUCUCGUUGA	XXXXX XXXXX XXXXX XXXXX XXXX	
WV-9848	fU * fG * fU * fC * fA * fC * fC * fC * fA * fG * fA * mG * mU * mA * mA * mC * mA * mG * mU * fC * fU * fG * fA * fG * fU * fA * fG * fG * fA * fG * fG	UGUCACCAGAGUAAC A GUCUGAGUAGGAG	XXXXX XXXXX XXXXX XXXXX XXXXXXX	
WV-9849	fG * fU * fC * fA * fC * fC * fA * fG * fA * mG * mU * mA * mA * mC * mA * mG * mU * fC * fU * fG * fA * fG * fU * fA * fG * fG * fA * fG	GUCACCAGAGUAACA G UCUGAGUAGGAG	XXXXX XXXXX XXXXX XXXXX XXXXXXX	
WV-	fU * fC * fA * fC * fC * fA * fG * fA * mG * mU * mA * mA * mC * mA *	UCACCAGAGUAACAG	XXXXX XXXXX	

9850	mG * mU * fC * fU * fG * fA * fG * fU * fA * fG * fG * fA * fG	U CUGAGUAGGAG	XXXXX XXXXX XXXXXX
WV-9851	fC * fA * fC * fC * fA * fG * fA * mG * mU * mA * mA * mC * mA * mG * mU * fC * fU * fG * fA * fG * fU * fA * fG * fG * fA * fG	CACCAGAGUAACAGU CU GAGUAGGAG	XXXXX XXXXX XXXXX XXXXX XXXXX
WV-9852	fA * fC * fC * fA * fG * fA * mG * mU * mA * mA * mC * mA * mG * mU * fC * fU * fG * fA * fG * fU * fA * fG * fG * fA * fG	ACCAGAGUAACAGUC U GAGUAGGAG	XXXXX XXXXX XXXXX XXXXX XXXXX

WV-9858	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfUL004	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSSOOS SSSSSO
WV-9875	fU * SfU * SfU * SfU * SfG * S mGfC * S mA mG mC * SfU * SfU * SfU * SfC * SfC * SfA * SfC * SfC * SfA * SfA	UUUUGGCAGCUUUCC ACCAA	SSSSSOSOOSSSSS SSSSS
WV-9876	fU * SfU * SfU * SfU * SfG * SfG * SfC * SfA * S mG mC * SfU * S mU mUfC * SfC * SfA * SfC * SfC * SfA * SfA	UUUUGGCAGCUUUCC ACCAA	SSSSSSSOSSOOS SSSSS
WV-9877	fU * SfU * SfU * SfU * SfG * SfG * S mCfA * SfG * S mC * SfU * S mU mUfC * SfC * SfA * SfC * SfC * SfA * SfA	UUUUGGCAGCUUUCC ACCAA	SSSSSOSSSSOOS SSSSS
WV-9878	fU * SfU * SfU * SfU * SfG * SfG * S mCfA * S mG mC * SfU * SfU * S mUfC * SfC * SfA * SfC * SfC * SfA * SfA	UUUUGGCAGCUUUCC ACCAA	SSSSSSOSOSSSOS SSSSS
WV-9879	fU * SfU * SfU * SfU * SfG * SfG * S mCfA * S mG mC * SfU * S mUfU * SfC * SfC * SfA * SfC * SfC * SfA * SfA	UUUUGGCAGCUUUCC ACCAA	SSSSSSOSOSSOSS SSSSS
WV-9897	fC * SfU * SfC * SfC * SfG * SfG * SfU * S mCfU * S mG * SfA * S mAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSSSOSS SSSS
WV-9898	fC * SfU * SfC * SfC * SfC * SfG * SfG * SfU * SfU * S mCfU * S mG * SfA * S mA mG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSSSOSS SSSS
WV-9899	fC * SfU * SfC * SfC * SfC * SfG * SfG * SfU * SfU * SfC * SfU * S mG * SfA * S mA mGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSSSSOOS SSSS
WV-9900	fC * SfU * SfC * SfC * SfC * SfG * SfG * SfU * SfU * S mC * SfU * S mG * SfA * S mA mGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSSSSOOS SSSS
WV-9901	fC * SfU * SfC * SfC * SfG * SfG * S mGfU * SfU * SfC * SfU * S mG * SfA * S mA mGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSOSSSSSOO SSSSS
WV-9902	fC * SfU * SfC * SfC * SfC * SfG * SfG * S mGfU * SfU * S mC * SfU * S mG * SfA * S mA mGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSOSSSSSOO SSSSS
WV-9903	fC * SfU * SfC * SfC * SfG * SfG * S mUfU * SfC * SfU * S mG * SfA * S mA mGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSOSSSSSOO SSSSS
WV-	fC * SfU * SfC * SfC * SfG * SfG * S mUfU * S mC * SfU * S mG * SfA * S	CUCCGGUUCUGAAGG	SSSSSOSSSSSOO

9904	mA mGfG * SfU * SfG * SfU * SfU * SfC	UGUUC	SSSSS
WV-9905	fC * SfU * SfC * SfC * SfG * SfG mU * SfU * S mC * SfU * S mG * SfA * S mA * SfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSOSSSSSSSSS SSSS
WV-9906	fC * SfU * SfC * SfC * SfG * SfG * S mUfU * S mC * SfU * S mG * SfA * S mA * SfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSOSSSSSSSS SSSS
WV-9907	fC * SfU * SfC * SfC * SfG * SfG * S mU * SfU mC * SfU * S mG * SfA * S mA * SfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSOSSSSSSS SSSS
WV-9908	fC * SfU * SfC * SfC * SfG * SfG * S mU * SfU * S mCfU * S mG * SfA * S mA * SfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSOSSSSSS SSSS
WV-9909	fC * SfU * SfC * SfC * SfG * SfG * S mU * SfU * S mC * SfU mG * SfA * S mA * SfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSSOSSSSS SSSS
WV-9910	fC * SfU * SfC * SfC * SfG * SfG * S mU * SfU * S mC * SfU * S mGfA * S mA * SfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSSSOSSSS SSSS
WV-9911	fC * SfU * SfC * SfC * SfG * SfG * S mU * SfU * S mC * SfU * S mG * SfA mA * SfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSSSOSSS SSSS
WV-9912	fC * SfU * SfC * SfC * SfG * SfG * S mU * SfU * S mC * SfU * S mG * SfA * S mAfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSSSOSS SSSS
WV-9913	fC * SfU * SfC * SfC * SfG * SfG * S mU * SfU * S mC * SfU * S mG * SfA * S mA * SfGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSSSOS SSSS
WV-9914	fC * SfU * SfC * SfC * SfG * SfG * S mU * SfU * S mC * SfU * S mG * SfA * S mA * SfG * SfGfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSSSSSO SSSS
WV-10255	fU * SfC * SfA * SfA * SfG * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * S mU	UCAAGGAAGAUGGCA UUUCU	SSSSSSOSOSSOOS SSSSS
WV-10256	fU * SfC * SfA * SfC * SfU * SfC * S mAfG * S mA mU * SfA * S mG mUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSSSSSOSOSSOOS SSSSS
WV-10257	fU * SfC * SfA * SfC * SfU * SfC * SfA * SfG * S mA mU * SfA * S mG mUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSSSSSSSOSSOOS SSSSS
WV-10258	fU * SfC * SfA * SfC * SfU * SfC * S mAfG * SfA * S mU * SfA * S mG mUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSSSSSOSSSSOOS SSSSS
WV-10259	fU * SfC * SfA * SfC * SfU * SfC * S mAfG * S mA mU * SfA * SfG * S mUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSSSSSOSOSSSOS SSSSS
WV-10260	fU * SfC * SfA * SfC * SfU * SfC * S mAfG * S mA mU * SfA * S mGfU * SfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSSSSSOSOSSOSS SSSSS
WV-10261	fG * SfC * SfA * SfA * SfG * S mAfA * S mG mA * SfU * S mG mGfC * SfA * SfU * SfU * SfU * SfC * SfU	GCAAAGAAGAUGGCA UUUCU	SSSSSOSOSOSOOS SSSSS
WV-	fG * fC * fA * fA * fG * mAfA * mG mA * fU * mG mGfC * fA * fU	GCAAAGAAGAUGGCA	XXXXXOXOXOXXO

10262	* fU * fU * fC * fU	UUUCU	OXXXXXX
WV-10439	fU * fU * fC * fU * fU * fG * fU * fA * fC * mU * mU * mC * mA * mC * mC * mA * mC * mU * mG * fA * fU * fU * fC * fU * fG * fA * fA * fU	UUCUUGUACUUCAUC CCACU GAUUCUGAAU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10440	fG * fU * fG * fU * fU * fC * fU * fU * fG * mU * mA * mC * mU * mU * mC * mA * mU * mC * mC * mC * mA * fC * fU * fG * fA * fU * fU * fC * fU * fG	GUGUUCUUGUACUUC AUCCC ACUGAUUCUG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10441	fA * fA * fG * fG * fU * fG * fU * fU * fC * mU * mU * mG * mU * mA * mC * mU * mU * mC * mA * mU * mC * fC * fC * fA * fC * fU * fG * fA * fU * fU	AAGGUGUUCUUGUAC UUCAU CCCACUGAUU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10442	fC * fU * fG * fA * fA * fG * fG * fU * fG * mU * mU * mC * mU * mU * mG * mU * mA * mC * mU * mU * mC * fA * fU * fC * fC * fC * fA * fC * fU * fG	CUGAAGGUGUUCUUG UACUU CAUCCCACUG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10443	fG * fU * fU * fC * fU * fG * fA * fA * fG * mG * mU * mG * mU * mU * mC * mU * mU * mG * mU * mA * mC * fU * fU * fC * fA * fU * fC * fC * fC * fA	GUUCUGAAGGUGUUC UUGUA CUUCAUCCCA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10444	fC * fC * fG * fG * fU * fU * fC * fU * fG * mA * mA * mG * mG * mU * mG * mU * mC * mU * mU * mG * fU * fA * fC * fU * fU * fC * fC * fA * fU * fC	CCGGUUCUGAAGGUG UUCUU GUACUUCAUC	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10445	fC * fC * fU * fC * fC * fG * fG * fU * fU * mC * mU * mG * mA * mA * mG * mU * mG * mU * mC * fU * fU * fG * fU * fA * fC * fU * fU * fC	CCUCCGGUUCUGAAG GUGUU CUUGUACUUC	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10446	fU * fU * fG * fC * fC * fC * fU * fC * fC * fG * mG * mU * mU * mC * mC * mU * mG * mA * mA * mG * mG * mU * fU * fC * fU * fU * fG * fU * fA * fC	UUGCCUCCGGUUCUG AAGGU GUUCUUGUAC	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10447	fC * fU * fG * fU * fU * fG * fC * fC * fC * fU * mC * mC * mG * mG * mU * mU * mC * mU * mG * mA * mA * mG * fG * fU * fG * fU * fU * fC * fC * fU * fU * fG	CUGUUGCCUCCGGUU CUGAA GGUGUUCUUG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10448	fC * fA * fA * fC * fC * fU * fG * fU * fU * fG * fG * mC * mC * mC * mU * mC * mC * mG * mG * mU * mU * mC * mU * mG * fA * fA * fG * fG * fU * fG * fU * fU * fC	CAACUGUUGCCUCCG GUUCU GAAGGUGUUC	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10449	fA * fU * fU * fC * fA * fA * fC * fC * fU * fG * mU * mU * mG * mC * mC * mC * mU * mC * mG * mG * mU * mU * fC * fC * fU * fG * fA * fA * fG * fG * fG * fU	AUUCAACUGUUGCCU CCGGU UCUGAAGGUG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-	fU * fU * fC * fA * fU * fU * fC * fA * fA * mC * mU * mG * mU * mU *	UUCAUUCAACUGUUG	XXXXX XXXXX

10450	mG * mC * mC * mU * mC * mC * mG * fG * fU * fU * fC * fU * fG * fA * fA * fG	CCUCC GGUUCUGAAG	XXXXX XXXXX XXXXX XXXX
WV-10451	fC * fA * fU * fU * fU * fC * fA * fU * fU * mC * mA * mA * mC * mU * mG * mU * mU * mG * mC * mC * mU * fC * fC * fG * fG * fU * fU * fC * fU * fG	CAUUUCAUUCAACUG UUGCC UCCGGUUCUG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10452	fU * fA * fA * fC * fA * fU * fU * fU * fC * mA * mU * mU * mC * mA * mA * mC * mU * mG * mU * mU * mG * fC * fC * fU * fC * fC * fG * fG * fU * fU	UAACAUUUCAUUCAA CUGUU GCCUCCGGUU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10453	fC * fU * fU * fU * fU * fA * fA * fC * fA * fU * mU * mU * mC * mA * mU * mU * mC * mA * mA * mC * mU * fU * fG * fC * fC * fU * fC * fC * fG	CUUUAACAUUUCAUU CAACU GUUGCCUCCG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10454	fU * fA * fC * fC * fU * fU * fC * fA * mU * mC * mC * mC * mA * mC * mU * mG * mA * mU * fU * fC * fU * fG * fA * fA * fU * fU	UACUUCAUCCCACUG AUUCU GAAUU	XXXXX XXXXX XXXXX XXXX
WV-10455	fU * fU * fG * fU * fA * fC * fU * mU * mC * mA * mU * mC * mC * mC * mA * mC * mU * fG * fA * fU * fU * fC * fU * fG * fA	UUGUACUUCAUCCCA CUGAU UCUGA	XXXXX XXXXX XXXXX XXXX
WV-10456	fU * fU * fC * fU * fU * fU * fG * fU * mA * mC * mU * mU * mC * mA * mU * mC * mC * fA * fC * fU * fG * fA * fU * fU * fC	UUCUUGUACUUCAUC CCACU GAUUC	XXXXX XXXXX XXXXX XXXX
WV-10457	fG * fU * fG * fU * fU * fC * fU * mU * mG * mU * mA * mC * mU * mU * mC * mA * mU * fC * fC * fA * fC * fU * fG * fA	GUGUUCUUGUACUUC AUCCC ACUGA	XXXXX XXXXX XXXXX XXXX
WV-10458	fA * fA * fG * fG * fU * fG * fU * mU * mC * mU * mU * mG * mU * mA * mC * mU * mU * fC * fA * fU * fC * fC * fC * fA * fC	AAGGUGUUCUUGUAC UUCAU CCCAC	XXXXX XXXXX XXXXX XXXX
WV-10459	fC * fU * fG * fA * fA * fG * fG * mU * mG * mU * mU * mC * mU * mU * mG * mU * mA * fC * fU * fU * fC * fA * fU * fC * fC	CUGAAGGUGUUCUUG UACUU CAUCC	XXXXX XXXXX XXXXX XXXX
WV-10460	fG * fU * fU * fC * fU * fG * fA * mA * mG * mG * mU * mG * mU * mU * mC * mU * mU * fG * fU * fA * fC * fU * fU * fC * fA	GUUCUGAAGGUGUUC UUGUA CUUCA	XXXXX XXXXX XXXXX XXXX
WV-10461	fC * fC * fG * fG * fU * fU * fC * mU * mG * mA * mA * mG * mG * mU * mG * mU * mU * fC * fU * fU * fG * fU * fA * fC * fU	CCGGUUCUGAAGGUG UUCUU GUACU	XXXXX XXXXX XXXXX XXXX
WV-	fC * fC * fU * fC * fC * fG * fG * mU * mU * mC * mU * mG * mA * mA *	CCUCCGGUUCUGAAG	XXXXX XXXXX

10462	mG * mG * mU * fG * fU * fU * fC * fU * fU * fG * fU	GUGUU CUUGU	XXXXX XXXXX XXXX
WV-10463	fU * fU * fG * fC * fC * fU * fC * mC * mG * mG * mU * mU * mC * mU * mG * mA * mA * fG * fG * fU * fU * fU * fC * fU	UUGCCUCCGGUUCUG AAGGU GUUCU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10464	fC * fU * fG * fU * fU * fG * fC * mC * mU * mC * mC * mG * mG * mU * mU * mC * mU * fG * fA * fA * fG * fG * fU * fG * fU	CUGUUGCCUCCGGUU CUGAA GGUGU	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10465	fC * fA * fA * fC * fU * fG * fU * mU * mG * mC * mC * mU * mC * mC * mG * mG * mU * fU * fC * fU * fG * fA * fA * fG * fG	CAACUGUUGCCUCCG GUUCU GAAGG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10466	fA * fU * fU * fC * fC * fA * fA * fC * mU * mG * mU * mU * mG * mC * mC * mU * mC * mC * fG * fG * fU * fU * fC * fU * fG * fA	AUUCAACUGUUGCCU CCGGU UCUGA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10467	fU * fU * fC * fA * fU * fU * fC * mA * mA * mC * mU * mG * mU * mU * mG * mC * mC * fU * fC * fC * fG * fG * fU * fU * fC	UUCAUUCAACUGUUG CCUCC GGUUC	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10468	fC * fA * fU * fU * fU * fC * fA * mU * mU * mC * mA * mA * mC * mU * mG * mU * mU * fG * fC * fC * fU * fC * fC * fG * fG	CAUUUCAUUCAACUG UUGCC UCCGG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10469	fU * fA * fA * fC * fC * fA * fA * fU * fU * mU * mC * mA * mU * mU * mC * mA * mA * mC * mU * fG * fU * fU * fG * fC * fC * fU * fC	UAACAUUUCAUUCAA CUGUU GCCUC	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10470	fC * fU * fU * fU * fU * fA * fA * fC * mA * mU * mU * mU * mC * mA * mU * mU * mC * mA * fA * fC * fU * fG * fU * fU * fG * fC	CUUUAACAUUUCAUU CAACU GUUGC	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10487	fA * fU * fC * fC * fC * fA * fC * fC * fU * fG * mC * mC * mU * mC * mG * mG * mC * mC * mU * mC * mC * fA * fA * fA * fG * fU * fG * fC * fU * fG	AUCCACCUGCCUCGG CCUCC CAAAGUGCUG	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10488	fC * fC * fU * fC * fA * fG * fG * fU * fG * mA * mU * mC * mC * mA * mC * mC * mU * mG * mC * mC * mU * fC * fG * fC * fC * fC * fC * fU * fC * fC	CCUCAGGUGAUCCAC CUGCC UCGGCCUCCC	XXXXX XXXXX XXXXX XXXXX XXXX
WV-10489	fA * fA * fA * fC * fU * fC * fC * fU * fG * mA * mC * mC * mU * mC * mA * mG * mG * mU * mG * mA * mU * fC * fC * fA * fC * fC * fU * fG * fC * fC	AAACUCCUGACCUCA GGUGA UCCACCUGCC	XXXXX XXXXX XXXXX XXXXX XXXX
WV-	fA * fU * fU * fU * fU * fU * fA * fU * mA * mG * mA * mG * mA *	AUUUUUAAUAGAGA	XXXXX XXXXX

10490	mC * mA * mG * mG * mG * mU * mU * fU * fC * fC * fA * fC * fC * fA * fU * fG * fU	CAGGGU UUCACCAUGU	XXXXX XXXXX XXXXX XXX
WV-10491	fC * fU * fA * fC * fA * fG * fG * fC * fA * mC * mG * mU * mG * mC * mC * mA * mU * mC * mA * mU * mG * fC * fC * fC * fA * fG * fC * fU * fA * fA	CUACAGGCACGUGCC AUCAU GCCCAGCUAA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10492	fC * fC * fU * fC * fC * fU * fG * fU * fC * mU * mC * mA * mG * mC * mC * mU * mC * mC * mC * mG * mA * fG * fU * fA * fG * fC * fA * fG * fG * fA	CCUCCUGUCUCAGCC UCCCG AGUAGCAGGA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10493	fU * fC * fC * fG * fC * fU * fC * fA * fC * mU * mG * mC * mA * mA * mC * mC * mU * mC * mC * mG * mC * fC * fU * fC * fC * fC * fG * fG * fU	UCCGCUCACUGCAAC CUCCG CCUCCCGGGU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10494	fU * fC * fU * fU * fG * fU * fA * fA * fC * mC * mC * mA * mG * mG * mC * mU * mG * mG * mA * mG * mU * fG * fC * fA * fA * fU * fG * fG * fU * fG	UCUUGUAACCCAGGC UGGAG UGCAAUGGUG	XXXXX XXXXX XXXXX XXXX XXXXX XXX
WV-10495	fA * fG * fU * fG * fA * fA * fC * fC * fC * mA * mA * mG * mG * mG * mA * mA * mG * mA * mU * mA * mA * fG * fU * fG * fU * fA * fU * fU * fA * fG	AGUGAACCCAAGGGA AGAUA AGUGUAUUAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10496	fU * fG * fA * fU * fU * fA * fA * fU * fU * mU * mA * mC * mC * mC * mC * mC * mA * mA * mU * fA * fA * fA * fU * fC * fA * fC * fC * fU * fU	UGAUUAAUUUACCCC CCAAA UAAAUCACUU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10497	fA * fC * fU * fG * fG * fC * fU * fG * fC * mC * mU * mU * mG * mC * mC * mU * mC * mA * mC * mC * mU * fG * fU * fC * fU * fC * fA * fU * fU * fU	ACUGGCUGCCUUGCC UCACC UGUCUCAUUU	XXXXX XXXXX XXXXX XXXX XXXXX XXX
WV-10498	fG * fG * fG * fA * fU * fA * fA * fA * fG * mC * mU * mC * mC * mA * mG * mU * mG * mA * mC * mC * fA * fC * fC * fA * fA * fC * fG * fC * fA	GGGAUAAAGCUCCAG UGACC CACAACAGCA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10499	fU * fU * fC * fC * fC * fA * fG * fG * fA * fG * fU * mU * mU * mC * mC * mC * mA * mA * mA * mG * mG * mG * mA * mU * fA * fA * fA * fG * fC * fU * fC * fC * fC * fA	UUCCAGAGUUUCCCA AGGGA UAAAGCUCCA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10500	fG * fG * fG * fG * fA * fA * fA * fA * fU * fA * mA * mC * mC * mU * mC * mU * mG * mG * mA * mG * mC * mA * mU * fG * fU * fA * fU * fU * fU * fU * fA * fC	GGGGAAAUAACUCUG AGGCA UGUAUUUUAC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10501	fC * fU * fU * fG * fA * fU * fG * fC * fU * mA * mG * mG * mG * mG * mA * mA * mA * mU * mA * mA * mC * fU * fC * fU * fG * fA * fG * fG * fC * fA	CUUGAUGCUAGGGGA AAUAA CUCUGAGGCA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-	fA * fC * fU * fA * fG * fC * fU * fC * fC * mC * mU * mU * mG * mA *	ACUAGCUCCCCUUGAU	XXXXX XXXXX

10502	mU * mG * mC * mU * mA * mG * fG * fG * fA * fA * fA * fU * fA * fA * fC	GCUAG GGGAAAUAAC	XXXXX XXXXX XXXXX XXXX
WV-10503	fC * fA * fG * fA * fG * fC * fA * fG * mC * mC * mU * mG * mU * mA * mU * mA * mU * mA * mU * fG * fA * fC * fU * fA * fA * fU * fU * fG	CAGAGGCAGCCUGUA UAUAA UGACUAAUUG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10504	fC * fU * fC * fC * fA * fG * fC * fU * fC * mC * mC * mA * mG * mA * mG * mG * mC * mA * mG * mC * mC * fU * fG * fU * fA * fU * fA * fU * fA * fA	CUCCAGCUCCCAGAG GCAGC CUGUAUAUAA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10505	fA * fU * fG * fC * fC * fU * fC * fC * fC * mC * mU * mC * mC * mA * mG * mC * mU * mC * mC * mA * fG * fA * fG * fC * fA * fG * fC * fC	AUGCCUCCCCUCCAG CUCCC AGAGGCAGCC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10506	fC * fA * fG * fG * fC * fA * fA * fC * fU * mG * mA * mU * mG * mC * mC * mU * mC * mC * mC * mU * fC * fC * fA * fG * fC * fU * fC * fC	CAGGCAACUGAUGCC UCCCC UCCAGCUCCC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10507	fA * fU * fG * fU * fG * fA * fC * fA * fA * fG * mG * mC * mU * mA * mG * mA * mC * mA * mU * mA * mC * mC * fA * fG * fG * fC * fA * fA * fC * fU * fG	AUGUGACAGGCUAGA CAUAC CAGGCAACUG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10508	fA * fG * fU * fG * fC * fC * fA * fG * fC * mA * mU * mU * mC * mA * mU * mG * mC * mC * mU * fG * fC * fA * fA * fG * fG * fC * fU * fU * fU	AGUGCCAGCAUUUCA UUGCC UGAAGGCUUU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10509	fA * fC * fC * fC * fA * fU * fC * fA * fG * mC * mC * mU * mG * mA * mU * mU * mU * mC * mC * mC * mA * fG * fU * fG * fC * fC * fA * fG * fC * fA	ACCCAUCAGCCUGAU UUCCC AGUGCCAGCA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10510	fC * fC * fA * fC * fU * fU * fC * fA * fG * mC * mA * mC * mC * mC * mA * mU * mC * mA * mG * mC * fU * fG * fA * fU * fU * fU * fC * fC * fC	CCACUUCAGCACCCA UCAGC CUGAUUUCCC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10511	fU * fC * fC * fC * fA * fU * fA * fU * fC * fC * mC * mU * mC * mA * mU * mC * mC * mU * mU * mG * mC * fC * fA * fC * fU * fU * fC * fA * fG * fC	UCCAUAUCCCCCUCAU CCUUG CCACUUCAGC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10512	fA * fA * fU * fU * fC * fU * fU * fG * fA * mU * mC * mC * mC * mU * mA * mG * mA * mA * mC * mC * mA * fA * fA * fU * fA * fU * fG * fA * fA * fU	AAUUCUUGAUCCCUA GAACC AAAUAUGAAU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10513	fA * fA * fC * fA * fU * fC * fA * fC * mA * mU * mA * mU * mA * mU * mA * mA * mA * fU * fU * fU * fA * fA * fC * fC * fU * fC	AACAUCAACACAUAUAU AUAAA AUUUUAACUC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-	fU * fU * fA * fU * fG * fC * fU * fA * mG * mA * mU * mG *	UUAUGGCUAGGAUG	XXXXX XXXXX

10514	mA * mU * mG * mA * mA * mC * mA * fA * fC * fA * fG * fG * fA * fU * fU * fC	AUGAAC AACAGGAUUC	XXXXX XXXXX XXXXX XXX
WV-10515	fG * fU * fA * fA * fA * fU * fG * fC * fU * mA * mG * mU * mC * mU * mG * mG * mA * mG * mA * mG * fA * fC * fA * fU * fU * fU * fA * fA	GUAAAUGCUAGUCUG GAGGA GACAUUUUAA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10516	fG * fG * fA * fA * fA * fA * fA * fU * fA * mA * mA * mU * mA * mU * mA * mA * mG * mU * mA * mG * fU * fA * fA * fU * fG * fC * fU * fA	GGAAAAAUAAAAUAU AUAGUA GUAAAUGCUA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10517	fG * fG * fC * fC * fA * fA * fC * fU * fU * mC * mU * mU * mU * mU * mA * mA * mC * mA * mA * mA * mU * mA * fC * fC * fC * fU * fA * fA * fA * fG * fA * fA * fU	GGCCAACUUCUUUUA ACAAU ACCUAAGAAU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10518	fA * fU * fG * fU * fU * fG * fC * fU * fU * mA * mU * mU * mU * mA * mA * mA * mA * mA * mU * mU * fA * fU * fU * fC * fA * fU * fU * fG * fU	AUGUUGCUUAUUUA AAAAAU UAUUCAUUGU	XXXXX XXXXX XXXXX XXXX XXXXX XXX
WV-10519	fC * fA * fA * fA * fC * fG * fU * fU * fA * mU * mC * mU * mC * mA * mC * mA * mU * mU * mU * mA * mU * fG * fU * fU * fG * fC * fU * fU * fA * fU	CAAACGUUAUCUCAC AUUUA UGUUGCUUAU	XXXXX XXXXX XXXXX XXXX XXXXX XXXX
WV-10520	fA * fG * fA * fC * fA * fU * fU * fU * mA * mA * mA * mU * mG * mU * mA * mA * mC * mU * mU * mC * fC * fA * fA * fC * fG * fU * fU * fA	AGACAUUUUAAAUG UAACUU CCAAACGUUA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10521	fC * fU * fA * fG * fA * fA * fU * fA * fA * mA * mG * mG * mA * mA * mA * mA * mU * mA * mA * mA * fA * fU * fA * fU * fA * fA * fG * fU	CUAGAAUAAAAGGA AAAAUA AAUAUAUAGU	XXXXX XXXXX XXXXX XXXX XXXXX XXX
WV-10522	fU * fU * fA * fU * fU * fU * fU * fA * fA * mA * mA * mA * mG * mG * mU * mA * mU * mC * mU * mU * fG * fA * fU * fC * fU * fA * fA * fC	UUAUUUUAAAAAGG UAUCUU UGAUACUAAC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10523	fU * fA * fU * fC * fA * fA * fA * fU * fG * mU * mA * mA * mC * mC * mA * mG * mU * mA * mU * mU * fU * fA * fU * fU * fU * fU * fA * fA * fA	UAUCAAAUGUAACCA GUAUU UUAUUUUAAA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10524	fU * fA * fC * fA * fA * fU * fC * fU * fA * mU * mG * mG * mU * mA * mU * mA * mA * mU * mU * mU * mU * fA * fU * fC * fA * fA * fA * fU * fG * fU	UACAAUCUAUGGUAU AAUUU UAUCAAAUGU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10525	fU * fA * fC * fA * fU * fU * fA * fA * fA * mC * mA * mU * mC * mA * mU * mU * mA * mA * mA * mU * mU * fA * fC * fA * fU * fC * fU * fA * fU	UACAUUAAACAUCAU UAAAU UACAAUCUAU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-	fU * fG * fA * fU * fU * fU * fU * fC * fU * mG * mU * mU * mA * mA *	UGAUUUUCUGUUAA	XXXXX XXXXX

10526	mU * mA * mA * mC * mU * mU * fA * fC * fA * fU * fU * fA * fA * fA * fC	UAACUU UACAUUAAAAC	XXXXX XXXXX XXXXX XXXX
WV-10527	fA * fU * fA * fA * fA * fU * fA * fU * fA * mC * mA * mA * mA * mG * mU * mC * mU * mA * mC * mU * mG * fU * fU * fC * fA * fU * fU * fU * fC * fA	AUAAAUAUACAAAG UCUACU GUUCAUUUCA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10528	fG * fG * fG * fU * fG * fA * fC * fA * fG * mU * mG * mA * mG * mA * mC * mU * mG * mU * mC * fU * fC * fU * fA * fA * fG * fA * fA	GGGUGACAGUGAGAC UCUGU CUCUAAGAAA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10529	fA * fC * fU * fU * fU * fA * fG * fC * fC * mU * mG * mG * mU * mG * mA * mC * mA * mG * mU * mG * fA * fG * fA * fC * fU * fC * fU * fG * fU	ACUUUAGCCUGGGUG ACAGU GAGACUCUGU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10530	fA * fG * fC * fC * fU * fG * fG * fU * mG * mA * mC * mA * mG * mU * mG * mA * mG * mA * mC * mU * fC * fU * fG * fU * fC * fU * fC * fU * fA	AGCCUGGGUGACAGU GAGAC UCUGUCUCUA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10531	fG * fA * fU * fU * fG * fU * fG * fC * fC * mA * mC * mU * mG * mC * mA * mC * mU * mU * mU * mA * mG * fC * fC * fU * fG * fG * fG * fU * fG * fA	GAUUGUGCCACUGCA CUUUA GCCUGGGUGA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10532	fA * fG * fG * fC * fU * fC * fA * fG * fU * mG * mA * mG * mC * mU * mA * mU * mG * mA * mU * mG * fU * fG * fC * fC * fA * fC * fU * fG * fC	AGGCUCAGUGAGCUA UGAUU GUGCCACUGC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10533	fG * fC * fA * fG * fG * fA * fG * fG * fA * mC * mU * mG * mC * mU * mU * mG * mA * mG * mC * mC * fC * fA * fG * fA * fG * fU * fU * fC * fA	GCAGGAGGACUGCUU GAGCC CCAGAGUUCA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10534	fG * fG * fA * fG * fG * fC * fU * fG * fA * mG * mG * mC * mA * mG * mG * mA * mG * mA * mC * mU * fG * fC * fU * fU * fG * fA * fG * fC	GGAGGCUGAGGGCAGG AGGAC UGCUUGAGCC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10535	fU * fA * fC * fU * fA * fG * fG * fA * mG * mG * mC * mU * mG * mA * mG * mC * mA * mG * mG * fA * fG * fG * fA * fC * fU * fG * fC	UACUAGGGAGGCUGA GGCAG GAGGACUGCU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10536	fA * fC * fA * fC * fG * fC * fC * fU * fG * mG * mC * mU * mA * mG * mU * mA * mG * mU * mC * mC * mC * fA * fG * fC * fU * fA * fC * fU * fA * fG	ACACGCCUGGCUAGU AGUCC CAGCUACUAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10537	fG * fC * fG * fU * fG * fG * fU * fG * fG * mU * mA * mC * mA * mC * mG * mC * mC * mU * mG * mC * fU * fA * fG * fU * fA * fG * fU * fC * fC	GCGUGGUGGUACACG CCUGG CUAGUAGUCC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-	fA * fG * fG * fC * fC * fA * fG * fG * mU * mU * mC * mA *	AGGCCAAGAGUUCAA	XXXXX XXXXX

10538	mA * mG * mA * mA * mC * mC * mC * fA * fU * fC * fU * fC * fU * fA * fC * fA	GAACC CAUCUCUACA	XXXXX XXXXX XXXXX XXXX
WV-10539	fC * fA * fA * fG * fG * fA * fA * fG * fG * mA * mG * mA * mA * mU * mU * mG * mC * mU * mU * mG * mA * fG * fG * fC * fC * fA * fA * fA * fG * fA * fG	CAAGGAAGGAGAAU UGCUUG AGGCCAAGAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10540	fU * fU * fU * fU * fG * fG * fG * fA * fG * fG * mC * mC * mA * mA * mG * mG * mA * mA * mG * mG * mA * mG * fA * fA * fU * fU * fG * fC * fU * fU * fG	UUUGGGAGGCCAAGG AAGGA GAAUUGCUUG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10541	fC * fA * fU * fG * fC * fU * fA * fA * fC * mU * mC * mA * mU * mG * mC * mC * mU * mG * mU * mA * mA * fU * fC * fC * fU * fA * fG * fU * fG * fC	CAUGCUAACUCAUGC CUGUA AUCCUAGUGC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10542	fU * fC * fA * fA * fA * fA * fG * fU * fC * fU * mU * mA * mC * mU * mG * mG * mC * mU * mA * mG * mC * mC * fA * fU * fG * fC * fU * fA * fA * fC * fU	UCAAAAGUCUACUGG CUAGG CAUGCUAACU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10543	fC * fU * fA * fG * fG * fA * fA * fG * fG * mA * mA * mU * mU * mA * mA * mG * mC * mC * mC * mG * mA * fA * fU * fG * fG * fU * fU * fG * fG * fA * fC	CUAGGAAGGAAUUA AGCCCG AAUGGUUGAC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10544	fA * fA * fG * fA * fU * fA * fU * fG * fA * mA * mA * mG * mA * mG * mU * mA * mG * mA * mC * mC * mU * fG * fU * fA * mA * mG * mG * fU * fU * fU * fA * fC * fU * fU * fU	AAGAUAUGAAAGAG UAGACC UGUUACUUUU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10545	fA * fC * fC * fC * fC * fA * fC * fU * fC * fA * mC * mC * mC * mC * mA * mU * mU * mU * mC * mU * mU * mU * fG * fA * fU * fC * fC * fA * fA * fG * fG * fG	ACCCACUCACCCCCA UUUCU UGAUCCAGGG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10546	fA * fG * fU * fA * fC * fU * fC * fC * fU * mU * mA * mU * mU * mC * mC * mU * mC * mC * mC * mA * fA * fU * fC * fC * fU * fG * fA * fU * fA	AGUACUCCUUAUUCC UCCCC AAUCCUGAUA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10547	fA * fG * fA * fA * fU * fG * fG * fG * mG * mG * mA * mG * mA * mA * mA * mG * mU * mG * mA * fG * fA * fG * fU * fA * fC * fU * fC * fC * fU	AGAAUGGGGGGAGA AAGUGA GAGUACUCCU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10548	fA * fU * fU * fU * fU * fG * fA * fG * fG * fA * mA * mA * mU * mU * mU * mC * mA * mG * mA * mG * mG * mA * fA * fA * fG * fA * fG * fA * fA * fG * fA * fG	AUUUGAGGAAAUUU CAGAGG AAAGAGAAAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10549	fU * fA * fG * fA * fC * fC * fU * fA * fC * fU * mA * mA * mG * mC * mA * mG * mA * mC * mA * mG * mA * mU * fA * fU * fU * fG * fA * fG * fG * fA	UAGACUACUAAGCAG ACAGA UAUUUGAGGA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-	fU * fC * fU * fU * fU * fU * fA * fU * fC * mC * mU * mG * mA * mG *	UCUUUUAUCCUGAGG	XXXXX XXXXX

10550	mG * mA * mA * mU * mU * mA * mU * fA * fG * fA * fC * fU * fA * fC * fU * fA	AAUUA UAGACUACUA	XXXXX XXXXX XXXXX XXX
WV-10551	fU * fA * fA * fG * fU * fU * fU * fG * fA * mA * mG * mG * mG * mA * mU * mU * mA * mA * mA * mC * mG * fC * fA * fU * fG * fC * fA * fA * fA * fG	UAAGUUUGAAGGGA UUAAAC GCAUGCAAAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10552	fC * fC * fU * fC * fC * fU * fA * fC * fC * mA * mU * mG * mU * mU * mA * mC * mU * mU * mC * mC * mC * fU * fG * fC * fC * fU * fC * fA * fA * fA * fA	CCUCCUACCAUGUUA CUUCC CUGCUCAAAA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10553	fC * fA * fA * fG * fU * fG * fC * fC * fC * mA * mA * mU * mC * mU * mG * mA * mU * mC * mA * mA * mC * fC * fU * fC * fC * fU * fA * fC * fC * fA	CAAGUGCCCAAUCUG AUCAA CCUCCUACCA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10554	fA * fU * fA * fG * fA * fG * fG * fU * mU * mU * mU * mG * mA * mU * mC * mA * mA * mG * mU * mG * fC * fC * fC * fA * fA * fU * fC * fU * fG	AUAGAGGGUUUUGA UCAAGU GCCCAAUCUG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10555	fC * fC * fA * fU * fG * fU * fU * fG * fG * mG * mG * mG * mA * mC * mA * mG * mC * mU * mC * mC * mU * fA * fA * fG * fA * fA * fU * fG * fG * fC	CCAUGUUGGGGGACA GCUCC UAAGAAUGGC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10556	fU * fA * fU * fA * fC * fA * fU * fA * fA * mU * mU * mU * mC * mC * mA * mG * mC * mC * mU * mG * fG * fC * fC * fC * fA * fU * fA * fA * fA * fA	UAUACAUAAUUUCCA GGCCU GGCCAUAAAA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10557	fU * fG * fG * fC * fC * fU * fA * fU * fG * fA * mC * mA * mG * mA * mA * mU * mU * mG * mG * mC * mU * fA * fA * fA * fG * fC * fU * fC * fA	UGGCUAUGACAGAGA UUGGC UAAAAGCUCA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10558	fU * fA * fG * fC * fA * fG * fC * fU * fC * mA * mG * mG * mU * mC * mC * mC * mU * mU * mC * mG * mA * fU * fA * fA * fA * fU * fG * fG * fC	UAGCAGCUCAGGUCC CUUCG AUAAAAUGGC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10559	fA * fG * fA * fU * fU * fC * fU * fA * fU * mA * mU * mA * mU * mU * mA * mC * mA * mU * mA * mG * mU * fC * fA * fG * fC * fA * fC * fC * fA * fG * fG	AGAUUCUAUAUAUU ACAUAG UCAGACCAGG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10560	fA * fG * fA * fA * fU * fA * fA * fC * fC * mA * mC * mA * mU * mG * mA * mU * mU * mC * mU * mA * mU * fA * fU * fU * fA * fU * fC * fA * fU	AGAAUAACCACACAUGA UUCUA UAUAUUACAU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10561	fC * fU * fA * fU * fC * fA * fC * fU * fG * mU * mA * mU * mG * mC * mC * mU * mC * mU * mC * mA * mU * fC * fU * fC * fC * fU * fC * fU * fC	CUAUCACUGUAUGCC UCUCA UCUCUCCUUC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-	fC * fU * fA * fC * fC * fA * fG * fA * fG * mU * mC * mC * mU * mC	CUACCAGAGUCCUCU	XXXXX XXXXX

10562	mU * mU * mG * mC * mC * mC * mU * fA * fG * fU * fC * fA * fA * fA * fU * fC	UGCCC UAGUCAAAUC	XXXXX XXXXX XXXXX XXX
WV-10563	fA * fU * fU * fC * fC * fU * fA * fA * fA * mC * mC * mA * mG * mA * mG * mC * mA * mC * mA * fA * fC * fA * fA * fA * fA * fU	AUUCCUAAACACAGA GCACA AACAAAAAAU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10564	fA * fA * fA * fC * fC * fA * fA * fU * fA * mU * mA * mU * mA * mA * mA * mG * mU * mG * mA * fC * fU * fA * fG * fC * fA * fU * fA * fC	AAACCAAUAUAUAUA AAGUG ACUAGCAUAC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10565	fC * fA * fA * fA * fG * fA * fG * fU * fG * mU * mU * mU * mU * mG * mA * mA * mA * mG * mG * mA * fU * fG * fA * fA * fA * fU * fA * fA	CAAAGAGUGUUUUU GAAAGG AUGAAAUAAA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10566	fG * fA * fA * fG * fA * fG * fG * fA * fA * mG * mC * mC * mU * mG * mU * mG * mA * mG * mU * mC * fA * fU * fC * fU * fA * fC * fA * fA * fG	GAAGAGGAAGCCUGU GAGGU CAUCUACAAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10567	fA * fG * fA * fC * fA * fA * fU * fU * fG * mG * mA * mA * mG * mA * mG * mA * mA * mG * mC * mC * fU * fG * fU * fG * fA * fG * fG * fU * fC	AGACAAUUGGAAGA GGAAGC CUGUGAGGUC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10568	fA * fC * fC * fA * fU * fU * fU * fU * fA * mU * mU * mU * mG * mC * mU * mC * mC * mU * mA * mC * fC * fU * fU * fU * fU * fA * fG * fA * fA	ACCAUUUUAUUUGCU CCCUA CCUUUUAGAA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10569	fC * fG * fG * fA * fG * fC * fA * fA * fG * mG * mG * mG * mU * mG * mU * mU * mG * mC * mU * mU * fU * fA * fG * fC * fC * fA * fA * fU * fU * fU	CGGAGCAAGGGGGUG UUGCU UUAGCCAUUU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10570	fA * fU * fC * fU * fU * fA * fG * fC * mA * mC * mA * mC * mA * mG * mA * mC * mU * mC * mA * fA * fA * fG * fA * fC * fA * fU * fU	AUCUUAGGCACACAG ACUCA GAAAGAACUU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10571	fC * fC * fU * fU * fG * fU * fG * fA * fG * mG * mC * mU * mC * mA * mC * mA * mG * mC * mU * mC * fU * fC * fU * fG * fU * fU * fA * fA	CCUUGUGAGGCUCAC AGGCU CUCUUGUUAA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10572	fA * fA * fU * fC * fA * fC * fA * fG * fC * mU * mC * mU * mC * mC * mA * mA * mG * mC * mU * mG * fU * fA * fG * fA * fC * fA * fU * fA * fG	AAUCACAGCUCUCCA AGGCU GUAGACAUAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10573	fG * fA * fG * fG * fU * fG * fC * fU * fG * mC * mA * mA * mA * mG * mG * mA * mG * mC * mU * mG * fG * fC * fU * fG * fC * fU * fG * fA	GAGGUGCUGCAAAGG AGGCU GGCUGCUGUA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-	fA * fC * fU * fG * fG * fC * fU * fC * fA * mA * mU * mU * mU *	ACUGGCUCAAAUUUU	XXXXX XXXXX

10574	mU * mA * mA * mG * mA * mG * mU * fU * fA * fU * fA * fA * fC * fA * fG * fU	AAGAG UUAUAACAGU	XXXXX XXXXX XXXXX XXXX
WV-10575	fU * fA * fA * fA * fU * fG * fU * fC * fA * mG * mA * mC * mC * mA * mG * mC * mA * mA * mG * mG * mA * fC * fA * fU * fA * fA * fA * fG * fA * fU	UAAAUGUCAGACCAG CAAGG ACAUAAAGAU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10576	fU * fU * fU * fU * fU * fC * fU * fA * fA * mA * mU * mA * mA * mA * mA * mG * mG * mA * mG * mA * fG * fU * fU * fU * fU * fU * fU * fC * fU	UUUUUCUAAAUAAA AGGAGG AGUUUUUUCU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10577	fA * fG * fC * fC * fC * fA * fC * fC * fG * fC * mG * mC * mC * mC * mG * mG * mC * mC * mU * mC * mA * mC * fC * fA * fU * fU * fC * fU * fU * fU * fU * fU	AGCCACCGCGCCCGG CCUCA CCAUUCUUUU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10578	fC * fU * fG * fC * fC * fC * fU * fC * fG * fG * mC * mC * mU * mC * mC * mC * mA * mA * mA * mG * mU * mG * fC * fU * fG * fG * fG * fA * fU * fU * fA	CUGCCUCGGGCCUCCC AAAGU GCUGGGAUUA	XXXXX XXXXX XXXXX XXXX XXXXX XXXX
WV-10579	fC * fG * fU * fG * fA * fU * fC * fU * fG * mC * mC * mU * mG * mC * mC * mU * mC * mG * mC * mC * fU * fC * fC * fC * fA * fA * fA * fG * fU	CGUGAUCUGCCUGCC UCGGC CUCCCAAAGU	XXXXX XXXXX XXXXX XXXX XXXXX XXXX
WV-10580	fG * fU * fA * fU * fU * fU * fU * fA * mG * mU * mA * mG * mA * mA * mC * mA * mG * mG * fU * fU * fU * fC * fA * fC * fC * fC * fA * fU	GUAUUUUUAGUAGA GACAGG GUUUCACCAU	XXXXX XXXXX XXXXX XXXX XXXXX XXXX
WV-10581	fG * fC * fA * fU * fG * fC * fA * fG * fC * mA * mC * mC * mA * mC * mG * mC * mA * mG * mC * fU * fA * fG * fU * fU * fU * fU * fU * fU * fG	GCAUGCAGCACCACG CCAGG CUAGUUUUUG	XXXXX XXXXX XXXXX XXXX XXXXX XXXX
WV-10582	fC * fA * fA * fG * fU * fA * fG * fC * fU * mG * mG * mG * mA * mC * mU * mA * mC * mA * mG * mC * fA * fU * fG * fC * fA * fG * fC * fC * fA	CAAGUAGCUGGGACU ACAGG CAUGCAGCAC	XXXXX XXXXX XXXXX XXXX XXXXX XXXX
WV-10583	fC * fC * fC * fU * fC * fA * fG * fC * fC * fU * mC * mC * mC * mA * mA * mG * mU * mA * mG * mC * mU * mG * fG * fG * fA * fC * fU * fA * fC * fC	CCUCAGCCUCCCAAG UAGCU GGGACUACAG	XXXXX XXXXX XXXXX XXXX XXXXX XXXX
WV-10584	fU * fU * fU * fG * fG * fG * fA * fG * fA * mG * mA * mC * mA * mG * mA * mA * mA * mU * mC * mU * mG * fG * fA * fU * fU * fG * fG * fC * fC	UUUGGGAGAGACAG AAAUCU GGGAUUGGCC	XXXXX XXXXX XXXXX XXXX XXXXX XXXX
WV-10585	fA * fC * fC * fC * fU * fA * fU * fU * fC * fA * mC * mU * mG * mG * mG * mA * mG * mG * mU * mU * mG * fG * fA * fG * fG * fA * fA * fC * fC	ACCUAUUCACUGGGA GGUUG UGAGGAACAC	XXXXX XXXXX XXXXX XXXX XXXXX XXXX
WV-	fU * fG * fC * fA * fG * fA * fU * fG * mA * mG * mC * mA * mU *	UGCAGAGUGAGCAUG	XXXXX XXXXX

10586	mG * mG * mA * mG * mA * mA * mG * fA * fU * fA * fA * fU * fG * fA * fG * fU	GAGAA GAUAAUGAGU	XXXXX XXXXX XXXXX XXXX
WV-10587	fG * fG * fU * fU * fU * fA * fG * fG * fU * mG * mC * mC * mU * mG * mU * mU * mA * mG * mA * mU * mA * fG * fU * fG * fU * fG * fC * fU * fA	GGUUUAGGUGCCUGU UAGAU AGUGGUGCUA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10588	fA * fA * fA * fG * fG * fG * fU * fU * fU * mA * mA * mG * mA * mC * mA * mG * mA * mU * mU * mA * mC * fC * fU * fG * fC * fU * fU * fU * fC * fU	AAAGGGUUUAAGAC AGAUUA CCUGGCUUCU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10589	fC * fU * fA * fU * fC * fC * fC * fU * fC * mU * mG * mU * mG * mC * mA * mU * mC * mC * mC * mA * fC * fA * fC * fA * fU * fC * fC * fA * fU	CUAUCCCUCUGUGCA UCCCC ACACAUCCAU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10590	fU * fU * fA * fU * fA * fG * fG * fC * fU * mA * mG * mA * mG * mA * mC * mU * mC * mA * mC * mU * mC * fA * fA * fU * fA * fA * fU * fC * fC * fA	UUAUAGGCUAGAGAC UCACU CAAUAAUCCA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10591	fU * fA * fU * fG * fC * fU * fU * fU * mU * mC * mA * mC * mC * mC * mU * mU * mG * mA * mC * mC * fU * fU * fC * fA * fC * fU * fG * fU	UAUGCUUUUUCACCC UUGAC CUUCAACUGU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10592	fC * fU * fU * fG * fG * fG * fU * fG * mU * mG * mC * mA * mU * mC * mC * mA * mC * mU * mG * fA * fG * fG * fU * fA * fU * fG * fC	CUUGGGGUGUGCAUC CCACU GAGGGUAUGC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10593	fU * fA * fC * fC * fU * fU * fU * fA * fG * fU * mA * mC * mA * mC * mA * mU * mA * mC * mU * mU * mG * mG * fG * fA * fC * fU * fU * fU * fU * fU * fC	UACUUUAGUACACAU ACUUG GGACUUUUUC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10594	fC * fA * fA * fC * fU * fU * fU * fA * fU * fC * mA * mU * mA * mG * mC * mA * mG * mC * mU * mA * mC * fU * fU * fU * fA * fG * fU * fA * fC * fA	CAACUUAUCAUAGCA GGCUA CUUUAGUACA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10595	fA * fU * fU * fU * fC * fC * fA * fU * fU * mA * mC * mA * mA * mA * mC * mC * mC * mU * mU * mU * mU * fU * fC * fA * fC * fU * fU * fU * fA * fU	AUUCCAAUUACAAAC CCUUU UUCAACUUAU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10596	fA * fA * fA * fA * fA * fU * fA * fU * fA * fG * mU * mC * mC * mC * mC * mA * mG * mA * mA * mU * mA * mA * fU * fU * fA * fA * fA * fA * fC * fU * fC	AAAAUAUAGUCCCCA GAAUA AUUAAAACUC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10597	fU * fA * fG * fA * fA * fA * fG * fA * fC * mC * mC * mC * mA * mC * mA * mA * mA * mC * mU * mA * fG * fU * fA * fU * fG * fA	UAGAAAGACCCCACA AAACU AGUGAUUGUA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-	fC * fU * fC * fC * fA * fG * fC * fC * fU * mG * mG * mU * mG *	CUCCAGCCUGGGUGA	XXXXX XXXXX

10598	mA * mC * mA * mG * mA * mG * mC * fA * fA * fA * fC * fU * fC * fC * fA	CAGAG CAAAACUCCA	XXXXX XXXXX XXXXX XXXX
WV-10599	fU * fU * fG * fA * fA * fC * fC * fC * fG * mG * mG * mA * mG * mG * mC * mA * mG * mA * mG * mU * fU * fG * fC * fA * fG * fU * fG * fA * fG	UUGAACCCGGGAGGC AGAGG UUGCAGUGAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10600	fA * fG * fG * fC * fU * fG * fA * fG * fG * mC * mA * mG * mG * mA * mG * mA * mA * mU * mC * mA * mC * fU * fU * fG * fA * fA * fC * fC * fC * fG	AGGCUGAGGCAGGAG AAUCA CUUGAACCCG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10601	fG * fC * fU * fA * fC * fU * fC * fA * fG * mG * mA * mG * mG * mC * mU * mG * mA * mG * mC * mA * fG * fG * fA * fA * fA * fU * fC * fA	GCUACUCAGGAGGCU GAGGC AGGAGAAUCA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10602	fA * fG * fC * fC * fA * fC * fG * fC * mC * mU * mG * mU * mA * mA * mU * mC * mC * mA * mG * fC * fU * fA * fC * fC * fU * fC * fA * fG * fG	AGCACACGGCCUGUAA UCCCA GCUACUCAGG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10603	fA * fG * fC * fC * fU * fG * fA * fC * fC * mG * mA * mC * mA * mU * mG * mC * mU * mG * mA * mA * mA * fC * fC * fC * fA * fG * fU * fC * fU * fC	AGCCUGACCGACAUG CUGAA ACCCAGUCUC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10604	fG * fU * fU * fC * fG * fA * fG * fA * fC * mC * mA * mG * mC * mC * mU * mG * mA * mC * mC * mA * fC * fA * fU * fG * fC * fU * fG * fC * fA * fA	GUUCGAGACCAGCCU GACCG ACAUGCUGAA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10605	fG * fG * fU * fC * fU * fC * fU * fU * fG * fG * mG * mA * mG * mG * mC * mC * mA * mA * mA * mG * mC * mG * fG * fU * fG * fG * fA * fU * fC * fA	GGUCUCUGGGAGGCC AAAGC GGGUGGAUCA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10606	fG * fC * fU * fC * fA * fC * fG * fC * fC * mU * mG * mU * mA * mA * mU * mC * mC * mC * mA * mG * fU * fC * fC * fU * fC * fU * fG * fG * fG * fA	GCUCACGCCUGUAAU CCCAG GUCUCUGGGA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10607	fG * fG * fU * fG * fG * fC * fU * fC * fA * mC * mG * mC * mC * mU * mG * mU * mA * mA * mU * mC * mC * fC * fC * fA * fG * fG * fU * fC * fU * fC * fU	GGUGGCUCACGCCUG UAAUC CCAGGUCUCU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10608	fU * fU * fU * fU * fU * fU * fA * fA * fU * fU * mA * mA * mC * mC * mC * mC * mU * mG * mU * mU * mG * mC * mC * fU * fC * fC * fC * fA * fC * fA * fA * fG	UUUUUAAUUAACCCU GUUGC CUCCACAAAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10609	fU * fA * fA * fA * fG * fA * fG * fC * fA * mA * mG * mG * mG * mA * mG * mA * mG * mA * mA * mG * mG * fA * fC * fA * fA * fG * fA * fA * fU	UAAAGAGCAAGGGA GAGAAG GUCAAAGAAU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-	fU * fG * fA * fU * fG * fA * fC * fA * fA * mG * mG * mU * mC *	UGAUGACAGAGGUCA	XXXXX XXXXX

10610	mA * mG * mC * mC * mU * mC * mC * fC * fA * fG * fA * fA * fU * fA * fA * fA	GCCUC CCAGAAUAAA	XXXXX XXXXX XXXXX XXXX
WV-10611	fG * fC * fA * fU * fG * fG * fA * fG * mC * mC * mC * mA * mA * mU * mG * mA * mU * mG * mA * mC * fA * fG * fA * fG * fU * fC * fA * fG	GCAUGGGAGCCCAAU GAUGA CAGAGGUCAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10612	fG * fA * fA * fG * fC * fC * fA * fA * fA * mG * mG * mG * mC * mA * mU * mG * mG * mG * mA * mG * mC * fC * fC * fA * fA * fU * fG * fA * fU * fG	GAAGCCAAAGGGCAU GGGAG CCCAAUGAUG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10613	fA * fU * fA * fU * fC * fU * fG * fA * mC * mC * mU * mC * mA * mC * mU * mU * mA * mC * mC * fU * fC * fC * fU * fG * fU * fC * fU * fU	AUAUCUUGACCUCAC UUUAC CUCCUGUCUU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10614	fA * fA * fC * fC * fU * fC * fA * fA * fA * mG * mG * mG * mA * mG * mG * mA * mA * mU * mU * mA * fG * fG * fA * fA * fG * fA * fU * fA * fA	AACCUCAAAGGGAGG GAAUU AGGAGAAUAA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10615	fG * fG * fA * fC * fA * fU * fA * fG * fU * mC * mA * mG * mC * mC * mU * mG * mU * mG * mG * mC * mA * fA * fC * fC * fU * fC * fA * fA * fA * fG	GGACAUAGUCAGCCU GUGGC AACCUCAAAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10616	fU * fG * fA * fG * fA * fA * fA * fC * fC * mA * mC * mC * mC * mU * mG * mA * mA * mA * mG * mA * fG * fC * fA * fA * fU * fA * fA * fC * fC	UGAGAAACCACCCUG AGAAG AGCAAUAACC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10617	fA * fU * fG * fA * fG * fG * fG * fA * mG * mG * mA * mA * mA * mA * mG * mU * mG * mC * fC * fA * fA * fA * fG * fC * fA * fG	AUGAGGGGAGGGAA AAGUGG CCAAAAGCAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10618	fG * fG * fC * fC * fC * fA * fA * fG * fG * mG * mA * mU * mG * mA * mG * mG * mA * mG * fG * fA * fA * fG * fU * fG * fG	GGCCCAAGGGAUGAG GGGAG GGAAAAGUGG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10619	fA * fC * fU * fA * fC * fA * fU * fC * fU * mA * mG * mG * mC * mC * mC * mA * mA * mG * mG * mG * mA * fU * fG * fA * fG * fG * fG * fG * fA * fG	ACUACAUCUAGGCCC AAGGG AUGAGGGGAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10620	fA * fU * fA * fA * fA * fA * fC * fC * fC * mU * mU * mC * mA * mA * mU * mG * mU * mU * mU * mC * mC * fC * fU * fA * fC * fU * fG * fU * fC * fU	AUAAAACCCUUCAAU GUUUC CCUACUGUCU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10621	fA * fC * fU * fG * fC * fA * fC * fU * fC * mC * mU * mC * mU * mU * mA * mU * mA * mA * mA * fC * fC * fC * fU * fC * fC * fA * fA * fU	ACUGCACUCCCUCUU AUAAA ACCCUUCAAU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-	fU * fG * fU * fA * fA * fU * fU * fC * mU * mA * mC * mC * mC *	UGUAAAUUCUACCCC	XXXXX XXXXX

10622	mC * mA * mA * mU * mU * mA * mA * fA * fG * fA * fU * fU * fA * fA * fA * fA	AAUUA AAGAUUAAAA	XXXXX XXXXX XXXXX XXXX
WV-10623	fC * fU * fC * fC * fC * fA * fG * fA * fC * mC * mA * mA * mA * mU * mC * mU * mC * mU * mG * mU * fU * fU * fU * fA * fG * fA * fA * fU * fG	CUCCCAGACCCAAAU CUCUG UUUUAGAAUG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10624	fC * fC * fC * fU * fC * fA * fC * fA * fU * mC * mC * mA * mU * mA * mA * mG * mA * mG * mG * mC * mU * fC * fU * fA * fU * fA * fU * fC * fA * fU	CCCUCACAUCCAUAA GAGGC UCUAUAUCAU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10625	fC * fA * fU * fU * fU * fU * fU * fU * fG * mC * mC * mC * mU * mC * mA * mA * mC * mC * mU * mC * mC * mA * fU * fA * fA * fA * fG * fA * fG * fG * fC * fU	CAUUUUUUGCCCUCA CAUCC AUAAGAGGCU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10626	fU * fA * fA * fG * fC * fG * fU * fC * fA * mC * mC * mC * mA * mA * mC * mA * mC * mC * mU * mC * mA * fU * fA * fU * fA * fA * fU * fU * fA * fG	UAAGCGUCACCCAAC ACCUC AUAUAAUUAG	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10627	fC * fU * fA * fC * fC * fU * fU * fU * fA * fU * mC * mC * mC * mU * mU * mA * mA * mG * mC * mA * mU * mG * fA * fA * fA * fC * fC * fU * fG * fA * fU	CUACUUUAUCCCUUA AGCAU GAAACCUGAU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10628	fC * fC * fA * fA * fA * fG * fA * fG * fG * fG * mA * mG * mG * mU * mA * mC * mU * mA * mA * mU * mA * mU * mA * fG * fA * fA * fU * fU * fC * fU * fA * fC * fU	CCAAGAGGGAGGUAC UAUAU AGAUUCUACU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10629	fG * fU * fG * fG * fA * fG * fC * fC * fC * fA * fC * mC * mC * mG * mC * mC * mU * mG * mG * mC * mC * mA * fA * fC * fU * fU * fU * fC * fU * fU * fU * fU	GUGAGCCACCGCGCC UGGCC AACUUCUUUU	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10630	fU * fC * fG * fG * fC * fC * fC * fU * fC * fC * mC * mA * mA * mA * mG * mU * mG * mC * mU * mG * mG * mG * fA * fU * fU * fA * fC * fC * fA * fG * fG * fC	UCGGCCUCCCAAAGU GCUGG GAUUACAGGC	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-10634	fU * RfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * RmGmGfC * SfA * SfU * RfU * RfU * RfC * SfU	UCAAGGAAGAUGGCA UUUCU	RSSSSOSO SROOSSRRRS
WV-10635	fU * SfC * RfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * RfA * SfU * SfU * SfU * SfC * RfU	UCAAGGAAGAUGGCA UUUCU	SRSSSSOSO SSOORSSSSR
WV-10636	fU * SfC * SfA * RfA * RfG * SfG * SmAfA * RmGmA * SfU * SmGmGfC * SfA * RfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSRRSSORO SSOOSRSSSS
WV-10637	fU * SfC * SfA * SfA * SfG * RfG * RmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSRROSO SSOOSSSSSS
WV-10670	fC * SfU * SfC * SfC * SfG * SfG * SmU * SmU * SmCmU * SmG * SmA * SmAmG * SfG * SfU * SfG * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSO SSSOSSSSSS

WV-10671	fC * SfU * SfC * SfC * SfG * SfG * SmU * SmU * SmC * SmU * SmG * SmA * SmAmGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSS SSSOOSSSSS
WV-10672	fC * SfU * SfC * SfC * SfG * SfG * SmU * SmU * SmCmU * SmG * SmA * SmAmGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSO SSSOOSSSSS

WV-10868	fU * RfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	RSSSSS O S O SS O O SSSSSS
WV-10869	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * RmGmGfC * SfA * SfU * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSS O S O SR O O SSSSSS
WV-10870	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * RfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSS O S O SS O O SSSSRS
WV-10871	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * RfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSS O S O SS O O SSSRSS
WV-10872	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * RfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSS O S O SS O O SSRSSS
WV-10873	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * RfU	UCAAGGAAGAUGGCA UUUCU	SSSSSS O S O SS O O SSSSSR
WV-10874	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * RfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSS O S O SS O O RSSSSS
WV-10875	fU * SfC * RfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SRSSSS O S O SS O O SSSSSS
WV-10876	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * RfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSS O S O SS O O SRSSSS
WV-10877	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * RmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSS O R O SS O O SSSSSS
WV-10878	fU * SfC * SfA * SfA * SfA * RfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSRSS O S O SS O O SSSSSS
WV-10879	fU * SfC * SfA * RfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSRSSS O S O SS O O SSSSSS
WV-10880	fU * SfC * SfA * SfA * SfG * RfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSRS O S O SS O O SSSSSS
WV-10881	fU * SfC * SfA * SfA * SfG * SfG * RmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSR O S O SS O O SSSSSS
WV-10882	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * RfU * SmGmGfC * SfA * SfU * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSS O S O RS O O SSSSSS
WV-Mod012L001	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU *	UCAAGGAAGAUGGCA	O SSSSSS O S O SS

10883	SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UUUCU	O O SSSSS
WV-10884	Mod085L001fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	O SSSSS O S O SS O O SSSSS
WV-10885	Mod086L001fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	O SSSSS O S O SS O O SSSSS
WV-10886	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfUL004Mod012	UCAAGGAAGAUGGCA UUUCU	SSSSS O S O SS O O SSSSSO
WV-10887	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfUL004Mod085	UCAAGGAAGAUGGCA UUUCU	SSSSS O S O SS O O SSSSSO
WV-10888	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfUL004Mod086	UCAAGGAAGAUGGCA UUUCU	SSSSS O S O SS O O SSSSSO
WV-11047	fU * SfU * SfA * SfA * SfA * SmA * SmG * SmU * SmC * SmU * SmG * SmC * SmU * SfA * SfA * SfU * SfG	UUAAAAAGUCUGCUA AAAUG	SSSSSSSS SSSSSSSSS
WV-11048	fA * SfA * SfG * SfU * SfC * SfU * SmG * SmC * SmU * SmA * SmA * SmA * SmU * SfG * SfU * SfU * SfC	AAGUCUGCUAAAAUG UUUUC	SSSSSSSS SSSSSSSSS
WV-11049	fU * SfG * SfC * SfU * SfA * SfA * SmA * SmA * SmU * SmG * SmU * SmU * SmU * SmU * SfC * SfA * SfU * SfU * SfC * SfC	UGCUAAAAUGUUUUC AUUCC	SSSSSSSS SSSSSSSSS
WV-11050	fA * SfA * SfA * SfU * SfG * SfU * SmU * SmU * SmC * SmA * SmU * SmU * SmC * SfC * SfU * SfA * SfU * SfU * SfA	AAAUGUUUUCAUUCC UAUUA	SSSSSSSS SSSSSSSSS
WV-11051	fU * SfU * SfU * SfU * SfC * SfA * SmU * SmU * SmC * SmC * SmC * SmU * SmA * SmU * SmU * SfA * SfG * SfA * SfU * SfC * SfU	UUUUCAUUCCUAUUA GAUCU	SSSSSSSS SSSSSSSSS
WV-11052	fA * SfU * SfU * SfC * SfC * SfU * SmA * SmU * SmU * SmA * SmG * SmA * SmU * SmC * SfU * SfG * SfU * SfC * SfG * SfC	AUUCCUAUUAGAUCU GUCGC	SSSSSSSS SSSSSSSSS
WV-11053	fU * SfA * SfU * SfU * SfA * SfG * SmA * SmU * SmC * SmU * SmG * SmU * SmC * SmG * SfC * SfC * SfC * SfU * SfA * SfC	UAUUAGAUCUGUCGC CCUAC	SSSSSSSS SSSSSSSSS
WV-11054	fG * SfA * SfU * SfC * SfU * SfG * SmU * SmC * SmG * SmC * SmC * SmC * SmU * SmA * SfC * SfC * SfU * SfC * SfU * SfU	GAUCUGUCGCCCUAC CUCUU	SSSSSSSS SSSSSSSSS
WV-11055	fG * SfU * SfC * SfG * SfC * SfC * SmC * SmU * SmA * SmC * SmC * SmU * SmC * SmU * SfU * SfU * SfU * SfU * SfC	GUCGCCCUACCUCUU UUUUC	SSSSSSSS SSSSSSSSS
WV-11056	fC * SfC * SfU * SfA * SfC * SfC * SmU * SmC * SmU * SmU * SmU * SmU * SmU * SfC * SfU * SfG * SfU * SfC * SfU	CCUACCUCUUUUUUC UGUCU	SSSSSSSS SSSSSSSSS
WV-11057	fC * SfU * SfC * SfU * SfU * SfU * SmU * SmU * SmU * SmC * SmU * SmG * SmU * SmC * SfU * SfG * SfA * SfC * SfA * SfG	CUCUUUUUUCUGUCU GACAG	SSSSSSSS SSSSSSSSS
WV-11058	fU * SfU * SfU * SfU * SfC * SfU * SmG * SmU * SmC * SmU * SmG * SmA * SmC * SmA * SfG * SfC * SfU * SfG * SfU * SfU	UUUUCUGUCUGACAG CUGUU	SSSSSSSS SSSSSSSSS
WV-	fU * SfG * SfU * SfC * SfU * SfG * SmA * SmC * SmA * SmG * SmC *	UGUCUGACAGCUGUU	SSSSSSSS

11059	SmU * SmG * SmU * SfU * SfU * SfG * SfC * SfA * SfG	UGCAG	SSSSSSSSS
WV-11060	fG * SfA * SfC * SfA * SfG * SfC * SmU * SmG * SmU * SmU * SmG * SmC * SmA * SfG * SfA * SfC * SfC * SfU * SfC	GACAGCUGUUUGCAG ACCUC	SSSSSSSSS SSSSSSSSS
WV-11061	fC * SfU * SfG * SfU * SfU * SfU * SmG * SmC * SmA * SmG * SmA * SmC * SmC * SmU * SfC * SfC * SfU * SfG * SfC * SfC	CUGUUUGCAGACCUC CUGCC	SSSSSSSSS SSSSSSSSS
WV-11062	fU * SfG * SfC * SfA * SfG * SfA * SmC * SmC * SmU * SmC * SmC * SmU * SmG * SmC * SfC * SfA * SfC * SfC * SfG * SfC	UGCAGACCUCCUGCC ACCGC	SSSSSSSSS SSSSSSSSS
WV-11063	fA * SfC * SfC * SfU * SfC * SfC * SmU * SmG * SmC * SmC * SmA * SmC * SmC * SmG * SfC * SfA * SfG * SfA * SfU * SfU	ACCUCCUGCCACCGC AGAUU	SSSSSSSSS SSSSSSSSS
WV-11064	fC * SfU * SfG * SfC * SfC * SfA * SmC * SmC * SmG * SmC * SmA * SmG * SmA * SmU * SfU * SfC * SfA * SfG * SfG * SfC	CUGCCACCGCAGAUU CAGGC	SSSSSSSSS SSSSSSSSS
WV-11065	fA * SfC * SfC * SfG * SfC * SfA * SmG * SmA * SmU * SmU * SmC * SmA * SmG * SmG * SfC * SfU * SfU * SfC * SfC * SfC	ACCGCAGAUUCAGGC UUCCC	SSSSSSSSS SSSSSSSSS
WV-11066	fA * SfG * SfA * SfU * SfU * SfC * SmA * SmG * SmG * SmC * SmU * SmU * SmC * SmC * SfC * SfA * SfA * SfU * SfU * SfU	AGAUUCAGGCUUCCC AAUUU	SSSSSSSSS SSSSSSSSS
WV-11067	fC * SfA * SfG * SfC * SfC * SfU * SmU * SmC * SmC * SmC * SmA * SmA * SmU * SmU * SfU * SfU * SfC * SfC * SfU	CAGGCUUCCCAAUUU UUCCU	SSSSSSSSS SSSSSSSSS
WV-11068	fU * SfU * SfC * SfC * SfC * SfA * SmA * SmU * SmU * SmU * SmU * SmC * SmC * SfU * SfG * SfU * SfA * SfG * SfA	UUCCCAAUUUUCCU GUAGA	SSSSSSSSS SSSSSSSSS
WV-11069	fA * SfA * SfU * SfU * SfU * SfU * SmU * SmC * SmC * SmU * SmG * SmU * SmA * SmG * SfA * SfU * SfA * SfC * SfU	AAUUUUUCCUGUAGA AUACU	SSSSSSSSS SSSSSSSSS
WV-11070	fU * SfU * SfC * SfC * SfU * SfG * SmU * SmA * SmG * SmA * SmA * SmU * SmA * SmC * SfU * SfG * SfG * SfC * SfA * SfU	UUCCUGUAGAAUACU GGCAU	SSSSSSSSS SSSSSSSSS
WV-11071	fG * SfU * SfA * SfG * SfA * SfA * SmU * SmA * SmC * SmU * SmG * SmG * SmC * SmA * SfU * SfC * SfU * SfG * SfU * SfU	GUAGAAUACUGGCAU CUGUU	SSSSSSSSS SSSSSSSSS
WV-11072	fA * SfU * SfA * SfC * SfU * SfG * SmG * SmC * SmA * SmU * SmC * SmU * SmG * SmU * SfU * SfU * SfU * SfG * SfG * SfA	AUACUGGCAUCUGUU UUUGA	SSSSSSSSS SSSSSSSSS
WV-11073	fG * SfG * SfC * SfA * SfU * SfC * SmU * SmG * SmU * SmU * SmU * SmU * SmG * SfA * SfG * SfG * SfA * SfU * SfU	GGCAUCUGUUUUUGA GGAUU	SSSSSSSSS SSSSSSSSS
WV-11074	fC * SfU * SfG * SfU * SfU * SfU * SmU * SmU * SmG * SmA * SmG * SmG * SmA * SmU * SfU * SfG * SfC * SfU * SfG * SfA	CUGUUUUUGAGGAU UGCUGA	SSSSSSSSS SSSSSSSSS
WV-11075	fU * SfU * SfU * SfU * SfG * SfA * SfG * SmG * SmA * SmU * SmU * SmG * SmC * SmU * SmG * SfA * SfA * SfU * SfU * SfA * SfU	UUUGAGGAUUGCUG AAUUAU	SSSSSSSSS SSSSSSSSS
WV-11076	fG * SfG * SfA * SfU * SfU * SfG * SmC * SmU * SmG * SmA * SmA * SmU * SmU * SmA * SfU * SfU * SfU * SfC * SfU * SfU	GGAUUGCUGAAUUA UUUCUU	SSSSSSSSS SSSSSSSSS
WV-	fG * SfC * SfU * SfG * SfA * SfA * SmU * SmU * SmA * SmU * SmU *	GCUGAAUUAUUUCUU	SSSSSSSSS

11077	SmU * SmC * SmU * SfU * SfC * SfC * SfC * SfA	CCCCA	SSSSSSSSS
WV-11078	fA * SfU * SfU * SfA * SfU * SfU * SmU * SmC * SmU * SmU * SmC * SmC * SmC * SmC * SfA * SfG * SfU * SfU * SfG * SfC	AUUAUUUCUUCCCCA GUUGC	SSSSSSSSS SSSSSSSSS
WV-11079	fU * SfU * SfC * SfU * SfU * SfC * SmC * SmC * SmA * SmG * SmU * SmU * SmG * SfC * SfA * SfU * SfU * SfC * SfA	UUCUUCCCCAGUUGC AUUCA	SSSSSSSSS SSSSSSSSS
WV-11080	fC * SfC * SfC * SfC * SfA * SfG * SmU * SmU * SmG * SmC * SmA * SmU * SmU * SmC * SfA * SfA * SfU * SfG * SfU * SfU	CCCCAGUUGCAUUCA AUGUU	SSSSSSSSS SSSSSSSSS
WV-11081	fG * SfU * SfU * SfG * SfC * SfA * SmU * SmU * SmC * SmA * SmA * SmU * SmG * SmU * SfU * SfC * SfU * SfG * SfA * SfC	GUUGCAUUCAAUGUU CUGAC	SSSSSSSSS SSSSSSSSS
WV-11082	fA * SfU * SfU * SfC * SfA * SfA * SmU * SmG * SmU * SmU * SmC * SmU * SmG * SmA * SfC * SfA * SfC * SfA * SfG	AUUCAAUGUUCUGAC AACAG	SSSSSSSSS SSSSSSSSS
WV-11083	fA * SfU * SfG * SfU * SfU * SfC * SmU * SmG * SmA * SmC * SmA * SmA * SmC * SmA * SfG * SfU * SfU * SfU * SfG * SfC	AUGUUCUGACAACAG UUUGC	SSSSSSSSS SSSSSSSSS
WV-11084	fC * SfU * SfG * SfA * SfC * SfA * SmA * SmC * SmA * SmG * SmU * SmU * SmG * SfC * SfC * SfG * SfC * SfU * SfG	CUGACAACAGUUUGC CGCUG	SSSSSSSSS SSSSSSSSS
WV-11085	fA * SfA * SfC * SfA * SfG * SfU * SmU * SmU * SmG * SmC * SmC * SmG * SmC * SmU * SfG * SfC * SfC * SfA * SfA	AACAGUUUGCCGCUG CCCAA	SSSSSSSSS SSSSSSSSS
WV-11086	fU * SfU * SfU * SfG * SfC * SfC * SmG * SmC * SmU * SmG * SmC * SmC * SmA * SfA * SfU * SfG * SfC * SfC * SfA	UUUGCCGCUGCCCAA UGCCA	SSSSSSSSS SSSSSSSSS
WV-11087	fC * SfG * SfC * SfU * SfG * SfC * SmC * SmC * SmA * SmA * SmU * SmG * SmC * SmC * SfA * SfU * SfC * SfC * SfU * SfG	CGCUGCCCAAUGCCA UCCUG	SSSSSSSSS SSSSSSSSS
WV-11088	fC * SfC * SfC * SfC * SfA * SfA * SfU * SmG * SmC * SmC * SmA * SmU * SmC * SmC * SmU * SfG * SfA * SfG * SfU * SfU	CCCAAUGCCAUCCUG GAGUU	SSSSSSSSS SSSSSSSSS
WV-11089	fU * SfG * SfC * SfC * SfA * SfU * SmC * SmC * SmU * SmG * SmG * SmA * SmG * SmU * SfU * SfC * SfC * SfU * SfG * SfU	UGCCAUCCUGGAGUU CCUGU	SSSSSSSSS SSSSSSSSS
WV-11090	fU * SfC * SfC * SfU * SfG * SfG * SmA * SmG * SmU * SmU * SmC * SmC * SmU * SmG * SfU * SfA * SfG * SfG * SfA * SfU	UCCUGGAGUUCCUGU AAGAU	SSSSSSSSS SSSSSSSSS
WV-11091	fG * SfA * SfG * SfU * SfU * SfC * SmC * SmU * SmG * SmU * SmA * SmA * SmG * SmA * SfU * SfA * SfC * SfC * SfA * SfA	GAGUUCCUGUAAGAU ACCAA	SSSSSSSSS SSSSSSSSS
WV-11092	fC * SfC * SfU * SfG * SfU * SfA * SmA * SmG * SmA * SmU * SmA * SmC * SmC * SmA * SfA * SfA * SfA * SfG * SfG	CCUGUAAGAUACCAA AAAGG	SSSSSSSSS SSSSSSSSS
WV-11093	fA * SfA * SfG * SfA * SfU * SfA * SmC * SmC * SmA * SmA * SmA * SmA * SmA * SmG * SfG * SfC * SfA * SfA * SfA * SfA	AAGAUACCAAAAAGG CAAAA	SSSSSSSSS SSSSSSSSS
WV-11094	fA * SfC * SfC * SfC * SfA * SfA * SmA * SmA * SmG * SmG * SmC * SmA * SmA * SmA * SmA * SfC * SfA * SfA * SfA * SfA	ACCAAAAAGGCAAAA CAAAA	SSSSSSSSS SSSSSSSSS
WV-	fA * SfA * SfA * SfG * SfG * SfC * SmA * SmA * SmA * SmC *	AAAGGCAAAACAAAA	SSSSSSSSS

11095	SmA * SmA * SmA * SfA * SfA * SfU * SfG * SfA * SfA	AUGAA	SSSSSSSSS
WV-11096	fC * SfA * SfA * SfA * SfA * SfC * SmA * SmA * SmA * SmA * SmA * SmU * SmG * SmA * SfA * SfG * SfC * SfC * SfC * SfC	CAAAACAAAAAAUGAA GCCCC	SSSSSSSSS SSSSSSSSS
WV-11097	fC * SfA * SfA * SfA * SfA * SfA * SmU * SmG * SmA * SmA * SmG * SmC * SmC * SmC * SfC * SfA * SfU * SfG * SfU * SfC	CAAAAAUGAAGCCCC AUGUC	SSSSSSSSS SSSSSSSSS
WV-11098	fA * SfU * SfG * SfA * SfA * SfG * SmC * SmC * SmC * SmC * SmA * SmU * SmG * SmU * SfC * SfU * SfU * SfU * SfU	AUGAAGCCCCAUGUC UUUUU	SSSSSSSSS SSSSSSSSS
WV-11099	fG * SfC * SfC * SfC * SfC * SfA * SmU * SmG * SmU * SmC * SmU * SmU * SmU * SmU * SfA * SfU * SfU * SfU * SfG	GCCCCAUGUCUUUUU AUUUG	SSSSSSSSS SSSSSSSSS
WV-11100	fA * SfU * SfG * SfU * SfC * SfU * SmU * SmU * SmU * SmU * SmA * SmU * SmU * SmU * SfG * SfA * SfA * SfA * SfA	AUGUCUUUUUAUUU GAGAAA	SSSSSSSSS SSSSSSSSS
WV-11101	fU * SfU * SfU * SfU * SfA * SmU * SmU * SmU * SmG * SmA * SmG * SmA * SmA * SfA * SfG * SfA * SfU * SfU	UUUUAUUUGAGAA AAGAUU	SSSSSSSSS SSSSSSSSS
WV-11102	fA * SfU * SfU * SfU * SfG * SfA * SmG * SmA * SmA * SmA * SmA * SmG * SmA * SmU * SfU * SfA * SfA * SfC * SfA	AUUUGAGAAAAGAU UAAACA	SSSSSSSSS SSSSSSSSS
WV-11103	fA * SfG * SfA * SfA * SfA * SfA * SmG * SmA * SmU * SmU * SmU * SmA * SmA * SmC * SfA * SfG * SfU * SfG * SfU * SfG	AGAAAAGAUUAAAC AGUGUG	SSSSSSSSS SSSSSSSSS
WV-11104	fA * SfG * SfA * SfU * SfU * SfA * SmA * SmA * SmC * SmA * SmG * SmU * SmG * SmU * SfG * SfC * SfU * SfA * SfC * SfC	AGAUUAAACAGUGU GCUACC	SSSSSSSSS SSSSSSSSS
WV-11105	fA * SfA * SfA * SfC * SfA * SfG * SmU * SmG * SmU * SmG * SmC * SmU * SmA * SmC * SfC * SfA * SfC * SfA * SfU * SfG	AAACAGUGUGCUACC ACAUG	SSSSSSSSS SSSSSSSSS
WV-11231	fU * fC * fA * fC * fU * fC * mAfG * mAmU * fA * mGmUfU * fG * fA * fA * fG * fC * fC	UCACUCAGAUAGUUG AAGCC	XXXXX O X O XX O O XXXXX
WV-11232	fU * fC * fA * fC * fU * fC * fA * fG * mAmU * fA * mGmUfU * fG * fA * fA * fG * fC * fC	UCACUCAGAUAGUUG AAGCC	XXXXXXX O XX O O XXXXX
WV-11233	fU * fC * fA * fC * fU * fC * mAfG * fA * mU * fA * mGmUfU * fG * fA * fA * fG * fC * fC	UCACUCAGAUAGUUG AAGCC	XXXXX O XXXX O O XXXXX
WV-11234	fU * RfC * RfA * RfC * RfU * RfC * RmAfG * RmAmU * RfA * RmGmUfU * RfG * RfA * RfA * RfG * RfC * RfC	UCACUCAGAUAGUUG AAGCC	RRRRR O R O RR O O RRRRR
WV-11235	fU * RfC * RfA * RfC * RfU * RfC * RfA * RfG * RmAmU * RfA * RmGmUfU * RfG * RfA * RfA * RfG * RfC * RfC	UCACUCAGAUAGUUG AAGCC	RRRRRRR O RR O O RRRRR
WV-11236	fU * RfC * RfA * RfC * RfU * RfC * RmAfG * RfA * RmU * RfA * RmGmUfU * RfG * RfA * RfA * RfG * RfC * RfC	UCACUCAGAUAGUUG AAGCC	RRRRR O RRRR O O RRRRR
WV-11237	fU * SfC * SfA * SfA * SfG * SfG * SmAn001fA * SmGn001mA * SfU * SmGn001mGn001fC * SfA * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSn O Sn O SSn O n O SSSSSS
WV-	fU * SfC * SfA * SfA * SfG * SfG * SmAn001SfA * SmGn001SmA * SfU *	UCAAGGAAGAUGGCA	SSSSSnSSnSS

11238	SmGn001SmGn001SfC * SfA * SfU * SfU * SfU * SfC * SfU	UUUCU	SnSnSSSSSS
WV-11239	fU * SfC * SfA * SfA * SfG * SfG * SmAn001RfA * SmGn001RmA * SfU * SmGn001RmGn001RfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSnRSnRSSn RnRSSSSSS
WV-11340	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001fU * SmG * SfA * SmAn001mGn001fG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSn O SSSn O n O SSSSS
WV-11341	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001fU * SmG * SfA * SmAn001fG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSn O SSSn O SSSSSS
WV-11342	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001fU * SmG * SfA * SmAn001mG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSn O SSSn O SSSSSS
WV-11343	fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SmAn001mU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSSSSSn O Sn O SSn O n O SSSSSS
WV-11344	fU * SfC * SfA * SfC * SfU * SfC * SfA * SfG * SmAn001mU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSSSSSSn O SSn O n O SSSSSS
WV-11345	fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSSSSSn O SSSSn O n O SSSSSS
WV-11346	fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SmAn001mU * SfA * SfG * SmUn001fU * SfG * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSSSSSn O Sn O SSSn O SSSSSS
WV-11347	fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SmAn001mU * SfA * SmGn001fU * SfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSSSSSn O Sn O SSn O SSSSSSS

WV-11544	BrfUfCfAfCfUfCmAfGfAmU fAmGmUfUfGfAfAfGfCfC	UCACUCAGAUAGUUG AAGCC	SSSSSSOSSSS OOSSSSS
WV-11545	Acet5fUfCfAfCfUfCmAfGf AmUfAmGmUfUfGfAfAfGfCfC	UCACUCAGAUAGUUG AAGCC	SSSSSSOSSSS OOSSSSSS
WV-11546	BrfUfCfAfCfUfCmAfGfAmU fAmGmUfUfGfAfAfGfCfC	UCACUCAGAUAGUUG AAGCC	XXXXXXOXXXX OOXXXXX
WV-11547	Acet5fUfCfAfCfUfCmAfGf AmUfAmGmUfUfGfAfAfGfCfC	UCACUCAGAUAGUUG AAGCC	XXXXXXOXXXX OOXXXXXX

WV-12123	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001 fUn001 mGn001 fAn001 mAn001mG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnXnX nXnXnX SSSSSS
WV-12124	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001fUn001mG * SfA * SmAn001mG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnXnX SSnXSSSSSS
WV-12125	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001fU * SmGn001fA * SmAn001mG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnXS nXSnXSSSSSS
WV-	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001fU * SmG *	CUCCGGUUCUGAAGG	SSSSSSSSnXSS

12126	SfAn001mAn001mG * SfG * SfU * SfG * SfU * SfU * SfC	UGUUC	nXnXSSSSSS
WV-12127	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001fU * SmGn001fAn001mAn001mG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnXS nXnXnXSSSSSS
WV-12128	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001fUn001mG * SfAn001mAn001mG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnXnX SnXnXSSSSSS
WV-12129	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001fUn001mGn001fA * SmAn001mG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnXnX nXSnXSSSSSS
WV-12130	fU * SfC * SfA * SfA * SfG * SfG * SmAn001fAn001mGn001 mAn001 fUn001 mGn001 mGn001fC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSnXnX nXnXnX nXnX SSSSSS
WV-12131	fU * SfC * SfA * SfA * SfG * SfG * SmAn001fAn001mGn001mA * SfU * SmGn001mGn001fC * SfA * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSnXnXnXSSn XnX SSSSSS
WV-12132	fU * SfC * SfA * SfA * SfG * SfG * SmAn001fA * SmGn001mAn001fU * SmGn001mGn001fC * SfA * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSnXSnXnXSn XnX SSSSSS
WV-12133	fU * SfC * SfA * SfA * SfG * SfG * SmAn001fA * SmGn001mA * SfUn001mGn001mGn001fC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSnXSnXSnXn XnX SSSSSS
WV-12134	fU * SfC * SfA * SfA * SfG * SfG * SmAn001fA * SmGn001mAn001fUn001 mGn001 mGn001fC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSnXSnXnXn XnXnX SSSSSS
WV-12135	fU * SfC * SfA * SfA * SfG * SfG * SmAn001fAn001 mGn001mA * SfUn001mGn001mGn001fC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSnXnXnXS nXnXnXSSSSSS
WV-12136	fU * SfC * SfA * SfA * SfG * SfG * SmAn001fAn001 mGn001mAn001fU * SmGn001mGn001fC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	SSSSSSnXnXnX nXSnXnX SSSSSS
WV-12422	rGrGrCrUrUrUrCrArArCrUrArU rCrUrGrArGrUrUrGrA	GGCUUCAACUAUCUG AGUGA	OOOOOOOOOOO O OOOOO
WV-12423	rGrArArCrArCrCrUrUrUrCrArG rArArCrCrCrGrGrArG	GAACACCUUCAGAAC CGGAG	OOOOOOOOO OOO OOOOO
WV-12494	fA * SfU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	AUCAAGGAAGAUGGC AUUUCU	SSSSSSSOSOS SOOSSSS SS
WV-12495	fU * SfU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UUCAAGGAAGAUGGC AUUUCU	SSSSSSSOSOS SOOSSSS SS
WV-12496	fUfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGAUGGCA UUUCU	OSSSS SOSOSSOOSSSS SS
WV-12553	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001fU * SmG * SfA * SmAn001mGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnXS SSnXOSSSS S

WV-12554	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001RfU * SmG * SfA * SmAn001RmGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnRS SSnROSSSS S
WV-12555	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001RfU * SmG * SfA * SmAn001RfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnRS SSnRSSSSSS
WV-12556	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001RfU * SmG * SfA * SmAn001RmG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnRS SSnRSSSSSS
WV-12557	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001SfU * SmG * SfA * SmAn001SmGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnSSS SnSOSSSS S
WV-12558	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001SfU * SmG * SfA * SmAn001SfG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnSS SSnSSSSSSS
WV-12559	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001SfU * SmG * SfA * SmAn001SmG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnSS SSnSSSSSSS
WV-12566	L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	OSSSS SSOSSSS OOSSSS SS
WV-12567	Mod092L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	OSSSS SSOSSSS OOSSSS SS
WV-12568	Mod093L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	OSSSS SSOSSSS OOSSSS SS
WV-12569	L001TTTfU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	TTTUCACUCAGAUAG UUGAAGCC	OOOOSSSS SSOSSSS OOSSSS SS
WV-12570	Mod020L001TTTfU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	TTTUCACUCAGAUAG UUGAAGCC	OOOOSSSS SSOSSSS OOSSSS SS
WV-12571	fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfCTTTL005	UCACUCAGAUAGUUG AAGCCTTT	SSSSSSOSSSS OOSSSS SSOOOO
WV-12572	fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfCTTTL005Mod020	UCACUCAGAUAGUUG AAGCCTTT	SSSSSSOSSSS OOSSSS SSOOOO
WV-12872	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001RfU * SmG * SfA * SmAn001RmGn001RfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnRS SSnRnRSSSSS
WV-12873	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001SfU * SmG * SfA * SmAn001SmGn001SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSSSnSS SSnSnSSSSSS
WV-12876	fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCn001fU * SmG * SfA * SmAn001mGn001fG * SfU * SfGn001fU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSnXSSnXSSnX SSSnXnXSSnXSS
WV-12877	fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCn001fU * SmG * SfA * SmAn001fG * SfG * SfU * SfGn001fU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSnXSSnXSSnXS SSnXSSSnXSS

WV-12878	fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCn001fU * SmG * SfA * SmAn001mG * SfG * SfU * SfGn001fU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSnXSSnXSSnXS SSnXSSSnXSS
WV-12879	fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfGn001fU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSnXSSnXSSOS SSOOSSnXSS
WV-12880	fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001fU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSnXSSnXSSOS SSOSSSnXSS
WV-12881	fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmG * SfA * SmAmG * SfG * SfU * SfGn001fU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSnXSSnXSSOS SSOSSSnXSS
WV-12882	fC * SfU * SfC * SfC * SfG * SfG * SmUn001mU * SmCn001mU * SmGn001mA * SmAn001mG * SfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSnXSnXS nXSnXSSSSSS
WV-12883	fC * SfU * SfC * SfC * SfG * SfG * SmUn001mUn001 mCn001mUn001 mGn001mAn001 mAn001mGn001fG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGAAGG UGUUC	SSSSSSnXnXnXnXnXn X nXnXnXSSSSS
WV-12884	fU * SfC * SfAn001fC * SfU * SfCn001mAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfAn001fG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSnXSSnXnXSSS SnXnXSSSnXSS
WV-12885	fU * SfC * SfAn001fC * SfU * SfCn001mAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfAn001fG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSnXSSnXOSSSS OSSSSnXSS
WV-12886	fU * SfC * SfA * SfC * SfU * SfC * SmA * SmG * SmA * SmU * SmA * SmG * SmU * SmU * SfG * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSSSSSSSSS SSSSSSS
WV-12887	fU * SfC * SfA * SfC * SfU * SfC * SmAn001mG * SmAn001mU * SmAn001mG * SmUn001mU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSSSSSnXSnX SnXSnX SSSSSS
WV-12888	fU * SfC * SfA * SfC * SfU * SfC * SmAn001mGn001mAn001 mUn001 mAn001mGn001 mUn001 mUn001fG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUG AAGCC	SSSSSSnXnXnXnXnXn X nXnXnXSSSSS
WV-12904	GCGTGGTACCACGCL012mU * Geom5Ceom5CeomA * G * G * C * T * G * C * T * T * A * T * mG * mA * mC * mU * mC	GCGTGGTACCACGCU GCCA GGCTGGTTATGACUC	00000000000 00000X000 XXXXXXXXXXX XXX
WV-12905	GCGTGG * T * A * CCACGCL012mU * Geom5Ceom5CeomA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	GCGTGGTACCACGCU GCCA GGCTGGTTATGACUC	00000XXX00 00000X000 XXXXXXXXXXX XXX
WV-12906	G * C * G * T * G * G * T * A * C * C * A * C * G * CL012mU * Geom5Ceom5CeomA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	GCGTGGTACCACGCU GCCA GGCTGGTTATGACUC	XXXXXXXXXXX X00X000XXX XXXXXXXXXXX
WV-12907	GfCGfUGGTACfCAfCGfCL012mU * Geom5Ceom5CeomA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	GCGUGGTACCACGCU GCCA GGCTGGTTATGACUC	00000000000 0000X000 XXXXXXXXXXX

WV-12908	G * fCG * fUG * G * T * A * CfCA * fCG * fCL012mU * Geom5Ceom5CeomA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	GCGUGGTACCACGCU GCCA GGCTGGTTATGACUC		X0X0XXX00X0 X00X000 XXXXXXXXXXX XXX
WV-12909	G * fC * G * fU * G * G * T * A * C * fC * A * fC * G * fCL012mU * Geom5Ceom5CeomA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	GCGUGGTACCACGCU GCCA GGCTGGTTATGACUC		XXXXXXXXXXX X00X000 XXXXXXXXXXX XXX
WV-12910	GCGTGGTACCACGCL012BrmU * Geom5Ceom5CeomA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	GCGTGGTACCACGCU GCCA GGCTGGTTATGACUC		000000000000 0000X000 XXXXXXXXXXX XXX
WV-12911	GCGTGG * T * A * CCACGCL012BrmU * Geom5Ceom5CeomA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	GCGTGGTACCACGCU GCCA GGCTGGTTATGACUC		000000XXX000 0000X000 XXXXXXXXXXX XXX
WV-12912	G * C * G * T * G * G * T * A * C * C * A * C * G * CL012BrmU * Geom5Ceo m5CeomA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	GCGTGGTACCACGCU GCCA GGCTGGTTATGACUC		XXXXXXXXXXX X00X000 XXXXXXXXXXX XXX
WV-12913	GfCGfUGGTACfCAfCGfCL012BrmU * Geom5Ceom5CeomA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	GCGUGGTACCACGCU GCCA GGCTGGTTATGACUC		000000000000 0000X000 XXXXXXXXXXX XXX
WV-12914	G * fCG * fUG * G * T * A * CfCA * fCG * fCL012BrmU * Geom5Ceo m5CeomA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	GCGUGGTACCACGCU GCCA GGCTGGTTATGACUC		X0X0XXXX00X0 X00X000XXX XXXXXXXXXXX XXX
WV-12915	G * fC * G * fU * G * G * T * A * C * fC * A * fC * G * fCL012BrmU * Geom5Ceo m5CeomA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	GCGUGGTACCACGCU GCCA GGCTGGTTATGACUC		XXXXXXXXXXX X00X000XXX XXXXXXXXXXX XXX

WV-13319	fC * SfU * SfC * SfC * SfU * SfG * SfU * SfU * SmCfU * SmG * SfC * SmAmGfC * SfU * SfG * SfU * SfU * SfC	CUCCUGUUCUG CAGCUGUUC	SSSSSSSOSS SOOSSSSS
WV-13320	fC * SfU * SfC * SfC * SfU * SfG * SfU * SfU * SmCfU * SmG * SfC * SmAfG * SfC * SfU * SfG * SfU * SfU * SfC	CUCCUGUUCUG CAGCUGUUC	SSSSSSSOSS SOSSSSSS

WV-13321	fC * SfU * SfC * SfC * SfU * SfG * SfU * SfU * SmCfU * SmG * SfC * SmAmG * SfC * SfU * SfG * SfU * SfU * SfC	CUCCUGUUCUG CAGCUGUUC	SSSSSSSOSS SOSSSSSS
WV-13322	fC * SfU * SfC * SfC * SfU * SfG * SfU * SfC * SfU * SmG * SfC * SmAmGfC * SfU * SfG * SfU * SfU * SfC	CUCCUGUUCUG CAGCUGUUC	SSSSSSSSSS SOOSSSSS
WV-13405	GTTGCCTCCGGTTCTGA AGGTGTTC [all PMO]	GTTGCCTCCGG TTCTGAAGGTGTTC	OOOOOOOOOO OOOOOOOOOO
WV-13406	CTCCGGTTCTGAAGGTGTTC [all PMO]	CTCCGGTTCTG AAGGTGTTC	OOOOOOOOOO OOOOOOO
WV-13407	TGCCTCCGGTTCTGA AGGTGTTCTTGTA [all PMO]	TGCCTCCGGTT CTGAAGGTGTT CTTGTA	OOOOOOOOOO OOOOOOOOOO OOOOO
WV-13408	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001RfU * SmG * SfA * SmAn001RfGn001RfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUC UGAAGGUGUUC	SSSSSSSSnRS SSnRnRSSSSS
WV-13409	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCn001RfU * SmG * SfA * SmAn001RfGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUC UGAAGGUGUUC	SSSSSSSSnRSSS nROSSSSS

WV-13594	fU * fU * fG * fU * fA * fC * fU * mU * mC * mA * mU * mC * mC * mA * mC * mU * fG * fA * fUn001fUn001fCn001fUn001fGn001fA	UUGUACUUCAUCCCACUGAUUCUGA	XXXXXXXXXXXXXXX XXXXXnXnXnXnXnX
WV-13595	fC * fC * fG * fG * fU * fU * fC * mU * mG * mA * mA * mG * mG * mU * mG * mU * mU * fC * fU * fUn001fGn001fUn001fAn001fCn001fU	CCGGUUCUGAAGGUGUUCUUGUACU	XXXXXXXXXXXXXXX XXXXXnXnXnXnXnX
WV-13596	fUn001fUn001fGm001fUn001fAn001fC * fU * mU * mC * mA * mU * mC * mC * mA * mC * mU * fG * fA * fU * fC * fU * fG * fA	UUGUACUUCAUCCCACUGAUUCUGA	nXnXnXnXnXnXXXXXXX XXXXXXX XXXXXX
WV-13597	fCn001fCn001fGn001fGm001fUn001fU * fC * mU * mG * mA * mA * mG * mG * mU * mG * mU * mU * fC * fU * fU * fG * fU * fA * fC * fU	CCGGUUCUGAAGGUGUUCUUGUACU	nXnXnXnXnXnXXXXXXX XXXXXXX XXXXXX
WV-13701	fU * SfG * SfA * SfC * SfU * SfU * SmG * SmC * SmU * SmC * SmA * SmA * SmG * SmC * SfU * SfU * SfU * SfU * SfC * SfU	UGACUUGCUCAAGCUUUUCU	SSSSS SSSSS SSSSS SSSS
WV-13702	fC * SfA * SfA * SfG * SfC * SfU * SmU * SmU * SmU * SmC * SmU * SmU * SmU * SmU * SfA * SfG * SfU * SfU * SfG * SfC	CAAGCUUUUCUUUUAGUUGC	SSSSS SSSSS SSSSS SSSS
WV-13703	fC * SfU * SfU * SfU * SfU * SfA * SmG * SmU * SmU * SmG * SmC * SmU * SmG * SmC * SfU * SfC * SfU * SfU	CUUUUAGUUGCUGCUCUUUU	SSSSS SSSSS SSSSS SSSS

	* SfU * SfU		
WV-13704	fG * SfC * SfU * SfG * SfC * SfU * SmC * SmU * SmU * SmU * SmC * SmC * SmA * SfG * SfG * SfU * SfU * SfC * SfA	GCUGCUCUUUUCCAGGUUCA	SSSSS SSSSS SSSSS SSSS
WV-13705	fU * SfU * SfC * SfC * SfA * SfG * SmG * SmU * SmU * SmC * SmA * SmA * SmG * SmU * SfG * SfG * SfG * SfA * SfU * SfA	UUCCAGGUUCAAGUGGGAUA	SSSSS SSSSS SSSSS SSSS
WV-13706	fC * SfA * SfA * SfG * SfU * SfG * SmG * SmG * SmA * SmU * SmA * SmC * SmU * SmA * SfG * SfC * SfA * SfA * SfU * SfG	CAAGUGGGAUACUAGCAAUG	SSSSS SSSSS SSSSS SSSS
WV-13707	fU * SfA * SfC * SfU * SfA * SfG * SmC * SmA * SmA * SmU * SmG * SmU * SmU * SmA * SfU * SfC * SfU * SfG * SfC * SfU	UACUAGCAAUGUUAUCUGCU	SSSSS SSSSS SSSSS SSSS
WV-13708	fU * SfG * SfU * SfU * SfA * SfU * SmC * SmU * SmG * SmC * SmU * SmU * SmC * SmC * SfU * SfC * SfC * SfA * SfA * SfC	UGUUAUCUGCUUCCUCCAAC	SSSSS SSSSS SSSSS SSSS
WV-13709	fC * SfU * SfU * SfC * SfC * SfU * SmC * SmC * SmA * SmA * SmC * SmC * SmA * SmU * SfA * SfA * SfA * SfA * SfC * SfA	CUUCCUCCAACCAUAAAACA	SSSSS SSSSS SSSSS SSSS
WV-13710	fC * SfC * SfA * SfU * SfA * SfA * SmA * SmA * SmC * SmA * SmA * SmA * SmU * SmU * SfC * SfA * SfU * SfU * SfU * SfA	CCAUAAAACAAAUUCAUUUA	SSSSS SSSSS SSSSS SSSS
WV-13711	fA * SfA * SfU * SfU * SfC * SfA * SmU * SmU * SmU * SmA * SmA * SmA * SmU * SmC * SfU * SfC * SfU * SfU * SfU * SfG	AAUUCAUUUAAAUCUCUUUG	SSSSS SSSSS SSSSS SSSS
WV-13712	fA * SfA * SfU * SfC * SfU * SfC * SmU * SmU * SmU * SmG * SmA * SmA * SmA * SmU * SfU * SfC * SfU * SfG * SfA * SfC	AAUCUCUUUGAAAUUCUGAC	SSSSS SSSSS SSSSS SSSS
WV-13713	fU * SfG * SfA * SfA * SfA * SfU * SmU * SmC * SmU * SmG * SmA * SmC * SmA * SmA * SfG * SfA * SfU * SfA * SfU * SfU	UGAAAUUCUGACAAGAUAUU	SSSSS SSSSS SSSSS SSSS
WV-13714	fA * SfC * SfA * SfA * SfG * SfA * SmU * SmA * SmU * SmU * SmC * SmU * SmU * SmU * SfU * SfG * SfU * SfU * SfC * SfU	ACAAGAUAUUCUUUUGUUCU	SSSSS SSSSS SSSSS SSSS
WV-13715	fU * SfA * SfU * SfU * SfC * SfU * SmU * SmU * SmU * SmG * SmU * SmU * SmC * SmU * SfU * SfC * SfU * SfA	UAUUCUUUUGUUCUUCUAGC	SSSSS SSSSS SSSSS SSSS

	* SfG * SfC		
WV-13716	fU * SfU * SfC * SfU * SfU * SfU * SmU * SmG * SmU * SmU * SmC * SmU * SmC * SfU * SfA * SfG * SfC * SfC * SfU	UUCUUUUGUUCUUCUAGCCU	SSSSS SSSSS SSSSS SSSS
WV-13717	fA * SfU * SfC * SfC * SfA * SfC * SmU * SmG * SmG * SmA * SmG * SmA * SmU * SmU * SfU * SfG * SfU * SfC * SfU * SfG	AUCCACUGGAGAUUUGUCUG	SSSSS SSSSS SSSSS SSSS
WV-13718	fA * SfG * SfA * SfU * SfU * SfU * SmG * SmU * SmC * SmU * SmG * SmC * SmU * SmU * SfG * SfA * SfG * SfC * SfU * SfU	AGAUUUGUCUGCUUGAGCUU	SSSSS SSSSS SSSSS SSSS
WV-13719	fU * SfG * SfC * SfC * SfU * SfU * SfG * SmA * SmG * SmC * SmU * SmU * SmA * SmU * SmU * SfU * SfC * SfA * SfA * SfG	UGCUUGAGCUUAUUUUCAAG	SSSSS SSSSS SSSSS SSSS
WV-13720	fU * SfA * SfU * SfU * SfU * SfU * SmC * SmA * SmA * SmG * SmU * SmU * SmU * SmA * SfU * SfC * SfU * SfU * SfG * SfC	UAUUUUCAAGUUUAUCUUGC	SSSSS SSSSS SSSSS SSSS
WV-13721	fU * SfU * SfU * SfA * SfU * SfC * SmU * SmU * SmG * SmC * SmU * SmC * SmU * SmU * SfC * SfU * SfG * SfG * SfG * SfC	UUUAUCUUGCUCUUCUGGGC	SSSSS SSSSS SSSSS SSSS
WV-13722	fU * SfC * SfU * SfU * SfC * SfU * SmG * SmG * SmG * SmC * SmU * SmU * SmA * SmU * SfG * SfG * SfG * SfA * SfG * SfC	UCUUCUGGGCUUAUGGGAGC	SSSSS SSSSS SSSSS SSSS
WV-13723	fU * SfU * SfA * SfU * SfG * SfG * SmG * SmA * SmG * SmC * SmA * SmC * SmU * SmU * SfA * SfC * SfA * SfA * SfG * SfC	UUAUGGGAGCACUUACAAGC	SSSSS SSSSS SSSSS SSSS
WV-13724	fG * SfC * SfA * SfC * SfU * SfU * SmA * SmC * SmA * SmA * SmG * SmC * SmA * SmC * SfG * SfG * SfG * SfU * SfC * SfC	GCACUUACAAGCACGGGUCC	SSSSS SSSSS SSSSS SSSS
WV-13725	fG * SfC * SfA * SfC * SfG * SfG * SmG * SmU * SmC * SmC * SmU * SmC * SmC * SmA * SfG * SfU * SfU * SfU * SfC * SfA	GCACGGGUCCUCCAGUUUCA	SSSSS SSSSS SSSSS SSSS
WV-13726	fU * SfC * SfC * SfA * SfG * SfU * SmU * SmU * SmC * SmA * SmU * SmU * SmU * SmA * SfA * SfU * SfU * SfG * SfU * SfU	UCCAGUUUCAUUUAAUUGUU	SSSSS SSSSS SSSSS SSSS
WV-13727	fU * SfU * SfU * SfA * SfA * SfU * SmU * SmG * SmU * SmU * SmU * SmG * SmA * SmG * SfA * SfA * SfU * SfU	UUUAAUUGUUUGAGAAUUCC	SSSSS SSSSS SSSSS SSSS

	* SfC * SfC		
WV-13728	fG * SfA * SfG * SfA * SfA * SfU * SmU * SmC * SmC * SmC * SmU * SmG * SmG * SmC * SfG * SfC * SfA * SfG * SfG * SfG	GAGAAUUCCCUGGCGCAGGG	SSSSS SSSSS SSSSS SSSS
WV-13729	fC * SfU * SfG * SfG * SfC * SfG * SmC * SmA * SmG * SmG * SmG * SmG * SmC * SmA * SfA * SfC * SfU * SfC * SfU * SfU	CUGGCGCAGGGGCAACUCUU	SSSSS SSSSS SSSSS SSSS
WV-13730	fG * SfC * SfA * SfG * SfG * SfG * SmG * SmC * SmA * SmA * SmC * SmU * SmC * SmU * SfU * SfC * SfC * SfA * SfC * SfC	GCAGGGGCAACUCUUCCACC	SSSSS SSSSS SSSSS SSSS
WV-13731	fG * SfG * SfC * SfA * SfA * SfC * SmU * SmC * SmU * SmU * SmC * SmC * SmA * SmC * SfC * SfA * SfG * SfU * SfA * SfA	GGCAACUCUUCCACCAGUAA	SSSSS SSSSS SSSSS SSSS
WV-13732	fC * SfU * SfC * SfU * SfU * SfC * SmC * SmA * SmC * SmC * SmA * SmG * SmU * SmA * SfA * SfC * SfU * SfG * SfA * SfA	CUCUUCCACCAGUAACUGAA	SSSSS SSSSS SSSSS SSSS
WV-13733	fU * SfU * SfC * SfG * SfA * SfU * SmC * SmC * SmG * SmU * SmA * SmA * SmU * SmG * SfA * SfU * SfU * SfG * SfU * SfU	UUCGAUCCGUAAUGAUUGUU	SSSSS SSSSS SSSSS SSSS
WV-13734	fA * SfA * SfU * SfG * SfA * SfU * SmU * SmG * SmU * SmU * SmC * SmU * SmA * SmG * SfC * SfC * SfU * SfC * SfU * SfU	AAUGAUUGUUCUAGCCUCUU	SSSSS SSSSS SSSSS SSSS
WV-13735	fC * SfU * SfA * SfG * SfC * SfC * SmU * SmC * SmU * SmU * SmG * SmA * SmU * SmU * SfG * SfC * SfU * SfG * SfG * SfU	CUAGCCUCUUGAUUGCUGGU	SSSSS SSSSS SSSSS SSSS
WV-13736	fG * SfA * SfU * SfU * SfG * SfC * SmU * SmG * SmG * SmU * SmC * SmU * SmU * SmG * SfU * SfU * SfU * SfU * SfU	GAUUGCUGGUCUUGUUUUC	SSSSS SSSSS SSSSS SSSS
WV-13737	fC * SfU * SfU * SfG * SfU * SfU * SmU * SmU * SmU * SmC * SmA * SmA * SmA * SmU * SfU * SfU * SfG * SfG * SfG	CUUGUUUUUCAAAUUUUGGG	SSSSS SSSSS SSSSS SSSS
WV-13738	fA * SfA * SfA * SfU * SfU * SfU * SmU * SmG * SmG * SmG * SmC * SmA * SmG * SmC * SfG * SfG * SfU * SfA * SfA * SfU	AAAUUUUGGGCAGCGGUAAU	SSSSS SSSSS SSSSS SSSS
WV-13739	fC * SfA * SfG * SfC * SfG * SfG * SmU * SmA * SmA * SmU * SmG * SmA * SmG * SmU * SfU * SfC * SfU * SfU * SfU	CAGCGGUAAUGAGUUCUUCC	SSSSS SSSSS SSSSS SSSS

	* SfC * SfC		
WV-13740	fG * SfA * SfG * SfU * SfU * SfC * SmU * SmU * SmC * SmC * SmA * SmA * SmC * SmU * SfG * SfG * SfG * SfG * SfA * SfC	GAGUUCUUCCAACUGGGGAC	SSSSS SSSSS SSSSS SSSS
WV-13741	fA * SfA * SfC * SfU * SfG * SfG * SmG * SmG * SmA * SmC * SmG * SmC * SmC * SmU * SfC * SfU * SfG * SfU * SfU * SfC	AACUGGGGGACGCCUCUGUUC	SSSSS SSSSS SSSSS SSSS
WV-13742	fG * SfC * SfC * SfU * SfC * SfU * SmG * SmU * SmU * SmC * SmC * SmA * SmA * SfU * SfC * SfC * SfU * SfG * SfC	GCCUCUGUUCCAAAUCCUGC	SSSSS SSSSS SSSSS SSSS
WV-13743	fU * SfG * SfU * SfU * SfC * SfC * SmA * SmA * SmA * SmU * SmC * SmC * SmU * SmG * SfC * SfA * SfU * SfU * SfG * SfU	UGUUCCAAAUCCUGCAUUGU	SSSSS SSSSS SSSSS SSSS
WV-13744	fC * SfA * SfA * SfA * SfU * SfC * SmC * SmU * SmG * SmC * SmA * SmU * SmU * SmG * SfU * SfU * SfG * SfC * SfC * SfU	CAAAUCCUGCAUUGUUGCCU	SSSSS SSSSS SSSSS SSSS
WV-13745	fC * SfU * SfU * SfU * SfU * SfA * SmU * SmG * SmA * SmA * SmU * SmG * SmC * SmU * SfU * SfC * SfU * SfC * SfC * SfA	CUUUUAUGAAUGCUUCUCCA	SSSSS SSSSS SSSSS SSSS
WV-13746	fA * SfU * SfG * SfC * SfU * SfU * SmC * SmU * SmC * SmC * SmA * SmA * SmG * SmA * SfG * SfG * SfC * SfA * SfU * SfU	AUGCUUCUCCAAGAGGCAUU	SSSSS SSSSS SSSSS SSSS
WV-13747	fA * SfA * SfG * SfA * SfG * SfG * SmC * SmA * SmU * SmU * SmG * SmA * SmU * SmA * SfU * SfU * SfC * SfU * SfC * SfU	AAGAGGCAUUGAUAUUCUCU	SSSSS SSSSS SSSSS SSSS
WV-13748	fG * SfA * SfU * SfA * SfU * SfU * SmC * SmU * SmC * SmU * SmG * SmU * SmU * SmA * SfU * SfC * SfA * SfU * SfG * SfU	GAUAUUCUCUGUUAUCAUGU	SSSSS SSSSS SSSSS SSSS
WV-13749	fG * SfU * SfU * SfU * SfA * SfU * SfC * SmA * SmU * SmG * SmU * SmG * SmG * SmA * SmC * SfU * SfU * SfU * SfU * SfC * SfU	GUUAUCAUGUGGACUUUUCU	SSSSS SSSSS SSSSS SSSS
WV-13750	fG * SfG * SfA * SfC * SfU * SfU * SmU * SmU * SmC * SmU * SmG * SmG * SmU * SmA * SfU * SfC * SfA * SfU * SfC * SfU	GGACUUUUCUGGUAUCAUCU	SSSSS SSSSS SSSSS SSSS
WV-13751	fG * SfG * SfU * SfA * SfU * SfC * SmA * SmU * SmC * SmU * SmG * SmC * SmA * SmG * SfA * SfA * SfU * SfA	GGUAUCAUCUGCAGAAUAAU	SSSSS SSSSS SSSSS SSSS

	* SfA * SfU		
WV-13752	fG * SfC * SfA * SfG * SfA * SfA * SmU * SmA * SmA * SmU * SmC * SmC * SmC * SmG * SfG * SfA * SfG * SfA * SfA * SfG	GCAGAAUAAUCCCGGAGAAG	SSSSS SSSSS SSSSS SSSS
WV-13753	fC * SfC * SfG * SfG * SfA * SmG * SmA * SmA * SmG * SmU * SmU * SmU * SmC * SfA * SfG * SfG * SfG * SfC * SfC * SfA	CCGGAGAAGUUUCAGGGCCA	SSSSS SSSSS SSSSS SSSS
WV-13754	fU * SfU * SfU * SfC * SfA * SfG * SmG * SmG * SmC * SmC * SmA * SmA * SmG * SmU * SfC * SfA * SfU * SfU * SfU * SfG	UUUCAGGGCCAAGUCAUUUG	SSSSS SSSSS SSSSS SSSS
WV-13755	fA * SfA * SfG * SfU * SfC * SfA * SmU * SmU * SmU * SmG * SmC * SmC * SmA * SmC * SfA * SfU * SfC * SfU * SfA * SfC	AAGUCAUUUGCCACAUCUAC	SSSSS SSSSS SSSSS SSSS
WV-13756	fC * SfC * SfA * SfC * SfA * SfU * SmC * SmU * SmA * SmC * SmA * SmU * SmU * SmU * SfG * SfU * SfC * SfU * SfG * SfC	CCACAUCUACAUUUGUCUGC	SSSSS SSSSS SSSSS SSSS
WV-13757	fA * SfU * SfU * SfU * SfG * SfU * SmC * SmU * SmG * SmC * SmC * SmA * SmC * SmU * SfG * SfG * SfC * SfG * SfG * SfA	AUUUGUCUGCCACUGGCGGA	SSSSS SSSSS SSSSS SSSS
WV-13758	fC * SfA * SfC * SfU * SfG * SfG * SmC * SmG * SmG * SmA * SmG * SmG * SmU * SmC * SfU * SfU * SfU * SfG * SfG * SfC	CACUGGCGGAGGUCUUUGGC	SSSSS SSSSS SSSSS SSSS
WV-13759	fG * SfC * SfG * SfG * SfA * SfG * SmG * SmU * SmC * SmU * SmU * SmU * SmG * SmG * SfC * SfC * SfA * SfA * SfC * SfU	GCGGAGGUCUUUGGCCAACU	SSSSS SSSSS SSSSS SSSS
WV-13760	fG * SfG * SfU * SfC * SfU * SfU * SmU * SmG * SmG * SmC * SmC * SmA * SmA * SmC * SfU * SfG * SfC * SfC * SfU * SfA * SfU	GGUCUUUGGCCAACUGCUAU	SSSSS SSSSS SSSSS SSSS
WV-13761	fU * SfU * SfG * SfC * SfC * SfA * SmU * SmU * SmG * SmU * SmU * SmU * SmC * SmA * SfU * SfC * SfA * SfG * SfC * SfU	UUGCCAUUGUUUCAUCAGCU	SSSSS SSSSS SSSSS SSSS
WV-13762	fU * SfU * SfU * SfC * SfA * SfU * SmC * SmA * SmG * SmC * SmU * SmC * SmU * SmU * SfU * SfU * SfA * SfC * SfU * SfC	UUUCAUCAGCUCUUUUACUC	SSSSS SSSSS SSSSS SSSS
WV-13763	fU * SfC * SfU * SfU * SfU * SfU * SmA * SmC * SmU * SmC * SmC * SmC * SmU * SfG * SfG * SfA * SfG	UCUUUUACUCCCUUGGAGUC	SSSSS SSSSS SSSSS SSSS

	* SfU * SfC		
WV-13764	fC * SfC * SfU * SfU * SfG * SfG * SmA * SmG * SmU * SmC * SmU * SmU * SmC * SmU * SfA * SfG * SfG * SfA * SfG * SfC	CCUUGGAGUCUUCUAGGAGC	SSSSS SSSSS SSSSS SSSS
WV-13765	fU * SfU * SfC * SfU * SfA * SfG * SmG * SmA * SmG * SmC * SmC * SmU * SmU * SmU * SfC * SfC * SfU * SfU * SfA * SfC	UUCUAGGAGCCUUUCCUUAC	SSSSS SSSSS SSSSS SSSS
WV-13766	fC * SfU * SfU * SfU * SfC * SfC * SmU * SmU * SmA * SmC * SmG * SmG * SmU * SfA * SfG * SfC * SfA * SfU * SfC	CUUUCCUUACGGGUAGCAUC	SSSSS SSSSS SSSSS SSSS
WV-13767	fG * SfG * SfG * SfU * SfA * SfG * SmC * SmA * SmU * SmC * SmC * SmU * SmG * SmU * SfA * SfG * SfG * SfA * SfC * SfA	GGGUAGCAUCCUGUAGGACA	SSSSS SSSSS SSSSS SSSS
WV-13768	fC * SfU * SfG * SfU * SfA * SfG * SmG * SmA * SmC * SmA * SmU * SmU * SmG * SmG * SfC * SfA * SfG * SfU * SfU * SfG	CUGUAGGACAUUGGCAGUUG	SSSSS SSSSS SSSSS SSSS
WV-13769	fU * SfU * SfG * SfG * SfC * SfA * SmG * SmU * SmU * SmG * SmU * SmU * SmU * SmC * SfA * SfG * SfC * SfU * SfU * SfC	UUGGCAGUUGUUUCAGCUUC	SSSSS SSSSS SSSSS SSSS
WV-13770	fU * SfU * SfU * SfC * SfA * SfG * SmC * SmU * SmU * SmC * SmU * SmG * SmU * SmA * SfA * SfG * SfC * SfC * SfA * SfG	UUUCAGCUUCUGUAAGCCAG	SSSSS SSSSS SSSSS SSSS
WV-13771	fU * SfG * SfU * SfA * SfA * SfG * SmC * SmC * SmA * SmG * SmG * SmC * SmA * SmA * SfG * SfA * SfA * SfA * SfC * SfU	UGUAAGCCAGGCAAGAAACU	SSSSS SSSSS SSSSS SSSS
WV-13772	fG * SfC * SfA * SfA * SfG * SfA * SmA * SmA * SmC * SmU * SmU * SmU * SmC * SfC * SfA * SfG * SfG * SfU * SfC	GCAAGAAACUUUUCCAGGUC	SSSSS SSSSS SSSSS SSSS
WV-13773	fU * SfU * SfU * SfC * SfC * SfA * SmG * SmG * SmU * SmC * SmC * SmA * SmG * SmG * SfG * SfG * SfG * SfA * SfA * SfC	UUUCCAGGUCCAGGGGGAAC	SSSSS SSSSS SSSSS SSSS
WV-13774	fC * SfA * SfG * SfG * SfG * SfG * SmG * SmA * SmA * SmC * SmU * SmG * SmU * SmU * SfG * SfC * SfA * SfG * SfU * SfA	CAGGGGGAACUGUUGCAGUA	SSSSS SSSSS SSSSS SSSS
WV-13775	fU * SfG * SfU * SfU * SfG * SfC * SmA * SmG * SmU * SmA * SmA * SmU * SmC * SmU * SfA * SfU * SfG * SfA	UGUUGCAGUAAAUCUAUGAGU	SSSSS SSSSS SSSSS SSSS

	* SfG * SfU		
WV-13776	fA * SfU * SfC * SfU * SfA * SfU * SmG * SmA * SmG * SmU * SmU * SmU * SmC * SmU * SfU * SfC * SfC * SfA * SfA * SfA	AUCUAUGAGUUUCUUCCAAA	SSSSS SSSSS SSSSS SSSS
WV-13777	fU * SfU * SfC * SfU * SfU * SfC * SmC * SmA * SmA * SmA * SmG * SmC * SmA * SmG * SfC * SfC * SfU * SfC * SfU * SfC	UUCUUCCAAAGCAGCCUCUC	SSSSS SSSSS SSSSS SSSS
WV-13778	fG * SfC * SfA * SfG * SfC * SfC * SmU * SmC * SmU * SmC * SmG * SmC * SmU * SmC * SfA * SfC * SfU * SfC * SfA * SfC	GCAGCCUCUCGCUCACUCAC	SSSSS SSSSS SSSSS SSSS
WV-13779	fC * SfU * SfC * SfU * SfC * SfG * SmC * SmU * SmC * SmA * SmC * SmU * SmC * SmA * SfC * SfC * SfC * SfU * SfG * SfC	CUCUCGCUCACUCACCCUGC	SSSSS SSSSS SSSSS SSSS
WV-13780	fA * SfG * SfG * SfU * SfU * SfC * SmA * SmA * SmG * SmU * SmG * SmG * SmG * SmA * SfU * SfA * SfC * SfU * SfA * SfG	AGGUUCAAGUGGGAUACUAG	SSSSS SSSSS SSSSS SSSS
WV-13781	fU * SfC * SfC * SfA * SfG * SfG * SmU * SmU * SmC * SmA * SmA * SmG * SmU * SmG * SfG * SfG * SfA * SfU * SfA * SfC	UCCAGGUUCAAGUGGGAUAC	SSSSS SSSSS SSSSS SSSS
WV-13782	fU * SfU * SfG * SfC * SfU * SfG * SmG * SmU * SmC * SmU * SmU * SmG * SmU * SfU * SfU * SfU * SfC * SfA * SfA	UUGCUGGUCUUGUUUUUCAA	SSSSS SSSSS SSSSS SSSS
WV-13783	fA * SfC * SfU * SfG * SfG * SmG * SmA * SmC * SmG * SmC * SmC * SmU * SmC * SfU * SfG * SfU * SfU * SfC * SfC	ACUGGGGACGCCUCUGUUCC	SSSSS SSSSS SSSSS SSSS
WV-13784	fU * SfA * SfC * SfA * SfU * SfU * SmU * SmG * SmU * SmC * SmU * SmG * SmC * SmC * SfA * SfC * SfU * SfG * SfG * SfC	UACAUUUGUCUGCCACUGGC	SSSSS SSSSS SSSSS SSSS
WV-13785	fC * SfC * SfC * SfC * SfG * SfG * SfA * SmG * SmA * SmA * SmG * SmU * SmU * SmU * SmC * SfA * SfG * SfG * SfG * SfC * SfC	CCCGGAGAAGUUUCAGGGCC	SSSSS SSSSS SSSSS SSSS
WV-13786	fU * SfC * SfC * SfC * SfU * SfG * SfU * SmA * SmG * SmG * SmA * SmC * SmA * SmU * SmU * SfG * SfG * SfC * SfA * SfG * SfU	UCCUGUAGGACAUUGGCAGU	SSSSS SSSSS SSSSS SSSS
WV-13787	fG * SfA * SfG * SfU * SfC * SfU * SmU * SmC * SmU * SmA * SmG * SmG * SmA * SmG * SfC * SfC * SfU * SfU	GAGUCUUCUAGGAGCCUUUC	SSSSS SSSSS SSSSS SSSS

	* SfU * SfC		
WV-13788	fC * SfU * SfU * SfG * SfA * SfG * SmC * SmU * SmU * SmA * SmU * SmU * SmU * SmU * SfC * SfA * SfA * SfG * SfU * SfU	CUUGAGCUUAUUUUCAAGUU	SSSSS SSSSS SSSSS SSSS
WV-13789	fA * SfG * SfC * SfA * SfC * SfU * SmU * SmA * SmC * SmA * SmA * SmG * SmC * SmA * SfC * SfG * SfG * SfG * SfU * SfC	AGCACUUACAAGCACGGGUC	SSSSS SSSSS SSSSS SSSS
WV-13790	fU * SfU * SfG * SfU * SfA * SfC * SfU * SmU * SmC * SmA * SmU * SmC * SmC * SmC * SmA * SmC * SmU * SfG * SfA * SfU * SfU * SfC * SfU * SfG * SfA	UUGUACUUCAUCCCACUGAUUCUGA	SSSSSSSSSSSSS SSSSSSSSS
WV-13791	fU * SfU * SfG * SfU * SfA * SfC * SfU * SfU * SfC * SmAfU * SfC * SfC * SfC * SmAfC * SfU * SmGfA * SfU * SfU * SfC * SfU * SfG * SfA	UUGUACUUCAUCCCACUGAUUCUGA	SSSSSSSSSOSSSS OSSOSSSSSS
WV-13792	fU * SfU * SfG * SfU * SfA * SfC * SfU * SmUmCfA * SmUmCmCmCfA * SmCmUfG * SfA * SfU * SfU * SfC * SfU * SfG * SfA	UUGUACUUCAUCCCACUGAUUCUGA	SSSSSSOOSOOO OSOOSSSSSS
WV-13793	fU * SfU * SfG * SfU * SfA * SfC * SfU * SmUfC * SmAfU * SmCfC * SmCfA * SmCfU * SmGfA * SfU * SfU * SfC * SfU * SfG * SfA	UUGUACUUCAUCCCACUGAUUCUGA	SSSSSSOSOSOSO SOSOSSSSSS
WV-13794	fU * SfU * SfG * SfU * SfA * SfC * SfU * SfU * SmCfA * SmUfC * SmCfC * SmAfC * SmUfG * SfA * SfU * SfU * SfC * SfU * SfG * SfA	UUGUACUUCAUCCCACUGAUUCUGA	SSSSSSSOSOSOS OSOSSSSSS
WV-13795	fC * SfC * SfG * SfG * SfU * SfU * SfC * SmU * SmG * SmA * SmA * SmG * SmG * SmU * SmG * SmU * SmU * SfC * SfU * SfU * SfG * SfU * SfA * SfC * SfU	CCGGUUCUGAAGGUGUUCUUGUACU	SSSSSSSSSSSSS SSSSSSSS
WV-13796	fC * SfC * SfG * SfG * SfU * SfU * SfC * SfU * SmGmAmAmGmGfU * SmGfU * SfU * SfC * SfU * SfU * SfU * SfG * SfU * SfA * SfC * SfU	CCGGUUCUGAAGGUGUUCUUGUACU	SSSSSSSOOOOO SOSSSSSSSS
WV-13797	fC * SfC * SfG * SfG * SfU * SfU * SfC * SmUfG * SfA * SfA * SfG * SfG * SmUfG * SmUmUmCfU * SfU * SfG * SfU * SfA * SfC * SfU	CCGGUUCUGAAGGUGUUCUUGUACU	SSSSSSOSSSSSO SOOOSSSSSS
WV-13798	fC * SfC * SfG * SfG * SfU * SfU * SfC * SmUfG * SmAfA * SmGfG * SmUfG * SmUfU * SmCfU * SfU * SfG * SfU * SfU * SfA * SfC * SfU	CCGGUUCUGAAGGUGUUCUUGUACU	SSSSSSOSOSOS OSOSOSSSSS
WV-13799	fC * SfC * SfG * SfG * SfU * SfU * SfC * SfU * SmGfA * SmAfG * SmGfU * SmGfU * SmU * SfC * SfU * SfU * SfG	CCGGUUCUGAAGGUGUUCUUGUACU	SSSSSSSOSOSO SOSSSSSSSS

	* SfU * SfA * SfC * SfU		
WV-13810	fU * SfU * SfU * SfG * SfC * SfC * SfG * SfC * SmUfG * SmC * SfC * SmCmAfA * SfU * SfG * SfC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSSSSSSSOSSS OOSSSSS
WV-13811	fU * SfU * SfU * SfG * SfC * SfC * SfG * SfC * SmUfG * SmC * SfC * SmCfA * SfA * SfU * SfG * SfC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSSSSSSSOSSS OSSSSSS
WV-13812	fU * SfU * SfU * SfG * SfC * SfC * SfG * SfC * SmUn001fG * SmC * SfC * SmCn001mAn001fA * SfU * SfG * SfC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSSSSSSSnXSSS nXnXSSSSS
WV-13813	fU * SfU * SfU * SfG * SfC * SfC * SfG * SfC * SmUn001fG * SmC * SfC * SmCn001fA * SfA * SfU * SfG * SfC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSSSSSSSnXSSS nXSSSSSS
WV-13814	fU * SfU * SfUn001fG * SfC * SfCn001fG * SfC * SmUfG * SmC * SfC * SmCmAfA * SfU * SfGn001fC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSnXSSnXSSOSS SOOSSnXSS
WV-13815	fU * SfU * SfUn001fG * SfC * SfCn001fG * SfC * SmUfG * SmC * SfC * SmCfA * SfA * SfU * SfGn001fC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSnXSSnXSSOSS SOSSSnXSS
WV-13816	fU * SfU * SfUn001fG * SfC * SfCn001fG * SfC * SmUn001fG * SmC * SfC * SmCn001mAn001fA * SfU * SfGn001fC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSnXSSnXSSnXSSS nXnXSSnXSS
WV-13817	fU * SfU * SfUn001fG * SfC * SfCn001fG * SfC * SmUn001fG * SmC * SfC * SmCn001fA * SfA * SfU * SfGn001fC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSnXSSnXSSnXSSS nXSSSnXSS
WV-13818	fU * SfG * SfC * SfC * SfA * SfU * SfC * SfC * SmUfG * SmG * SfA * SmGmUfU * SfC * SfC * SfU * SfG * SfU	UGCCAUCCUGGAGUUCCUGU	SSSSSSSSOSSS OOSSSSS
WV-13819	fU * SfG * SfC * SfC * SfA * SfU * SfC * SfC * SmUfG * SmG * SfA * SmGfU * SfU * SfC * SfC * SfU * SfG * SfU	UGCCAUCCUGGAGUUCCUGU	SSSSSSSSOSSS OSSSSSS
WV-13820	fU * SfG * SfC * SfC * SfA * SfU * SfC * SfC * SmUn001fG * SmG * SfA * SmGn001mUn001fU * SfC * SfC * SfU * SfG * SfU	UGCCAUCCUGGAGUUCCUGU	SSSSSSSSnXSSS nXnXSSSSS
WV-13821	fU * SfG * SfC * SfC * SfA * SfU * SfC * SfC * SmUn001fG * SmG * SfA * SmGn001fU * SfU * SfC * SfC * SfU * SfG * SfU	UGCCAUCCUGGAGUUCCUGU	SSSSSSSSnXSSS nXSSSSSS
WV-13822	fU * SfG * SfCn001fC * SfA * SfUn001fC * SfC * SmUfG * SmG * SfA * SmGmUfU * SfC * SfCn001fU * SfG * SfU	UGCCAUCCUGGAGUUCCUGU	SSnXSSnXSSOSSSO OSSnXSS
WV-13823	fU * SfG * SfCn001fC * SfA * SfUn001fC * SfC * SmUfG * SmG * SfA * SmGfU * SfU * SfC * SfCn001fU * SfG * SfU	UGCCAUCCUGGAGUUCCUGU	SSnXSSnXSSOSSSO SSSnXSS
WV-	fU * SfG * SfCn001fC * SfA * SfUn001fC * SfC *	UGCCAUCCUGGAGUUCCUGU	SSnXSSnXSSnXSSS

13824	SmUn001fG * SmG * SfA * SmGn001mUn001fU * SfC * SfCn001fU * SfG * SfU	UGCCAUCCUGGAGUUCCUGU	nXnXSSnXSS
WV-13825	fU * SfG * SfCn001fC * SfA * SfUn001fC * SfC * SmUn001fG * SmG * SfA * SmGn001fU * SfU * SfC * SfCn001fU * SfG * SfU	UCCGGUUCUGAAGGUGUUC	SSnXSSnXSSnXSSS nXSSSnXSS
WV-13826	fU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfC	UCCGGUUCUGAAGGUGUUC	SSSSSSSOSSS OOSSSSS
WV-13827	fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU	CUCCGGUUCUGAAGGUGUU	SSSSSSSSOSSS OOSSSS
WV-13828	fU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU	UCCGGUUCUGAAGGUGUU	SSSSSSSOSSS OOSSSS
WV-13835	fU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUCUGAAGGUGUUCU	SSSSSSSOSSS OOSSSSSS
WV-13836	fC * SfC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU	CCUCCGGUUCUGAAGGUGUU	SSSSSSSSSOSSS OOSSSS
WV-13857	fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001fU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnXSSnXSSOS nXSOSSSnXSS
WV-13858	fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001fU * SfU	CUCCGGUUCUGAAGGUGUU	SSnXSSnXSSOSS SOSSSnXS
WV-13859	fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmGn001fA * SmAfG * SfG * SfU * SfGn001fU * SfU	CUCCGGUUCUGAAGGUGUU	SSnXSSnXSSOS nXSOSSSnXS
WV-13860	fU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001fU * SfU * SfC	UCCGGUUCUGAAGGUGUUC	SnXSSnXSSOSSSO SSSnXSS
WV-13861	fU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmGn001fA * SmAfG * SfG * SfU * SfGn001fU * SfU * SfC	UCCGGUUCUGAAGGUGUUC	SnXSSnXSSOSnX SOSSSnXSS
WV-13862	fU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001fU * SfU	UCCGGUUCUGAAGGUGUU	SnXSSnXSSOSSS OSSSnXS
WV-13863	fU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmGn001fA * SmAfG * SfG * SfU * SfGn001fU * SfU	UCCGGUUCUGAAGGUGUU	SnXSSnXSSOSnX SOSSSnXS
WV-13864	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnRSSnRSSOSS SOSSSnRSS
WV-13865	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmGn001RfA * SmAfG * SfG * SfU *	CUCCGGUUCUGAAGGUGUUC	SSnRSSnRSSOS nRSOSSSnRSS

	SfGn001RfU * SfU * SfC		
WV-13963	fA * SfC * SfA * SfA * SfG * SfU * SmU * SmC * SmU * SmC * SmC * SmU * SmU * SmC * SfU * SfG * SfG * SfA * SfA * SfA	ACAAGUUCUCCUUCUGGAAA	SSSSS SSSSS SSSSS SSSS
WV-13964	fC * SfU * SfU * SfC * SfU * SfG * SmG * SmA * SmA * SmA * SmG * SmG * SmU * SmU * SfC * SfC * SfA * SfA * SfC * SfA	CUUCUGGAAAGGUUCCAACA	SSSSS SSSSS SSSSS SSSS
WV-13965	fG * SfG * SfU * SfU * SfC * SfC * SmA * SmA * SmC * SmA * SmU * SmA * SmA * SmA * SfG * SfC * SfC * SfG * SfA * SfA	GGUUCCAACAUAAAGCCGAA	SSSSS SSSSS SSSSS SSSS
WV-13966	fA * SfA * SfA * SfG * SfC * SfC * SmG * SmA * SmA * SmA * SmU * SmA * SmC * SmA * SfC * SfA * SfC * SfU * SfG * SfC	AAAGCCGAAAUACACACUGC	SSSSS SSSSS SSSSS SSSS
WV-13967	fA * SfC * SfA * SfC * SfC * SfA * SfC * SmU * SmG * SmC * SmC * SmC * SmC * SmA * SmA * SfA * SfG * SfC * SfC * SfA * SfC	ACACACUGCCCCAAAGCCAC	SSSSS SSSSS SSSSS SSSS
WV-13968	fC * SfA * SfA * SfA * SfG * SfC * SmC * SmA * SmC * SmA * SmA * SmA * SmA * SmC * SfA * SfC * SfC * SfU * SfU * SfG	CAAAGCCACAAAACACCUUG	SSSSS SSSSS SSSSS SSSS
WV-13969	fA * SfA * SfC * SfC * SfA * SfC * SfC * SmU * SmU * SmG * SmC * SmU * SmG * SmU * SmU * SfA * SfC * SfG * SfA * SfU * SfG	AACACCUUGCUGUUACGAUG	SSSSS SSSSS SSSSS SSSS
WV-13970	fG * SfU * SfU * SfA * SfC * SfG * SmA * SmU * SmG * SmC * SmU * SmU * SmC * SmC * SfC * SfU * SfC * SfU * SfG * SfU	GUUACGAUGCUUCCCUCUGU	SSSSS SSSSS SSSSS SSSS
WV-13971	fU * SfC * SfC * SfC * SfU * SfC * SmU * SmG * SmU * SmC * SmA * SmC * SmA * SmG * SfA * SfU * SfU * SfC * SfA * SfA	UCCCUCUGUCACAGAUUCAA	SSSSS SSSSS SSSSS SSSS
WV-13972	fC * SfA * SfG * SfA * SfU * SfU * SmC * SmA * SmA * SmU * SmU * SmA * SmU * SmA * SfU * SfU * SfU * SfU * SfG * SfC	CAGAUUCAAUUAUAUUUUGC	SSSSS SSSSS SSSSS SSSS
WV-13973	fA * SfU * SfA * SfU * SfU * SmU * SmG * SmC * SmA * SmG * SmU * SmU * SmU * SfA * SfU * SfC * SfA * SfG * SfA	AUAUUUUGCAGUUUAUCAGA	SSSSS SSSSS SSSSS SSSS
WV-13974	fU * SfU * SfU * SfA * SfU * SfC * SmA * SmG * SmA * SmU * SmA * SmA * SmA * SmC * SfC * SfA * SfG * SfC	UUUAUCAGAUAAACCAGCUC	SSSSS SSSSS SSSSS SSSS

	* SfU * SfC		
WV-13975	fA * SfA * SfC * SfC * SfA * SfG * SmC * SmU * SmC * SmC * SmG * SmU * SmC * SmC * SfA * SfG * SfG * SfC * SfA * SfA	AACCAGCUCCGUCCAGGCAA	SSSSS SSSSS SSSSS SSSS
WV-13976	fU * SfC * SfC * SfA * SfG * SfG * SmC * SmA * SmA * SmA * SmC * SmU * SmC * SmU * SfC * SfU * SfC * SfA * SfU * SfC	UCCAGGCAAACUCUCUCAUC	SSSSS SSSSS SSSSS SSSS
WV-13977	fU * SfC * SfU * SfC * SfU * SfC * SmA * SmU * SmC * SmC * SmU * SmG * SmA * SmC * SfA * SfC * SfA * SfA * SfA * SfA	UCUCUCAUCCUGACACAAAA	SSSSS SSSSS SSSSS SSSS
WV-13978	fG * SfA * SfC * SfC * SfA * SfC * SfA * SmA * SmA * SmA * SmA * SmG * SmU * SmC * SmC * SfA * SfU * SfA * SfG * SfC * SfA	GACACAAAAAGUCCAUAGCA	SSSSS SSSSS SSSSS SSSS
WV-13979	fU * SfC * SfC * SfC * SfA * SfU * SfA * SmG * SmC * SmA * SmC * SmC * SmG * SmU * SmG * SfC * SfU * SfC * SfU * SfA * SfA * SfA	UCCAUAGCACCGUGCUCUAA	SSSSS SSSSS SSSSS SSSS
WV-13980	fG * SfU * SfG * SfC * SfU * SfC * SmU * SmA * SmA * SmU * SmA * SmU * SmU * SmA * SfU * SfC * SfA * SfU * SfU * SfA	GUGCUCUAAUAUUAUCAUUA	SSSSS SSSSS SSSSS SSSS
WV-13981	fU * SfU * SfA * SfU * SfC * SfA * SmU * SmU * SmA * SmU * SmG * SmA * SmU * SmA * SfA * SfU * SfU * SfU * SfU * SfC	UUAUCAUUAUGAUAAAUUUUC	SSSSS SSSSS SSSSS SSSS
WV-13982	fA * SfU * SfA * SfA * SfU * SfU * SmU * SmU * SmC * SmU * SmU * SmU * SmC * SmU * SfA * SfG * SfU * SfU * SfA * SfA * SfU	AUAAUUUUCUUUCUAGUAAU	SSSSS SSSSS SSSSS SSSS
WV-13983	fA * SfA * SfU * SfG * SfA * SfU * SmG * SmA * SmC * SmA * SmA * SmA * SmC * SmA * SfC * SfA * SfG * SfU * SfC * SfC * SfA	AAUGAUGACAACAACAGUCA	SSSSS SSSSS SSSSS SSSS
WV-13984	fC * SfA * SfA * SfC * SfA * SfG * SmU * SmC * SmA * SmA * SmA * SmA * SmG * SmU * SfA * SfA * SfU * SfU * SfU * SfC	CAACAGUCAAAAGUAAUUUC	SSSSS SSSSS SSSSS SSSS
WV-13985	fA * SfG * SfU * SfA * SfA * SfU * SmU * SmU * SmC * SmC * SmA * SmU * SmC * SmA * SfC * SfC * SfC * SfU * SfU * SfC	AGUAAUUUCCAUCACCCUUC	SSSSS SSSSS SSSSS SSSS
WV-13986	fU * SfC * SfA * SfC * SfC * SfC * SmU * SmU * SmC * SmA * SmG * SmA * SmA * SmC * SfC * SfU * SfG * SfA	UCACCCUUCAGAACCUGAUC	SSSSS SSSSS SSSSS SSSS

	* SfU * SfC		
WV-13987	fA * SfA * SfC * SfC * SfU * SfG * SmA * SmU * SmC * SmU * SmU * SmU * SmA * SmA * SfG * SfA * SfA * SfG * SfU * SfU	AACCUGAUCUUUAAGAAGUU	SSSSS SSSSS SSSSS SSSS
WV-13988	fU * SfA * SfA * SfG * SfA * SfA * SmG * SmU * SmU * SmA * SmA * SmA * SmG * SmA * SfG * SfU * SfC * SfC * SfA * SfG	UAAGAAGUUAAAGAGUCCAG	SSSSS SSSSS SSSSS SSSS
WV-13989	fA * SfG * SfA * SfG * SfU * SfC * SmC * SmA * SmG * SmA * SmU * SmG * SmU * SmG * SfC * SfU * SfG * SfA * SfA * SfG	AGAGUCCAGAUGUGCUGAAG	SSSSS SSSSS SSSSS SSSS
WV-13990	fG * SfU * SfG * SfC * SfC * SfU * SfG * SmA * SmA * SmG * SmA * SmU * SmA * SmA * SmA * SfU * SfA * SfC * SfA * SfA * SfU	GUGCUGAAGAUAAAUACAAU	SSSSS SSSSS SSSSS SSSS
WV-13991	fU * SfA * SfA * SfA * SfU * SfA * SmC * SmA * SmA * SmU * SmU * SmU * SmC * SmG * SfA * SfA * SfA * SfA * SfA	UAAAUACAAUUUCGAAAAAA	SSSSS SSSSS SSSSS SSSS
WV-13992	fA * SfC * SfA * SfA * SfU * SfU * SmU * SmC * SmG * SmA * SmA * SmA * SmA * SfA * SfC * SfA * SfA * SfA * SfU	ACAAUUUCGAAAAAACAAAU	SSSSS SSSSS SSSSS SSSS
WV-13993	fU * SfC * SfG * SfA * SfA * SmA * SmA * SmA * SmC * SmA * SmA * SmU * SfC * SfA * SfA * SfA * SfG * SfA	UCGAAAAAACAAAUCAAAGA	SSSSS SSSSS SSSSS SSSS
WV-13994	fA * SfA * SfA * SfC * SfA * SfA * SmA * SmU * SmC * SmA * SmA * SmA * SmG * SmA * SfC * SfU * SfU * SfA * SfC * SfC	AAACAAAUCAAAGACUUACC	SSSSS SSSSS SSSSS SSSS
WV-13995	fA * SfU * SfC * SfA * SfA * SfA * SmG * SmA * SmC * SmU * SmU * SmA * SmC * SmC * SfU * SfU * SfA * SfA * SfG * SfA	AUCAAAGACUUACCUUAAGA	SSSSS SSSSS SSSSS SSSS
WV-13996	fG * SfA * SfC * SfC * SfU * SfU * SfA * SmC * SmC * SmU * SmU * SmA * SmA * SmG * SmA * SfU * SfA * SfC * SfC * SfA * SfU	GACUUACCUUAAGAUACCAU	SSSSS SSSSS SSSSS SSSS
WV-13997	fU * SfU * SfA * SfC * SfC * SfU * SmU * SmA * SmA * SmG * SmA * SmU * SmA * SmC * SfC * SfA * SfU * SfU * SfU * SfG	UUACCUUAAGAUACCAUUUG	SSSSS SSSSS SSSSS SSSS
WV-13998	fU * SfA * SfC * SfC * SfU * SfU * SmA * SmA * SmG * SmA * SmU * SmA * SmC * SmC * SfA * SfU * SfU * SfU	UACCUUAAGAUACCAUUUGU	SSSSS SSSSS SSSSS SSSS

	* SfG * SfU		
WV-13999	fA * SfC * SfC * SfU * SfU * SfA * SmA * SmG * SmA * SmU * SmA * SmC * SmC * SmA * SfU * SfU * SfU * SfG * SfU * SfA	ACCUUAAGAUACCAUUUGUA	SSSSS SSSSS SSSSS SSSS
WV-14000	fC * SfC * SfU * SfU * SfA * SfA * SmG * SmA * SmU * SmA * SmC * SmC * SmA * SmU * SfU * SfU * SfG * SfU * SfA * SfU	CCUUAAGAUACCAUUUGUAU	SSSSS SSSSS SSSSS SSSS
WV-14001	fG * SfA * SfU * SfA * SfC * SfC * SmA * SmU * SmU * SmU * SmG * SmU * SmA * SmU * SfU * SfU * SfA * SfG * SfC * SfA	GAUACCAUUUGUAUUUAGCA	SSSSS SSSSS SSSSS SSSS
WV-14002	fA * SfU * SfU * SfU * SfU * SfG * SfU * SmA * SmU * SmU * SmU * SmA * SmG * SmC * SmA * SfU * SfG * SfU * SfU * SfC * SfC	AUUUGUAUUUAGCAUGUUCC	SSSSS SSSSS SSSSS SSSS
WV-14003	fA * SfU * SfU * SfU * SfA * SfG * SmC * SmA * SmU * SmG * SmU * SmU * SmC * SmC * SfC * SfA * SfA * SfU * SfU * SfC	AUUUAGCAUGUUCCCAAUUC	SSSSS SSSSS SSSSS SSSS
WV-14004	fC * SfA * SfU * SfG * SfU * SfU * SmC * SmC * SmC * SmA * SmA * SmU * SmU * SmC * SfU * SfC * SfA * SfG * SfG * SfA	CAUGUUCCCAAUUCUCAGGA	SSSSS SSSSS SSSSS SSSS
WV-14005	fC * SfC * SfC * SfA * SfA * SfU * SmU * SmC * SmU * SmC * SmA * SmG * SmG * SmA * SfA * SfU * SfU * SfU * SfG * SfU	CCCAAUUCUCAGGAAUUUGU	SSSSS SSSSS SSSSS SSSS
WV-14006	fU * SfC * SfU * SfC * SfA * SfG * SmG * SmA * SmA * SmU * SmU * SmU * SmG * SmU * SfG * SfU * SfC * SfU * SfU * SfU	UCUCAGGAAUUUGUGUCUUU	SSSSS SSSSS SSSSS SSSS
WV-14007	fG * SfA * SfA * SfU * SfU * SfU * SmG * SmU * SmG * SmU * SmC * SmU * SmU * SmU * SfC * SfU * SfG * SfA * SfG * SfA	GAAUUUGUGUCUUUCUGAGA	SSSSS SSSSS SSSSS SSSS
WV-14008	fG * SfU * SfG * SfU * SfC * SfU * SmU * SmU * SmC * SmU * SmG * SmA * SmG * SmA * SfA * SfA * SfC * SfU * SfG * SfU	GUGUCUUUCUGAGAAACUGU	SSSSS SSSSS SSSSS SSSS
WV-14009	fU * SfU * SfC * SfU * SfG * SfA * SmG * SmA * SmA * SmA * SmC * SmU * SmG * SmU * SfU * SfC * SfA * SfG * SfC * SfU	UUCUGAGAAACUGUUCAGCU	SSSSS SSSSS SSSSS SSSS
WV-14010	fG * SfA * SfA * SfA * SfC * SfU * SmG * SmU * SmU * SmC * SmA * SmG * SmC * SmU * SfU * SfC * SfU * SfG	GAAACUGUUCAGCUUCUGUU	SSSSS SSSSS SSSSS SSSS

	* SfU * SfU			
WV-14011	fG * SfU * SfU * SfC * SfA * SfG * SmC * SmU * SmU * SmC * SmU * SmG * SmU * SfA * SfG * SfC * SfC * SfA * SfC	GUUCAGCUUCUGUUAGCCAC	SSSSS SSSSS SSSSS SSSS	
WV-14012	fC * SfU * SfU * SfC * SfU * SfG * SmU * SmU * SmA * SmG * SmC * SmC * SmA * SmC * SfU * SfG * SfA * SfU * SfU * SfA	CUUCUGUUAGCCACUGAUUA	SSSSS SSSSS SSSSS SSSS	
WV-14013	fU * SfU * SfA * SfG * SfC * SfC * SmA * SmC * SmU * SmG * SmA * SmU * SmU * SmA * SfA * SfA * SfU * SfA * SfU * SfC	UUAGCCACUGAUUAAAUAUC	SSSSS SSSSS SSSSS SSSS	
WV-14014	fA * SfC * SfU * SfG * SfA * SfU * SmU * SmA * SmA * SmA * SmU * SmA * SmU * SmC * SfU * SfU * SfU * SfA * SfU * SfA	ACUGAUUAAAUAUCUUUAUA	SSSSS SSSSS SSSSS SSSS	
WV-14015	fA * SfU * SfC * SfU * SfU * SfU * SmA * SmU * SmA * SmU * SmC * SmA * SmU * SmA * SfA * SfU * SfG * SfA * SfA * SfA	AUCUUUAUAUCAUAAUGAAA	SSSSS SSSSS SSSSS SSSS	
WV-14016	fA * SfU * SfA * SfA * SfU * SfG * SmA * SmA * SmA * SmA * SmC * SmG * SmC * SmC * SfG * SfC * SfC * SfA * SfU * SfU	AUAAUGAAAACGCCGCCAUU	SSSSS SSSSS SSSSS SSSS	
WV-14017	fG * SfC * SfC * SfC * SfG * SfC * SfC * SmA * SmU * SmU * SmU * SmC * SmU * SmC * SmA * SfA * SfC * SfA * SfG * SfA * SfU	GCCGCCAUUUCUCAACAGAU	SSSSS SSSSS SSSSS SSSS	
WV-14018	fU * SfC * SfA * SfA * SfC * SfC * SfA * SmG * SmA * SmU * SmC * SmU * SmG * SmU * SmC * SfA * SfA * SfA * SfU * SfC * SfG	UCAACAGAUCUGUCAAAUCG	SSSSS SSSSS SSSSS SSSS	
WV-14019	fU * SfG * SfA * SfA * SfG * SfA * SmU * SmA * SmA * SmA * SmU * SmA * SmC * SfA * SfU * SfU * SfU * SfU * SfC * SfG	UGAAGAUAAAUACAAUUUCG	SSSSS SSSSS SSSSS SSSS	
WV-14020	fA * SfU * SfU * SfU * SfC * SfG * SmA * SmA * SmA * SmA * SmA * SmA * SmC * SmA * SfA * SfA * SfU * SfC * SfA * SfA	AUUUCGAAAAAACAAAUCAA	SSSSS SSSSS SSSSS SSSS	
WV-14021	fA * SfA * SfA * SfA * SfA * SfA * SmC * SmA * SmA * SmA * SmU * SmC * SmA * SmA * SfA * SfG * SfA * SfC * SfU * SfU	AAAAAACAAAUCAAAGACUU	SSSSS SSSSS SSSSS SSSS	
WV-14022	fC * SfA * SfA * SfA * SfU * SfC * SmA * SmA * SmA * SmG * SmA * SmC * SmU * SmU * SfA * SfC * SfC * SfU	CAAAUCAAAGACUUACCUUA	SSSSS SSSSS SSSSS SSSS	

	* SfU * SfA		
WV-14023	fA * SfA * SfA * SfG * SfA * SfC * SmU * SmU * SmA * SmC * SmC * SmU * SmU * SmA * SfA * SfG * SfA * SfU * SfA * SfC	AAAGACUUACCUUAAGAUAC	SSSSS SSSSS SSSSS SSSS
WV-14024	fU * SfA * SfA * SfG * SfA * SfU * SmA * SmC * SmC * SmA * SmU * SmU * SmU * SmG * SfU * SfA * SfU * SfU * SfU * SfU * SfA	UAAGAUACCAUUUGUAUUUA	SSSSS SSSSS SSSSS SSSS
WV-14025	fA * SfC * SfC * SfA * SfU * SfU * SmU * SmG * SmU * SmA * SmU * SmU * SmU * SmA * SfG * SfC * SfA * SfU * SfG * SfU	ACCAUUUGUAUUUAGCAUGU	SSSSS SSSSS SSSSS SSSS
WV-14026	fU * SfG * SfU * SfA * SfU * SfU * SmU * SmA * SmG * SmC * SmA * SmU * SmG * SmU * SfU * SfC * SfC * SfC * SfA * SfA * SfA	UGUAUUUAGCAUGUUCCCAA	SSSSS SSSSS SSSSS SSSS
WV-14027	fU * SfG * SfC * SfU * SfG * SfA * SmA * SmG * SmA * SmU * SmA * SmA * SfA * SfU * SfA * SfC * SfA * SfA	UGCUGAAGAUAAAUACAA	SSSSS SSSSS SSSSS SS
WV-14028	fA * SfA * SfA * SfU * SfA * SfC * SmA * SmA * SmU * SmU * SmU * SmC * SfG * SfA * SfA * SfA * SfA * SfA	AAAUACAAUUUCGAAAAA	SSSSS SSSSS SSSSS SS
WV-14029	fC * SfA * SfA * SfU * SfU * SfU * SmC * SmG * SmA * SmA * SmA * SmA * SfA * SfA * SfC * SfA * SfA * SfA	CAAUUUCGAAAAAACAAA	SSSSS SSSSS SSSSS SS
WV-14030	fC * SfG * SfA * SfA * SfA * SfA * SmA * SmA * SmC * SmA * SmA * SmA * SfU * SfC * SfA * SfA * SfA * SfG	CGAAAAAACAAAUCAAAG	SSSSS SSSSS SSSSS SS
WV-14031	fA * SfA * SfC * SfA * SfA * SfA * SmU * SmC * SmA * SmA * SmA * SmG * SfA * SfC * SfU * SfU * SfA * SfC	AACAAAUCAAAGACUUAC	SSSSS SSSSS SSSSS SS
WV-14032	fU * SfC * SfA * SfA * SfA * SfG * SmA * SmC * SmU * SmU * SmA * SmC * SfC * SfU * SfU * SfA * SfA * SfG	UCAAAGACUUACCUUAAG	SSSSS SSSSS SSSSS SS
WV-14033	fA * SfC * SfU * SfU * SfU * SfA * SfC * SmC * SmU * SmU * SmA * SmA * SmG * SfA * SfU * SfA * SfC * SfC * SfA	ACUUACCUUAAGAUACCA	SSSSS SSSSS SSSSS SS
WV-14034	fU * SfA * SfC * SfC * SfC * SfU * SfU * SmA * SmA * SmG * SmA * SmU * SmA * SfC * SfC * SfA * SfU * SfU * SfU	UACCUUAAGAUACCAUUU	SSSSS SSSSS SSSSS SS
WV-14035	fA * SfC * SfC * SfU * SfU * SfA * SmA * SmG * SmA * SmU * SmA * SmC * SfC * SfA * SfU * SfU * SfU * SfG	ACCUUAAGAUACCAUUUG	SSSSS SSSSS SSSSS SS
WV-14036	fC * SfC * SfU * SfU * SfA * SfA * SmG * SmA * SmU * SmA * SmC * SmC * SfA * SfU * SfU * SfU * SfG * SfU	CCUUAAGAUACCAUUUGU	SSSSS SSSSS SSSSS SS
WV-14037	fC * SfU * SfU * SfA * SfA * SfG * SmA * SmU * SmA * SmC * SmC * SmA * SfU * SfU * SfU * SfG * SfU * SfA	CUUAAGAUACCAUUUGUA	SSSSS SSSSS SSSSS SS
WV-	fA * SfU * SfA * SfC * SfC * SfA * SmU * SmU * SmU *	AUACCAUUUGUAUUUAGC	SSSSS SSSSS SSSSS SS

14038	SmG * SmU * SmA * SfU * SfU * SfU * SfA * SfG * SfC		
WV-14039	fU * SfU * SfU * SfG * SfU * SfA * SmU * SmU * SmU * SmA * SmG * SmC * SfA * SfU * SfG * SfU * SfU * SfC	UUUGUAUUUAGCAUGUUC	SSSSS SSSSS SSSSS SS
WV-14040	fU * SfU * SfU * SfA * SfG * SfC * SmA * SmU * SmG * SmU * SmU * SmC * SfC * SfC * SfA * SfA * SfU * SfU	UUUAGCAUGUUCCCAAUU	SSSSS SSSSS SSSSS SS
WV-14041	fA * SfU * SfG * SfU * SfU * SfC * SmC * SmC * SmA * SmA * SmU * SmU * SfC * SfU * SfC * SfA * SfG * SfG	AUGUUCCCAAUUCUCAGG	SSSSS SSSSS SSSSS SS
WV-14042	fC * SfC * SfA * SfA * SfU * SfU * SmC * SmU * SmC * SmA * SmG * SmG * SfA * SfA * SfU * SfU * SfU * SfG	CCAAUUCUCAGGAAUUUG	SSSSS SSSSS SSSSS SS
WV-14043	fC * SfU * SfC * SfA * SfG * SfG * SmA * SmA * SmU * SmU * SmU * SmG * SfU * SfG * SfU * SfC * SfU * SfU	CUCAGGAAUUUGUGUCUU	SSSSS SSSSS SSSSS SS
WV-14044	fA * SfA * SfU * SfU * SfU * SfG * SmU * SmG * SmU * SmC * SmU * SmU * SfU * SfC * SfU * SfG * SfA * SfG	AAUUUGUGUCUUUCUGAG	SSSSS SSSSS SSSSS SS
WV-14045	fU * SfG * SfU * SfC * SfU * SfU * SmU * SmC * SmU * SmG * SmA * SmG * SfA * SfA * SfA * SfC * SfU * SfG	UGUCUUUCUGAGAAACUG	SSSSS SSSSS SSSSS SS
WV-14046	fU * SfC * SfU * SfG * SfA * SfG * SmA * SmA * SmA * SmC * SmU * SmG * SfU * SfU * SfC * SfA * SfG * SfC	UCUGAGAAACUGUUCAGC	SSSSS SSSSS SSSSS SS
WV-14047	fA * SfA * SfA * SfC * SfU * SfG * SmU * SmU * SmC * SmA * SmG * SmC * SfU * SfU * SfC * SfU * SfG * SfU	AAACUGUUCAGCUUCUGU	SSSSS SSSSS SSSSS SS
WV-14048	fU * SfU * SfC * SfA * SfG * SfC * SmU * SmU * SmC * SmU * SmG * SmU * SfU * SfA * SfG * SfC * SfC * SfA	UUCAGCUUCUGUUAGCCA	SSSSS SSSSS SSSSS SS
WV-14049	fU * SfU * SfC * SfU * SfG * SfU * SmU * SmA * SmG * SmC * SmC * SmA * SfC * SfU * SfG * SfA * SfU * SfU	UUCUGUUAGCCACUGAUU	SSSSS SSSSS SSSSS SS
WV-14050	fU * SfA * SfG * SfC * SfC * SfA * SmC * SmU * SmG * SmA * SmU * SmU * SfA * SfA * SfU * SfA * SfA * SfU	UAGCCACUGAUUAAAUAU	SSSSS SSSSS SSSSS SS
WV-14051	fG * SfA * SfA * SfG * SfA * SfU * SmA * SmA * SmA * SmU * SmA * SmC * SfA * SfA * SfU * SfU * SfC	GAAGAUAAAUACAAUUUC	SSSSS SSSSS SSSSS SS
WV-14052	fU * SfU * SfU * SfC * SfG * SfA * SmA * SmA * SmA * SmA * SmA * SmC * SfA * SfA * SfU * SfC * SfA	UUUCGAAAAAACAAAUCA	SSSSS SSSSS SSSSS SS
WV-14053	fA * SfA * SfA * SfA * SfA * SfC * SmA * SmA * SmA * SmU * SmC * SmA * SfA * SfA * SfG * SfA * SfC * SfU	AAAAACAAAUCAAAGACU	SSSSS SSSSS SSSSS SS
WV-14054	fA * SfA * SfA * SfU * SfC * SfA * SmA * SmA * SmG * SmA * SmC * SmU * SfU * SfA * SfC * SfC * SfU * SfU	AAAUCAAAGACUUACCUU	SSSSS SSSSS SSSSS SS
WV-14055	fA * SfA * SfG * SfA * SfC * SfU * SmU * SmA * SmC * SmC * SmU * SmU * SfA * SfA * SfG * SfA * SfU * SfA	AAGACUUACCUUAAGAUA	SSSSS SSSSS SSSSS SS
WV-	fA * SfA * SfG * SfA * SfU * SfA * SmC * SmC * SmA *	AAGAUACCAUUUGUAUUU	SSSSS SSSSS SSSSS SS

14056	SmU * SmU * SmU * SfG * SfU * SfA * SfU * SfU * SfU		
WV-14057	fC * SfC * SfA * SfU * SfU * SfU * SmG * SmU * SmA * SmU * SmU * SmU * SfA * SfG * SfC * SfA * SfU * SfG	CCAUUUGUAUUUAGCAUG	SSSSS SSSSS SSSSS SS
WV-14058	fG * SfU * SfA * SfU * SfU * SfU * SmA * SmG * SmC * SmA * SmU * SmG * SfU * SfU * SfC * SfC * SfC * SfA	GUAUUUAGCAUGUUCCCA	SSSSS SSSSS SSSSS SS
WV-14107	fA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfU * SfC * SfU	AGGAAGAUGGCAUUUCU	SSSOSOSS OOSSSSSS
WV-14108	fG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfU * SfC * SfU	GGAAGAUGGCAUUUCU	SSOSOSS OOSSSSSS
WV-14109	fG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	GAAGAUGGCAUUUCU	SOSOSSO OSSSSSS
WV-14110	mAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	AAGAUGGCAUUUCU	OSOSSOOSSSSS
WV-14111	fA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfU * SfC * SfU	AGAUGGCAUUUCU	SOSSOOSSSSS
WV-14112	mGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	GAUGGCAUUUCU	OSSOOSSSSS
WV-14113	mA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	AUGGCAUUUCU	SSOOSSSSS
WV-14114	fU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UGGCAUUUCU	SOOSSSSS
WV-14115	mGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	GGCAUUUCU	OOSSSSS
WV-14116	mGfC * SfA * SfU * SfU * SfU * SfC * SfU	GCAUUUCU	OSSSSS
WV-14117	fC * SfA * SfU * SfU * SfU * SfC * SfU	CAUUUCU	SSSSS
WV-14118	fA * SfU * SfU * SfU * SfC * SfU	AUUUCU	SSSSS
WV-14119	fU * SfU * SfC * SfU	UUCU	SSS
WV-14120	fU * SfC * SfU	UCU	SS
WV-14121	fC * RfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	CAAGGAAGAUGGCAUUUCU	RSSSSOSOSS OOSSSSSS
WV-	fA * RfA * SfG * SfG * SmAfA * SmGmA * SfU *	AAGGAAGAUGGCAUUUCU	RSSSOSOSS

14122	SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU		OOSSSSSS
WV-14123	fA * RfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	AGGAAGAUGGCAUUUCU	RSSOSOSS OOSSSSSS
WV-14124	fG * RfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	GGAAGAUGGCAUUUCU	RSOSOSSOOSSSSSS
WV-14125	fG * RmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	GAAGAUGGCAUUUCU	ROSOSSOOSSSSSS
WV-14126	fA * RmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	AGAUGGCAUUUCU	ROSSOOSSSSSS
WV-14127	mA * RfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	AUGGCAUUUCU	RSOOSSSSSS
WV-14128	fU * RmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UGGCAUUUCU	ROOSSSSSS
WV-14129	fC * RfA * SfU * SfU * SfU * SfC * SfU	CAUUUCU	RSSSSS
WV-14130	fA * RfU * SfU * SfU * SfC * SfU	AUUUCU	RSSSS
WV-14131	fU * RfU * SfC * SfU	UUCU	RSS
WV-14132	fU * RfC * SfU	UCU	RS
WV-14332	Mod097L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	OSSSSSSOSSSS OOSSSSSS
WV-14333	Mod059L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	OSSSSSSOSSSS OOSSSSSS
WV-14334	Mod070L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	OSSSSSSOSSSS OOSSSSSS
WV-14335	Mod057L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	OSSSSSSOSSSS OOSSSSSS
WV-14342	fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001fU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnXSSnXSSOS SSOOSSnXSS
WV-	fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU *	CUCCGGUUCUGAAGGUGUUC	SSnXSSnXSSOS

14343	SmGn001fA * SmAfGfG * SfU * SfGn001fU * SfU * SfC		nXSOOSSnXSS
WV-14344	fC * SfU * SfCn001RfC * SfG * SfGm001RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnRSSnRSSOS SSOOSSnRSS
WV-14345	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmGn001RfA * SmAfGfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnRSSnRSSOS nRSOOSSnRSS
WV-14346	Mod098L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	OSSSSSSOSSSS OOSSSSSS
WV-14347	Mod099L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	OSSSSSSOSSSS OOSSSSSS
WV-14348	Mod100L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	OSSSSSSOSSSS OOSSSSSS
WV-14522	fU * SfC * SfAn001fA * SfG * SfGn001mAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfUn001fU * SfC * SfU	UCAAGGAAGAUGGCAUUUCU	SSnXSSnXOSOS SOOSSSnXSS
WV-14523	fU * SfC * SfAn001fA * SfG * SfGn001mAfA * SmGmA * SfU * SmGmGfCn001fA * SfU * SfUn001fU * SfC * SfU	UCAAGGAAGAUGGCAUUUCU	SSnXSSnXOSOS SOOnXSSnXSS
WV-14524	fU * SfU * SfU * SfG * SfC * SfC * SmGfC * SmUmG * SfC * SmCmCmA * SfA * SfU * SfG * SfC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSSSSSOSOSS OOSSSSSS
WV-14525	fU * SfU * SfUn001fG * SfC * SfCn001mGfC * SmUmG * SfC * SmCmCmA * SfA * SfU * SfGn001fC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSnXSSnXOSOSS OOSSSnXSS
WV-14526	fU * SfU * SfUn001fG * SfC * SfCn001mGfC * SmUmG * SfC * SmCmCmAn001fA * SfU * SfGn001fC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSnXSSnXOSOSS OOnXSSnXSS
WV-14527	fU * SfG * SfC * SfC * SfA * SfU * SmCfC * SmUmG * SfG * SmAmGfU * SfU * SfC * SfC * SfU * SfG * SfU	UGCCAUCCUGGAGUUCCUGU	SSSSSSOSOSS OOSSSSSS
WV-14528	fU * SfG * SfCn001fC * SfA * SfUn001mCfC * SmUmG * SfG * SmAmGfU * SfU * SfC * SfCn001fU * SfG * SfU	UGCCAUCCUGGAGUUCCUGU	SSnXSSnXOSOS SOOSSSnXSS
WV-14529	fU * SfG * SfCn001fC * SfA * SfUn001mCfC * SmUmG * SfG * SmAmGfUn001fU * SfC * SfCn001fU * SfG * SfU	UGCCAUCCUGGAGUUCCUGU	SSnXSSnXOSOS SOOnXSSnXSS
WV-14530	fU * SfC * SfAn001fC * SfU * SfCn001mAfG * SfA * SmU * SfA * SmGmUfUn001fG * SfA * SfAn001fG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	SSnXSSnXOSSSS OOnXSSnXSS
WV-14531	fU * SfU * SfU * SfG * SfC * SfC * SmGfC * SmUmG * SfC * SmCmCfA * SfA * SfU * SfG * SfC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSSSSSOSOSS OOSSSSSS

WV-14532	fU * SfU * SfUn001fG * SfC * SfCn001mGfC * SmUmG * SfC * SmCmCfA * SfA * SfU * SfGn001fC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSnXSSnXOSOSS OOSSSnXSS
WV-14533	fU * SfU * SfUn001fG * SfC * SfCn001mGfC * SmUmG * SfC * SmCmCfAn001fA * SfU * SfGn001fC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSnXSSnXOSOSS OOnXSSnXSS
WV-14565	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU	CUCCGGUUCUGAAGGUGUU	SSnRSSnRSSOSSS OSSSnRS
WV-14566	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001RfU * SfU	CUCCGGUUCUGAAGGUGUU	SSnRSSnRSSOSS SOOSSnRS

WV-14773	fU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfGn001RfU * SfU * SfC * SfU	UCCGGUUCUGA AGGUGUUCU	SnRSSnRSSOS SSOOSSnRSSS
WV-14774	fU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfUn001RfG * SfU * SfUn001RfC * SfU	UCCGGUUCUGA AGGUGUUCU	SnRSSnRSSOS SSOOSnRSSnRS
WV-14775	fU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUCUGA AGGUGUUCU	SSSSSSSOSSS OOSSSSSS
WV-14776	fU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001RfU * SfU * SfC * SfU	UCCGGUUCUGA AGGUGUUCU	SnRSSnRSSOS SSOOSSnRSSS
WV-14777	fU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfUn001RfG * SfU * SfUn001RfC * SfU	UCCGGUUCUGA AGGUGUUCU	SnRSSnRSSOS SSOOSnRSSnRS
WV-14778	fU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfUn001RfU * SfC * SfU	UCCGGUUCUGA AGGUGUUCU	SnRSSnRSSOS SSOOSSSnRSS
WV-14779	fU * SfC * SfCn001RfG * SfG * SfUn001RfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfUn001RfU * SfC * SfU	UCCGGUUCUGA AGGUGUUCU	SSnRSSnRSO SSSOOSSSnRSS
WV-14790	fU * SfC * SfCn001RfG * SfG * SfUn001RfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfGn001fU * SfU * SfC * SfU	UCCGGUUCUGA AGGUGUUCU	SSnRSSnRSO SSSOOSSnXSSS
WV-14791	fU * SfC * SfCn001RfG * SfG * SfUn001RfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfGn001RfU * SfU * SfC * SfU	UCCGGUUCUGA AGGUGUUCU	SSnRSSnRSO SSSOOSSnRSSS
WV-15052	BrfU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSSSSSnXSSSS nXnXSSSSSS
WV-15053	Acet5fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSSSSSnXSSSS nXnXSSSSSS
WV-15074	Mod102L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	OSSSSSSOSSS SOOSSSSSS
WV-	Mod103L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU *	UCACUCAGAUA	OSSSSSSOSSS

15075	SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	GUUGAAGCC	SOOSSSSS
WV-15076	Mod104L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	OSSSSSSOSSS SOOSSSSSS
WV-15143	fC * SfU * SfCn001SfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGA AGGUGUUC	SSnSSSnRSSOS SSOOSSnRSS
WV-15322	fC * SfU * SfCn001SfC * SfG * SfGn001SfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001SfU * SfU * SfC	CUCCGGUUCUGA AGGUGUUC	SSnSSSnSSSOSSS OOSSnSSS
WV-15323	fC * fU * fCn001SfC * fG * fGn001SfU * fU * mCfU * mG * fA * mAfGfG * fU * fGn001SfU * fU * fC	CUCCGGUUCUGA AGGUGUUC	XXnSXXnSXXO XXXOOXXnSXX
WV-15324	fC * fU * fCn001RfC * fG * fGn001RfU * fU * mCfU * mG * fA * mAfGfG * fU * fGn001RfU * fU * fC	CUCCGGUUCUGA AGGUGUUC	XXnRXXnRXXO XXXOOXXnRXX
WV-15325	fC * fU * fCn001fC * fG * fGn001fU * fU * mCfU * mG * fA * mAfGfG * fU * fGn001fU * fU * fC	CUCCGGUUCUGA AGGUGUUC	XXnXXXnXXXO XXXOOXXnXXX
WV-15326	fU * SfC * SfCn001SfG * SfG * SfUn001SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfGn001SfU * SfU * SfC * SfU	UCCGGUUCUGA AGGUGUUCU	SSnSSSnSSOSSS OOSSnSSSS
WV-15327	fU * fC * fCn001SfG * fG * fUn001SfU * mCfU * mG * fA * mAmGfG * fU * fGn001SfU * fU * fC * fU	UCCGGUUCUGA AGGUGUUCU	XXnSXXnSX OXXXOOXX nSXXX
WV-15328	fU * fC * fCn001RfG * fG * fUn001RfU * mCfU * mG * fA * mAmGfG * fU * fGn001RfU * fU * fC * fU	UCCGGUUCUGA AGGUGUUCU	XXnRXXnRX OXXXOOXX nRXXX
WV-15329	fU * fC * fCn001fG * fG * fUn001fU * mCfU * mG * fA * mAmGfG * fU * fGn001fU * fU * fC * fU	UCCGGUUCUGA AGGUGUUCU	XXnXXXnXXO XXXOOXXnXXX
WV-15330	fC * SfU * SfCn001SfC * SfG * SfGn001SfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001SfU * SfU * SfC	CUCCGGUUCUGA AGGUGUUC	SSnSSSnSSSOSSS OSSSnSSS
WV-15331	fC * fU * fCn001SfC * fG * fGn001SfU * fU * mCfU * mG * fA * mAfG * fG * fU * fGn001SfU * fU * fC	CUCCGGUUCUGA AGGUGUUC	XXnSXXnSXXO XXXOXXXnSXX
WV-15332	fC * fU * fCn001RfC * fG * fGn001RfU * fU * mCfU * mG * fA * mAfG * fG * fU * fGn001RfU * fU * fC	CUCCGGUUCUGA AGGUGUUC	XXnRXXnRXXO XXXOXXXnRXX
WV-15333	fC * fU * fCn001fC * fG * fGn001fU * fU * mCfU * mG * fA * mAfG * fG * fU * fGn001fU * fU * fC	CUCCGGUUCUGA AGGUGUUC	XXnXXXnXXXO XXXOXXXnXXX
WV-15334	fU * SfC * SfCn001RfG * SfG * SfUn001RfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfUn001fU * SfC * SfU	UCCGGUUCUGA AGGUGUUCU	SSnRSSnRSO SSSOOSSSnXSS
WV-15335	fU * SfC * SfCn001SfG * SfG * SfUn001SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfUn001SfU * SfC * SfU	UCCGGUUCUGA AGGUGUUCU	SSnSSSnSSOSSS OOSSSnSSS
WV-15336	L001fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	OSSSSSSnXSSSS nXnXSSSSSS
WV-	Mod059L001fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA *	UCACUCAGAUA	OSSSSSSnXSSSS

15337	SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	GUUGAAGCC	nXnXSSSSS
WV-15338	Mod098L001fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	OSSSSSSnX SSSS nXnXSSSSSS
WV-15366	L001L005fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	OOSSSSSSnX SSSS nXnXSSSSSS
WV-15367	Mod105L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	OSSSSSSOSSS SOOSSSSSS
WV-15368	Mod074L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	OSSSSSSOSSS SOOSSSSSS
WV-15369	fU * SfC * SfCn001RfG * SfG * SfUn001RfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUCUGA AGGUGUUCU	SSnRSSnRSO SSSOOSSSSSS
WV-15588	fU * SfC * SfA * SfC * SfU * SfC * SfA * SmGfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSSSSSSOSSS OOSSSSSS
WV-15589	fU * SfC * SfAn001fC * SfU * SfCn001fA * SmGfA * SmU * SfA * SmGmUfU * SfG * SfA * SfAn001fG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSnXSSnXSOSS SOOSSSnXSS
WV-15646	Mod098L001fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGA AGGUGUUC	OSSSSSSSSOSSS OOSSSSS
WV-15647	Mod098L001fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001fU * SfU * SfC	CUCCGGUUCUGA AGGUGUUC	OSSnXSSnXSSOSSS OSSSnXSS
WV-15844	Mod106fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSSSSSnXSSSS nXnXSSSSSS
WV-15845	Mod107fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSSSSSnXSSSS nXnXSSSSSS
WV-15846	Mod071L001fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	OSSSSSSnXSSSS nXnXSSSSSS
WV-15847	L001fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGA AGGUGUUC	OSSSSSSSSOSSS OOSSSSS
WV-15848	Mod071L001fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGA AGGUGUUC	OSSSSSSSSOSSS OOSSSSS
WV-15849	Mod102L001fC * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC	CUCCGGUUCUGA AGGUGUUC	OSSSSSSSSOSSS OOSSSSS
WV-15850	L001fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001fU * SfU * SfC	CUCCGGUUCUGA AGGUGUUC	OSSnXSSnXSSOSSS OSSSnXSS
WV-15851	Mod071L001fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001fU * SfU * SfC	CUCCGGUUCUGA AGGUGUUC	OSSnXSSnXSSOSSS OSSSnXSS
WV-	Mod102L001fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU	CUCCGGUUCUGA	OSSnXSSnXSSOSSS

15852	* SmG * SfA * SmAfG * SfG * SfU * SfGn001fU * SfU * SfC	AGGUGUUC	OSSSnXSS
WV-15853	fU * SfC * SfAn001fC * SfU * SfC * SfA * SmGfA * SmU * SfA * SmGmUfUn001fG * SfA * SfAn001fG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSnXSSSS OSSS OOnXSSnXSS
WV-15854	fU * SfC * SfAn001fC * SfU * SfCn001fA * SmGfA * SmU * SfA * SmGmUfUn001fG * SfA * SfAn001fG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSnXSSnXSOSSS OOnXSSnXSS
WV-15855	fU * SfC * SfAn001fC * SfU * SfCn001fA * SmGfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSnXSSnXSOSSS OOSSSSSS
WV-15856	fU * SfC * SfA * SfC * SfU * SfC * SfA * SmGfA * SmU * SfA * SmGmUfUn001fG * SfA * SfAn001fG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSSSSSSOSSS OOnXSSnXSS
WV-15857	fU * SfC * SfAn001fC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfUn001fG * SfA * SfAn001fG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSnXSSSOSSS SOOnXSSnXSS
WV-15858	fU * SfC * SfAn001fC * SfU * SfCn001mAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSnXSSnXOSSSS OOSSSSSS
WV-15859	fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfUn001fG * SfA * SfAn001fG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSSSSSOSSS SOOnXSSnXSS
WV-15860	fU * SfC * SfAn001fA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfCn001fA * SfU * SfUn001fU * SfC * SfU	UCAAGGAAGAU GGCAUUUCU	SSnXSSSOSOSSO OnXSSnXSS
WV-15861	fU * SfC * SfAn001fA * SfG * SfGn001mAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfC * SfU	UCAAGGAAGAU GGCAUUUCU	SSnXSSnXOSOSS OOSSSSSS
WV-15862	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfCn001fA * SfU * SfUn001fU * SfC * SfU	UCAAGGAAGAU GGCAUUUCU	SSSSSSOSOSSOO nXSSnXSS

WV-15882	Mod071L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	O SSSSSSO SSSSOO SSSSSS
WV-15883	fC * SfU * SfCn002 RfC * SfG * SfGn002 RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn002 RfU * SfU * SfC	CUCCGGUUCUGAAG GUGUUC	SSnR SSnR SSOSSSOOSSnR SS
WV-15884	mU * SGeon002 m5Ceon002 m5Ceon002 mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGG TTATGACUC	SnXnXnXSS RSSRSSR SSSSSS
WV-15885	mU * SGeon002 Rm5Ceon002 Rm5Ceon002 RmA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGG TTATGACUC	SnRnRnR SSRSSRSSR SSSSSS
WV-15886	fC * SfU * SfCn002 fC * SfG * SfGn002 fU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn002 fU * SfU * SfC	CUCCGGUUCUGAAG GUGUUC	SSnXSSnXSSOSSSOOSS nXSS
WV-15912	fCn001 fUn001 fCn001 fCn001 fGn001 fUn001 fUn001 mCfUn001 mGn001 fAn001 mAfGfGn001 fUn001 fGn001 fUn001 fUn001 fC	CUCCGGUUCUGAAG GUGUUC	nXnXnXnXnX nXnXnXOnXnXnX OOnXnXnXnXnX
WV-	fCn001 fUn001 fCn001 fCn001 fGn001 fUn001 fUn001 mCn001	CUCCGGUUCUGAAG	nXnXnXnXnX nXnX

15913	fUn001 mGn001 fAn001 mAn001 fGn001 fGn001 fUn001 fGn001 fUn001 fUn001 fC	GUGUUC	nXnXnX nXnXnXnXnX nXnXnXnX
WV-15927	fA * SfU * SfU * SfU * SfA * SfG * SfC * SfA * SmU * SfG * SmU * SfU * SmC * SfC * SfC * SfA * SfA * SfU * SfU * SfC	AUUUAGCAUGUU CCCAAUUC	SSSS SSSS SSSS SSSSSSS
WV-15928	fA * SfU * SfUn001 fU * SfA * SfGn001 fC * SfA * SmUn001 fG * SmU * SfU * SmCn001 fC * SfC * SfA * SfAn001 fU * SfU * SfC	AUUUAGCAUGUU CCCAAUUC	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15929	fA * SfU * SfUn001 fU * SfA * SfGn001 fC * SfA * SmU * SfG * SmU * SfU * SmCn001 fC * SfC * SfA * SfAn001 fU * SfU * SfC	AUUUAGCAUGUU CCCAAUUC	SSnXSSnX SSSSSSnX SSSnXSS
WV-15930	fA * SfU * SfUn001 fU * SfA * SfGn001 fC * SfA * SmU * SfG * SmU * SfU * SmC * SfC * SfC * SfA * SfAn001 fU * SfU * SfC	AUUUAGCAUGUU CCCAAUUC	SSnXSSnX SSSS SSSSSSnXSS
WV-15931	fA * SfU * SfU * SfU * SfA * SfGn001 fC * SfA * SmUn001 fG * SmU * SfU * SmCn001 fC * SfC * SfA * SfU * SfU * SfC	AUUUAGCAUGUU CCCAAUUC	SSSSSnXSSnX SSSnX SSSSSS
WV-15932	fA * SfU * SfUn001 fU * SfA * SfG * SfC * SfA * SmU * SfG * SmU * SfU * SmCn001 fC * SfC * SfA * SfAn001 fU * SfU * SfC	AUUUAGCAUGUU CCCAAUUC	SSnX SSSS SSSSSnX SSSnXSS
WV-15933	fA * SfU * SfUn001 fU * SfA * SfG * SfC * SfA * SmU * SfG * SmU * SfU * SmC * SfC * SfC * SfA * SfAn001 fU * SfU * SfC	AUUUAGCAUGUU CCCAAUUC	SSnX SSSS SSSS SSSSSnXSS
WV-15934	fA * SfU * SfUn001 fU * SfA * SfGn001 fC * SfA * SmU * SfG * SmU * SfU * SmC * SfC * SfC * SfA * SfA * SfU * SfU * SfC	AUUUAGCAUGUU CCCAAUUC	SSnXSSnX SSSS SSSS SSSSS
WV-15935	fA * SfU * SfU * SfU * SfA * SfG * SfC * SfA * SmU * SfG * SmU * SfU * SmCn001 fC * SfC * SfA * SfAn001 fU * SfU * SfC	AUUUAGCAUGUU CCCAAUUC	SSSS SSSS SSSSnX SSSnXSS
WV-15936	mA * SmU * SmU * SmU * SmA * SmG * SmC * SmA * SmU * SmG * SmU * SmU * SmC * SmC * SmC * SmA * SmA * SmU * SmU * SmC	AUUUAGCAUGUU CCCAAUUC	SSSS SSSS SSSS SSSSSSS
WV-15937	mA * SmU * SmUn001 mU * SmA * SmGn001 mC * SmA * SmUn001 mG * SmU * SmU * SmCn001 mC * SmC * SmA * SmAn001 mU * SmU * SmC	AUUUAGCAUGUU CCCAAUUC	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15938	Aeo * STeo * STeo * STeo * SAeo * SGeo * Sm5Ceo * SAeo * STeo * SGeo * STeo * STeo * Sm5Ceo * Sm5Ceo * Sm5Ceo * SAeo * SAeo * STeo * STeo * Sm5Ceo	ATTTAGCATGTT CCCAATTC	SSSS SSSS SSSS SSSSSSS
WV-15939	Aeo * STeo * STeon001 Teo * SAeo * SGeon001 m5Ceo * SAeo * STeon001 Geo * STeo * STeo * Sm5Ceon001 m5Ceo * Sm5Ceo * SAeo * SAeon001 Teo * STeo * Sm5Ceo	ATTTAGCATGTT CCCAATTC	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15940	fG * SfC * SfAn001 fU * SfG * SfUn001 fU * SfC * SmCn001 fC * SmA * SfA * SmUn001 fU * SfC * SfU * SfCn001 fA * SfG * SfG	GCAUGUUCCC AAUUCUCAGG	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15941	fA * SfG * SfCn001 fA * SfU * SfGn001 fU * SfU * SmCn001 fC * SmC * SfA * SmAn001 fU * SfU * SfC * SfUn001 fC * SfA * SfG	AGCAUGUU CC CAAUUCUCAG	SSnXSSnXSSnX SSSnX SSSnXSS
WV-	fU * SfA * SfGn001 fC * SfA * SfUn001 fG * SfU * SmUn001 fC * SmC	UAGCAUGUU	SSnXSSnXSSnX SSSnX

15942	* SfC * SmAn001 fA * SfU * SfU * SfCn001 fU * SfC * SfA	CCCAAUUCUCA	SSSnXSS
WV-15943	fU * SfU * SfAn001 fG * SfC * SfAn001 fU * SfG * SmUn001 fU * SmC * SfC * SmCn001 fA * SfA * SfU * SfUn001 fC * SfU * SfC	UUAGCAUGUU CCCAAUUCUC	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15944	fU * SfU * SfUn001 fA * SfG * SfCn001 fA * SfU * SmGn001 fU * SmU * SfC * SmCn001 fC * SfA * SfUn001 fU * SfC * SfU	UUUAGCAUGUU CCCAAUUCU	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15945	fU * SfA * SfUn001 fU * SfU * SfAn001 fG * SfC * SmAn001 fU * SmG * SfU * SmUn001 fC * SfC * SfC * SfAn001 fA * SfU * SfU	UAUUUAGCAUGUU CCCAAUU	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15946	fG * SfU * SfAn001 fU * SfU * SfUn001 fA * SfG * SmCn001 fA * SmU * SfG * SmUn001 fU * SfC * SfC * SfCn001 fA * SfA * SfU	GUAUUUAGCA UGUU CCCAAU	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15947	fU * SfG * SfUn001 fA * SfU * SfUn001 fA * SmGn001 fC * SmA * SfU * SmGn001 fU * SfU * SfC * SfCn001 fC * SfA * SfA	UGUAUUUAGCA UGUU CCCAA	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15948	fU * SfU * SfGn001 fU * SfA * SfUn001 fU * SfU * SmAn001 fG * SmC * SfA * SmUn001 fG * SfU * SfU * SfCn001 fC * SfC * SfA	UUGUAUUUAGCAUGU U CCCA	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15949	fU * SfU * SfUn001 fG * SfU * SfAn001 fU * SfU * SmUn001 fA * SmG * SfC * SmAn001 fU * SfG * SfU * SfUn001 fC * SfC * SfC	UUUGUAUUU AGCAUGUU CCC	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15950	fG * SfC * SfU * SfG * SfC * SfU * SfC * SfU * SmU * SfU * SmU * SfC * SmC * SfA * SfG * SfG * SfU * SfU * SfC * SfA	GCUGCUCUUU UCCAGGUUCA	SSSS SSSS SSSS SSSSSSS
WV-15951	fC * SfU * SfU * SfC * SfC * SfU * SfC * SfC * SmA * SfA * SmC * SfC * SmA * SfU * SfA * SfA * SfA * SfA * SfC * SfA	CUUCCUCCAACCA UAAAACA	SSSS SSSS SSSS SSSSSSS
WV-15952	fA * SfG * SfG * SfU * SfU * SfC * SfA * SfA * SmG * SfU * SmG * SfG * SmG * SfA * SfU * SfA * SfC * SfU * SfA * SfG	AGGUUCAAGU GGGAUACUAG	SSSS SSSS SSSS SSSSSSS
WV-15953	fG * SfC * SfA * SfC * SfU * SfU * SfA * SfC * SmA * SfA * SmG * SfC * SmA * SfC * SfG * SfG * SfU * SfC * SfC	GCACUUACAAG CACGGGUCC	SSSS SSSS SSSS SSSSSSS
WV-15954	fG * SfG * SfC * SfA * SfA * SfC * SfU * SfC * SmU * SfU * SmC * SfC * SmA * SfC * SfC * SfA * SfG * SfU * SfA * SfA	GGCAACUCUU CCACCAGUAA	SSSS SSSS SSSS SSSSSSS
WV-15955	fG * SfA * SfG * SfU * SfU * SfC * SfU * SfU * SmC * SfC * SmA * SfA * SmC * SfU * SfG * SfG * SfG * SfG * SfA * SfC	GAGUUCUUCC AACUGGGGAC	SSSS SSSS SSSS SSSSSSS
WV-15956	fG * SfG * SfU * SfA * SfU * SfC * SfA * SfU * SmC * SfU * SmG * SfC * SmA * SfG * SfA * SfA * SfU * SfA * SfU * SfA	GGUAUCAUCU GCAGAAUAAU	SSSS SSSS SSSS SSSSSSS
WV-15957	fU * SfU * SfU * SfC * SfA * SfG * SfG * SfG * SmC * SfC * SmA * SfA * SmG * SfU * SfC * SfA * SfU * SfU * SfU * SfG	UUUCAGGGCCA AGUCAUUUG	SSSS SSSS SSSS SSSSSSS
WV-15958	fC * SfC * SfA * SfC * SfA * SfU * SfC * SfU * SmA * SfC * SmA * SfU * SmU * SfU * SfG * SfU * SfC * SfU * SfG * SfC	CCACAUCUACAU UUGUCUGC	SSSS SSSS SSSS SSSSSSS
WV-15959	fC * SfU * SfU * SfU * SfC * SfC * SfU * SfU * SmA * SfC * SmG * SfG * SmG * SfU * SfA * SfG * SfC * SfA * SfU * SfC	CUUUCCUUACG GGUAGCAUC	SSSS SSSS SSSS SSSSSSS
WV-	fU * SfU * SfC * SfU * SfU * SfC * SfC * SfA * SmA * SfA * SmG *	UUCUUCC	SSSS SSSS SSSS

15960	SfC * SmA * SfG * SfC * SfC * SfU * SfC * SfU * SfC	AAAGCAGCCUCUC	SSSSSSS
WV-15961	fU * SfC * SfC * SfU * SfG * SfU * SfA * SfG * SmG * SfA * SmC * SfA * SmU * SfU * SfG * SfG * SfC * SfA * SfG * SfU	UCCUGUAGGA CAUUGGCAGU	SSSS SSSS SSSS SSSSSSS
WV-15962	fG * SfC * SfUUn001 fG * SfC * SfUUn001 fC * SfU * SmUUn001 fU * SmU * SfC * SmCn001 fA * SfG * SfG * SfUUn001 fU * SfC * SfA	GCUGCUCUUU UCCAGGUUCA	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15963	fC * SfU * SfUUn001 fC * SfC * SfUUn001 fC * SfC * SmAAn001 fA * SmC * SfC * SmAAn001 fU * SfA * SfA * SfAAn001 fA * SfC * SfA	CUUCCUCCAACCA UAAAACA	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15964	fA * SfG * SfGn001 fU * SfU * SfCn001 fA * SfA * SmGn001 fU * SmG * SfG * SmGn001 fA * SfU * SfA * SfCn001 fU * SfA * SfG	AGGUUCAAGU GGGAUACUAG	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15965	fG * SfC * SfAn001 fC * SfU * SfUUn001 fA * SfC * SmAAn001 fA * SmG * SfC * SmAAn001 fC * SfG * SfG * SfGn001 fU * SfC * SfC	GCACUUACAAG CACGGGUCC	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15966	fG * SfG * SfCn001 fA * SfA * SfCn001 fU * SfC * SmUn001 fU * SmC * SfC * SmAn001 fC * SfC * SfA * SfGn001 fU * SfA * SfA	GGCAACUCUU CCACCAGUAA	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15967	fG * SfA * SfGn001 fU * SfU * SfCn001 fU * SfU * SmCn001 fC * SmA * SfA * SmCn001 fU * SfG * SfG * SfGn001 fG * SfA * SfC	GAGUUCUUCC AACUGGGGAC	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15968	fG * SfG * SfUn001 fA * SfU * SfCn001 fA * SfU * SmCn001 fU * SmG * SfC * SmAn001 fG * SfA * SfA * SfUn001 fA * SfA * SfU	GGUAUCAUCU GCAGAAUAAU	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15969	fU * SfU * SfUn001 fC * SfA * SfGn001 fG * SfG * SmCn001 fC * SmA * SfA * SmGn001 fU * SfC * SfA * SfUn001 fU * SfU * SfG	UUUCAGGGCCA AGUCAUUUG	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15970	fC * SfC * SfAn001 fC * SfA * SfUn001 fC * SfU * SmAn001 fC * SmA * SfU * SmUn001 fU * SfG * SfU * SfCn001 fU * SfG * SfC	CCACAUCUACAU UUGUCUGC	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15971	fC * SfU * SfUn001 fU * SfC * SfCn001 fU * SfU * SmAn001 fC * SmG * SfG * SmGn001 fU * SfA * SfG * SfCn001 fA * SfU * SfC	CUUUCCUUACG GGUAGCAUC	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15972	fU * SfU * SfCn001 fU * SfU * SfCn001 fC * SfA * SmAn001 fA * SmG * SfC * SmAn001 fG * SfC * SfC * SfUn001 fC * SfU * SfC	UUCUUCC AAAGCAGCCUCUC	SSnXSSnXSSnX SSSnX SSSnXSS
WV-15973	fU * SfC * SfCn001 fU * SfG * SfUn001 fA * SfG * SmGn001 fA * SmC * SfA * SmUn001 fU * SfG * SfG * SfCn001 fA * SfG * SfU	UCCUGUAGGA CAUUGGCAGU	SSnXSSnXSSnX SSSnX SSSnXSS
WV-16004	L001fC * SfU * SfCn001 RfC * SfG * SfGn001 RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001 RfU * SfU * SfC	CUCCGGUUCUGAAG GUGUUC	OSSnR SSnR SSOSSSOOSSnR SS
WV-16005	Mod071L001fC * SfU * SfCn001 RfC * SfG * SfGn001 RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001 RfU * SfU * SfC	CUCCGGUUCUGAAG GUGUUC	OSSnR SSnR SSOSSSOOSSnR SS
WV-16006	fC * SfU * SfCn003RfC * SfG * SfGn003RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn003RfU * SfU * SfC	CUCCGGUUCUGAAG GUGUUC	SSnR SSnR SSOSSSOOSSnR SS
WV-16007	fC * SfU * SfCn004RfC * SfG * SfGn004RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn004RfU * SfU * SfC	CUCCGGUUCUGAAG GUGUUC	SSnR SSnR SSOSSSOOSSnR SS
WV-	fU * SfC * SfA * SfC * SfU * SfC * SmAn003fG * SfA * SmU * SfA *	UCACUCAGAUA	SSSSSSnX SSSSnXnX

16008	SmGn003mUn003fU * SfG * SfA * SfA * SfG * SfC * SfC	GUUGAAGCC	SSSSS
WV-16009	fU * SfC * SfA * SfC * SfU * SfC * SmAn004fG * SfA * SmU * SfA * SmGn004mUn004fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSSSSSnX SSSSnXnX SSSSSS
WV-16010	L001L005fC * SfU * SfCn001 RfC * SfG * SfGn001 RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001 RfU * SfU * SfC	CUCCGGUUCUGAAG GUGUUC	OOSSnR SSnR SSOSSSOOSSnR SS
WV-16011	Mod107fC * SfU * SfCn001 RfC * SfG * SfGn001 RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001 RfU * SfU * SfC	CUCCGGUUCUGAAG GUGUUC	SSnR SSnR SSOSSSOOSSnR SS
WV-16366	Mod108L001fC * SfU * SfCn001 RfC * SfG * SfGn001 RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001 RfU * SfU * SfC	CUCCGGUUCUGAAG GUGUUC	OSSnR SSnR SSOSSSOOSSnR SS
WV-16367	fC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	CCGGUUCUGAAG GUGUUCU	SSSSSSOSSSOO SSSSSS
WV-16368	fU * SfCn001 RfC * SfG * SfGn001 RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001 RfU * SfU * SfC	UCCGGUUCUGAAG GUGUUC	SnRSSnR SSOSSSOSSSnR SS
WV-16369	fU * SfCn001 RfC * SfG * SfGn001 RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001 RfU * SfU * SfC	UCCGGUUCUGAAG GUGUUC	SnRSSnR SSOSSSOOSSnR SS
WV-16370	fC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC	CCGGUUCUGAAG GUGUUC	SSSSSSOSSSOO SSSSS
WV-16371	fU * SfCn001 RfC * SfG * SfGn001 RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001 RfU * SfU	UCCGGUUCUGAAG GUGUU	SnRSSnR SSOSSSOSSSnRS
WV-16372	fU * SfCn001 RfC * SfG * SfGn001 RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001 RfU * SfU	UCCGGUUCUGAAG GUGUU	SnRSSnR SSOSSSOOSSnRS
WV-16499	Mod105L001fC * SfU * SfCn001 RfC * SfG * SfGn001 RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001 RfU * SfU * SfC	CUCCGGUUCUGAAG GUGUUC	OSSnR SSnR SSOSSSOOSSnR SS
WV-16500	mU * mC * mA * mC * mU * mC * mA * mG * mA * mU * mA * mG * mU * mU * mG * mA * mA * mG * mC * mC	UCACUCAGAUA GUUGAAGCC	XXXXX XXXXX XXXXX XXXX
WV-16501	fC * fA * fA * fG * fG * mAfA * mGmA * fU * mGmGfC * fA * fU * fU * fU * fC * fU	CAAGGAAGA UGG CAUUUCU	XXXXX OXOXXOOXXXXX X
WV-16502	fA * fA * fG * fG * mAfA * mGmA * fU * mGmGfC * fA * fU * fU * fU * fC * fU	AAGGAAGA UG GCAUUUCU	XXXXOXOXXOOXXXX X X
WV-16503	fUfC * fA * fA * fG * fG * mAfA * mGmA * fU * mGmGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGA UGGCAUUUCU	OXXXXX OXOXXOOXXXX X
WV-16504	fU * fU * fC * fA * fA * fG * fG * mAfA * mGmA * fU * mGmGfC * fA * fU * fU * fU * fC * fU	UUCAAGGAAGA UGGCAUUUCU	XXXXX XXOXOXXOOXXXXX X
WV-16505	Mod105L001fU * SfC * SfA * SfC * SfU * SfC * SmAn001 fG * SfA * SmU * SfA * SmGn001 mUn001 fU * SfG * SfA * SfA * SfG * SfC *	UCACUCAGAUA GUUGAAGCC	O SSSSSSnX SSSSnXnX SSSSSS

	SfC		
WV-16506	Mod108L001fU * SfC * SfA * SfC * SfU * SfC * SmAn001 fG * SfA * SmU * SfA * SmGn001 mUn001 fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	O SSSSSSnX SSSSnXnX SSSSSS
WV-16507	Mod099L001fU * SfC * SfA * SfC * SfU * SfC * SmAn001 fG * SfA * SmU * SfA * SmGn001 mUn001 fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	O SSSSSSnX SSSSnXnX SSSSSS

WV-17765	Mod102L001fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAU AGUUGAAGCC	OSSSS SSnXSS SSnXnXS SSSSS
WV-17774	fU * SfC * SfAn001RfC * SfU * SfCn001RmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfAn001RfG * SfC * SfC	UCACUCAGAU AGUUGAAGCC	SSnRSS nR OSSSS OOSS SnRSS
WV-17775	L001fU * SfC * SfAn001RfC * SfU * SfCn001RmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfAn001SfG * SfC * SfC	UCACUCAGAU AGUUGAAGCC	OSSnRS SnROSS SSOOS SSnRSS
WV-17801	fU * SfC * SfAn001SfC * SfU * SfCn001SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfAn001SfG * SfC * SfC	UCACUCAGAU AGUUGAAGCC	SSnSSSnS OSSSS OOSSSnS SS
WV-17802	fU * SfC * SfAn001RfC * SfU * SfC * SmAn001RfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfAn001RfG * SfC * SfC	UCACUCAGAU AGUUGAAGCC	SSnRSS SnRSSS SOOSS SnRSS
WV-17803	fU * SfC * SfAn001RfC * SfU * SfCn001RmA * SfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfAn001RfG * SfC * SfC	UCACUCAGAU AGUUGAAGCC	SSnRSS nR SSSSS OOSS SnRSS
WV-17831	Mod007L001fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAU AGUUGAAGCC	OSSSS SSnXSS SSnXnXS SSSSS
WV-17832	Mod027L001fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAU AGUUGAAGCC	OSSSS SSnXSS SSnXnXS SSSSS
WV-17833	Mod028L001fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAU AGUUGAAGCC	OSSSS SSnXSS SSnXnXS SSSSS
WV-17834	Mod029L001fU * SfC * SfA * SfC * SfU * SfC * SmAn001fG * SfA * SmU * SfA * SmGn001mUn001fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAU AGUUGAAGCC	OSSSS SSnXSS SSnXnXS SSSSS
WV-17835	fG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfC * SfU	GGUUCUGAAG GUGUUCU	SSSSO SSSOO SSSSS S
WV-17836	fUfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUCUG AAGGUGUUCU	OSSSS SSOSS SOOSS SSSS
WV-17837	fG * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	GUCCGGUUCU GAAGGUGUUCU	SSSSS SSSOS SSOOS SSSSS
WV-17838	fCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001RfU * SfU * SfC	CCGGUUCUGA AGGUGUUC	nRSSnRS SOSSS OOSSnRSS

WV-17839	fCfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCU GAAGGUGUUC	OSnRSSnR SSOSS SOOSSnRSS
WV-17840	fC * SfC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn001RfU * SfU * SfC	CCUCCGGUUC UGAAGGUGUUC	SSSnRS SnRSSO SSSOO SSnRSS
WV-17841	fCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CCGGUUCUGA AGGUGUUC	nRSSnRS SOSSS OSSSnRSS
WV-17842	fCfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCU GAAGGUGUUC	OSnRSSnR SSOSS SOSSSnRSS
WV-17843	fC * SfC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CCUCCGGUUC UGAAGGUGUUC	SSSnRS SnRSSOSSSOSSSnRSS
WV-17844	rC rA rG rA rG rU rA rA rC rA rG rU rC rU rG rA rG rU rA rG rG rU rU rU rU rA rG rA rG rC rU rA	CAGAGUAACA GUCUGAGUAG GUUUUAGAGC UA	00000 00000 00000 00000 00000 00000 00000 00000 0
WV-17845	rG rA rG rU rA rA rC rA rG rU rC rU rG rA rG rU rA rG rG rU rU rU rU rA rG rA rG rC rU rA	GAGUAACAGU CUGAGUAGGU UUUAGAGCUA	00000 00000 00000 00000 00000 0000
WV-17846	rG * rA * rG * rU * rA * rA * rC * rA * rG rU rC rU rG rA rG rU rU rU rU * rA * rG * rA * rG * rC * rU * rA	GAGUAACAGU CUGAGUAGGU UUUAGAGCUA	XXXXX XXX00 00000 00000 00XXXXXXX
WV-17847	rG * rA * rG * rU * rA * rA * rC * rA * rG * rU * rC * rU * rG * rA * rG * rU * rA * rG * rU * rU * rU * rA * rG * rA * rG * rC * rU * rA	GAGUAACAGU CUGAGUAGGU UUUAGAGCUA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-17848	mGmAmGmUmAmAmCmA rG rU rC rU rG rA rG rU rA rG rG rU rU rU rUmUmAmGmAmGmCmUmA	GAGUAACAGU CUGAGUAGGU UUUAGAGCUA	00000 00000 00000 00000 00000 0000
WV-17849	mG * mA * mG * mU * mA * mA * mC * mA * rG rU rC rU rG rA rG rU rA rG rU rU rUmU * mA * mG * mA * mG * mC * mU * mA	GAGUAACAGU CUGAGUAGGU UUUAGAGCUA	XXXXX XXX00 00000 00000 00XXXXXXX
WV-17850	mG * mA * mG * mU * mA * mA * mC * mA * rG * rU * rC * rU * rG * rA * rG * rU * rA * rG * rU * rU * rU * mU * mA * mG * mA * mG * mC * mU * mA	GAGUAACAGU CUGAGUAGGU UUUAGAGCUA	XXXXX XXXXX XXXXX XXXXX XXXX
WV-17851	fGfAfGfUfAfAfCfA rG rU rC rU rG rA rG rU rA rG rG rU rU rUfUfAfGfAfGfUfCfUfA	GAGUAACAGU CUGAGUAGGU UUUAGAGCUA	00000 00000 00000 00000 00000 0000
WV-17852	fG * fA * fG * fU * fU * fA * fA * fC * fA * rG rU rC rU rG rA rG rU rA rG rU rU rUfU * fA * fG * fA * fG * fC * fU * fA	GAGUAACAGU CUGAGUAGGU	XXXXX XXX00 00000 00000

		UUUAGAGCUA	0OXXXXXXX
WV-17853	fG * fA * fG * fU * fA * fA * fC * fA * rG * rU * rC * rU * rG * rA * rG * rU * rA * rG * rU * rU * fA * fG * fA * fG * fC * fU * fA	GAGUAACAGU CUGAGUAGGU UUUAGAGCUA	XXXXX XXXXX XXXXX XXXXX XXXXX XXXX
WV-17854	rG rA rG rU rAn001 rAn001 rCn001 rAn001 rG rU rC rU rG rA rG rU rA rG rG rU rU rU rU rA rG rA rGn001 rCn001 rUn0001 rA	GAGUAACAGU CUGAGUAGGU UUUAGAGCUA	0000nX nXnXnX00 00000 00000 00000 0nXnXnX
WV-17855	rG rA rG rU rA rA rC rA rG rU rC rU rG rA rG rU rA rG rG rU rU rU rU rA rG rA rGn001 rCn001 rUn001 rA	GAGUAACAGU CUGAGUAGGU UUUAGAGCUA	00000 00000 00000 00000 00000 0nXnXnX
WV-17856	rG rA rG rU rAn001 rAn001 rCn001 rAn001 rG rU rC rU rG rA rG rU rA rG rG rU rU rU rU rA rG rA rG rC rU rA	GAGUAACAGU CUGAGUAGGU UUUAGAGCUA	0000nX nXnXnX00 00000 00000 00000 0000
WV-17857	rG rA rG rU rA rAn001 rC rAn001 rG rU rC rU rG rA rG rU rA rG rG rU rU rU rU rA rG rA rGn001 rC rUn001 rA	GAGUAACAGU CUGAGUAGGU UUUAGAGCUA	00000 nX0nX00 00000 00000 00000 0nX0nX
WV-17858	rG rA rG rU rAn001 rA rCn001 rA rG rU rC rU rG rA rG rU rA rG rG rU rU rU rU rA rG rA rG rC rn001 rUn001 rA	GAGUAACAGU CUGAGUAGGU UUUAGAGCUA	0000nX 0nX000 00000 00000 00000 00nXnX
WV-17859	fU * SfC * SfAn001fA * SfG * SfG * SmA * SfA * SmGmA * SfU * SmGmGfCn001fA * SfU * SfUn001fU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSnXSS SSSOS SOOnXS SnXSS
WV-17860	fU * SfC * SfAn001fA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmG * SfCn001fA * SfU * SfUn001fU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSnXSS SOSOS SOSnXS SnXSS
WV-17861	fU * SfC * SfAn001fA * SfG * SfG * SmA * SfA * SmGmA * SfU * SmGmG * SfCn001fA * SfU * SfUn001fU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSnXSS SSSOS SOSnXS SnXSS
WV-17862	fU * SfC * SfAn001fA * SfG * SfG * SfA * SfA * SmGmA * SfU * SmGfG * SfCn001fA * SfU * SfUn001fU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSnXSS SSSOS SOSnXS SnXSS
WV-17863	fU * SfC * SfAn001fA * SfG * SfGn001mA * SfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfUn001fU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSnXSS nXSSOS SOOSS SnXSS
WV-17864	fU * SfC * SfAn001fA * SfG * SfGn001mAfA * SmGmA * SfU * SmGmG * SfC * SfA * SfU * SfUn001fU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSnXSS nXOSOS SOSSS SnXSS
WV-17865	fU * SfC * SfAn001fA * SfG * SfGn001mA * SfA * SmGmA * SfU * SmGmG * SfC * SfA * SfU * SfUn001fU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSnXSS nXSSOS SOSSS SnXSS
WV-17866	fU * SfC * SfAn001fA * SfG * SfGn001fA * SfA * SmGmA * SfU * SmGfG * SfC * SfA * SfU * SfUn001fU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSnXSS nXSSOS SOSSS SnXSS

WV-17881	fG fA fG fUn001 fA fA fCn001 fA rG rU rC rU rG rA rG rU rA rG rG rU rU rU fU fA fGn001 fA fG fCn001 fU fA	GAGUAACAGUCUGAGUA GGUU UUAGAGGCUA	XXXnXX XnXX0 00000 OOOOO OOOXX nXXXnXX
WV-17882	fG fA fG fUn001 fA fA fCn001 fA rG rU rC rU rG rA rG rU rA rG rG rU rU rUn001 fU fA fGn001 fA fG fCn001 fU fA	GAGUAACAGUCUGAGUA GGUU UUAGAGGCUA	XXXnXX XnXX0 00000 OOOOO OOnXXX nXXXnXX
WV-17883	fG fA fG fUn001 fA fA fCn001 fA rG rU rC rU rG rA rG rU rA rG rGn001 rU rU rU rUn001 fU fA fGn001 fA fG fCn001 fU fA	GAGUAACAGUCUGAGUA GGUU UUAGAGGCUA	XXXnXX XnXX0 00000 OOOOnX OOnXXX nXXXnXX
WV-18853	fC fC fUn001 fA fC fCn001 fC fU mA fU mG fU mAn001 fC fA fU fCn001 fG fU fU	CCUACCCUAUGUACAUC GUU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18854	fC fC fUn001 fA fU fGn001 fU fA mC fA mU fC mGn001 fU fU fC fUn001 fG fC fU	CCUAUGUACAUCGUUCU GCU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18855	fG fU fAn001 fC fA fUn001 fC fG mU fU mC fU mGn001 fC fU fU fCn001 fU fG fA	GUACAUCGUUCUGCUUC UGA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18856	fU fC fGn001 fU fU fCn001 fU fG mC fU mU fC mUn001 fG fA fA fCn001 fU fG fC	UCGUUCUGCUUCUGAAC UGC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18857	fU fC fUn001 fG fC fUn001 fU fC mU fG mA fA mCn001 fU fG fC fUn001 fG fG fA	UCUGCUUCUGAACUGCU GGA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18858	fU fU fCn001 fU fG fAn001 fA fC mU fG mC fU mGn001 fG fA fA fAn001 fG fU fC	UUCUGAACUGCUGGAAA GUC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18859	fA fA fCn001 fU fG fCn001 fU fG mG fA mA fA mGn001 fU fC fG fCn001 fC fU fC	AACUGCUGGAAAGUCGC CUC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18860	fA fA fGn001 fU fC fGn001 fC fC mU fC mC fA mAn001 fU fA fG fGn001 fU fG fC	AAGUCGCCUCCAAUAGG UGC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18861	fG fC fCn001 fU fC fCn001 fA fA mU fA mG fG mUn001 fG fC fC fUn001 fG fC fC	GCCUCCAAUAGGUGCCU GCC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18862	fC fA fAn001 fU fA fGn001 fG fU mG fC mC fU mGn001 fC fC fG fGn001 fC fU fU	CAAUAGGUGCCUGCCGG CUU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18863	fG fG fUn001 fG fC fCn001 fU fG mC fC mG fG mCn001 fU fU fA fAn001 fU fU fC	GGUGCCUGCCGGCUUAA UUC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18864	fC fU fGn001 fC fC fGn001 fG fC mU fU mA fA mUn001 fU fC fA fUn001 fC fA fU	CUGCCGGCUUAAUUCAU CAU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18865	fG fG fCn001 fU fU fAn001 fA fU mU fC mA fU mCn001 fA fU fC fUn001 fU fU fC	GGCUUAAUUCAUCAUCU UUC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18866	fA fA fUn001 fU fC fAn001 fU fC mA fU mC fU mUn001 fU fC fA fGn001 fC fU fG	AAUUCAUCAUCUUUCAG CUG	SSnXSS nXSSSS SSnXSS SnXSS
WV-18867	fA fU fCn001 fA fU fCn001 fU fU mU fC mA fG mCn001 fU	AUCAUCUUUCAGCUGUA	SSnXSS nXSSSS SSnXSS

	fG fU fAn001 fG fC fC	GCC	SnXSS
WV-18868	fC fU fU fUn001 fU fC fAn001 fG fC mU fG mU fA mGn001 fC fC fA fCn001 fA fC fC	CUUUCAGCUGUAGCCAC ACC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18869	fA fG fCn001 fU fG fUn001 fA fG mC fC mA fC mAn001 fC fC fA fGn001 fA fA fG	AGCUGUAGCCACACCAG AAG	SSnXSS nXSSSS SSnXSS SnXSS
WV-18870	fU fA fGn001 fC fC fAn001 fC fA mC fC mA fG mAn001 fA fG fU fUn001 fC fC fU	UAGCCACACCAGAAGUU CCU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18871	fA fC fAn001 fC fC fAn001 fG fA mA fG mU fU mCn001 fC fU fG fCn001 fA fG fA	ACACCAGAAGUUCCUGC AGA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18872	fA fG fAn001 fA fG fUn001 fU fC mC fU mG fC mAn001 fG fA fG fAn001 fA fA fG	AGAAGUUCCUGCAGAGA AAG	SSnXSS nXSSSS SSnXSS SnXSS
WV-18873	fU fC fCn001 fU fG fCn001 fA fG mA fG mA fA mAn001 fG fG fU fGn001 fC fA fG	UCCUGCAGAGAAAGGUG CAG	SSnXSS nXSSSS SSnXSS SnXSS
WV-18874	fC fA fGn001 fA fG fAn001 fA fA mG fG mU fG mCn001 fA fG fA fCn001 fG fC fU	CAGAGAAAGGUGCAGAC GCU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18875	fA fA fAn001 fG fG fUn001 fG fC mA fG mA fC mGn001 fC fU fU fCn001 fC fA fC	AAAGGUGCAGACGCUUC CAC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18876	fU fG fCn001 fA fG fAn001 fC fG mC fU mU fC mCn001 fA fC fU fGn001 fG fU fC	UGCAGACGCUUCCACUG GUC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18877	fA fC fGn001 fC fU fUn001 fC fC mA fC mU fG mGn001 fU fC fA fGn001 fA fA fC	ACGCUUCCACUGGUCAG AAC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18878	fU fC fCn001 fA fC fUn001 fG fG mU fC mA fG mAn001 fA fC fU fGn001 fG fC fU	UCCACUGGUCAGAACUG GCU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18879	fU fG fGn001 fU fC fAn001 fG fA mA fC mU fG mGn001 fC fU fU fCn001 fC fA fA	UGGUCAGAACUGGCUUC CAA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18880	fA fG fAn001 fA fC fUn001 fG fG mC fU mU fC mCn001 fA fA fA fUn001 fG fG fG	AGAACUGGCUUCCAAAU GGG	SSnXSS nXSSSS SSnXSS SnXSS
WV-18881	fU fG fGn001 fC fU fUn001 fC fC mA fA mA fU mGn001 fG fG fA fCn001 fC fU fG	UGGCUUCCAAAUGGGAC CUG	SSnXSS nXSSSS SSnXSS SnXSS
WV-18882	fA fG fGn001 fC fA fCn001 fG fA mG fG mC fU mUn001 fA fA fA fAn001 fA fU fG	AGGCACCGAGGCUUAAAA AUG	SSnXSS nXSSSS SSnXSS SnXSS
WV-18883	fG fG fCn001 fA fC fGn001 fA fG mG fC mU fU mAn001 fA fA fA fAn001 fU fG fU	GGCACCGAGGCUUAAAAA UGU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18884	fG fC fAn001 fC fG fAn001 fG fG mC fU mU fA mAn001 fA fA fA fUn001 fG fU fC	GCACCGAGGCUUAAAAAU GUC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18885	fC fA fCn001 fG fA fGn001 fG fC mU fU mA fA mAn001 fA	CACCGAGGCUUAAAAAUG	SSnXSS nXSSSS SSnXSS

	fA fU fGn001 fU fC fC	UCC	SnXSS
WV-18886	fA fC fGn001 fA fG fGn001 fC fU mU fA mA fA mAn001 fA fU fG fUn001 fC fC fU	ACGAGGCUUAAAAAUGU CCU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18887	fC fG fAn001 fG fG fCn001 fU fU mA fA mA fA mAn001 fU fG fU fCn001 fC fU fA	CGAGGCUUAAAAAUGUC CUA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18888	fG fA fGn001 fG fC fUn001 fU fA mA fA mA fA mUn001 fG fU fC fCn001 fU fA fC	GAGGCUUAAAAAUGUCC UAC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18889	fA fG fGn001 fC fU fUn001 fA fA mA fA mA fU mGn001 fU fC fC fUn001 fA fC fC	AGGCUUAAAAAUGUCCU ACC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18890	fG fG fCn001 fU fU fAn001 fA fA mA fA mU fG mUn001 fC fC fU fAn001 fC fC fC	GGCUUAAAAAUGUCCUA CCC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18891	fG fC fUn001 fU fA fAn001 fA fA mA fU mG fU mCn001 fC fU fA fCn001 fC fC fU	GCUUAAAAAUGUCCUAC CCU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18892	fC fU fUn001 fA fA fAn001 fA fA mU fG mU fC mCn001 fU fA fC fCn001 fC fU fA	CUUAAAAAUGUCCUACC CUA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18893	fU fU fAn001 fA fA fAn001 fA fU mG fU mC fC mUn001 fA fC fC fCn001 fU fA fU	UUAAAAAUGUCCUACCC UAU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18894	fU fA fAn001 fA fA fAn001 fU fG mU fC mC fU mAn001 fC fC fC fUn001 fA fU fG	UAAAAAUGUCCUACCCU AUG	SSnXSS nXSSSS SSnXSS SnXSS
WV-18895	fA fA fAn001 fA fA fUn001 fG fU mC fC mU fA mCn001 fC fC fU fAn001 fU fG fU	AAAAAUGUCCUACCCUA UGU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18896	fA fA fAn001 fA fU fGn001 fU fC mC fU mA fC mCn001 fC fU fA fUn001 fG fU fA	AAAAUGUCCUACCCUAU GUA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18897	fA fA fAn001 fU fG fUn001 fC fC mU fA mC fC mCn001 fU fA fU fGn001 fU fA fC	AAAUGUCCUACCCUAUG UAC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18898	fA fA fUn001 fG fU fCn001 fC fU mA fC mC fC mUn001 fA fU fG fUn001 fA fC fA	AAUGUCCUACCCUAUGU ACA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18899	fA fU fGn001 fU fC fCn001 fU fA mC fC mC fU mAn001 fU fG fU fAn001 fC fA fU	AUGUCCUACCCUAUGUA CAU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18900	fU fG fUn001 fC fC fUn001 fA fC mC fC mU fA mUn001 fG fU fA fCn001 fA fU fC	UGUCCUACCCUAUGUAC AUC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18901	fG fU fCn001 fC fU fAn001 fC fC mC fU mA fU mGn001 fU fA fC fAn001 fU fC fG	GUCCUACCCUAUGUACA UCG	SSnXSS nXSSSS SSnXSS SnXSS
WV-18902	fU fC fCn001 fU fA fCn001 fC fC mU fA mU fG mUn001 fA fC fA fUn001 fC fG fU	UCCUACCCUAUGUACAU CGU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18903	fC fU fAn001 fC fC fCn001 fU fA mU fG mU fA mCn001 fA	CUACCCUAUGUACAUCG	SSnXSS nXSSSS SSnXSS

	fU fC fGn001 fU fU fC	UUC	SnXSS
WV-18904	fU fA fCn001 fC fC fUn001 fA fU mG fU mA fC mAn001 fU fC fG fUn001 fU fC fU	UACCCUAUGUACAUCGU UCU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18905	fU fU fCn001 fG fA fAn001 fA fA mA fA mC fA mAn001 fA fU fC fAn001 fA fA fG	UUCGAAAAAAACAAAUCA AAG	SSnXSS nXSSSS SSnXSS SnXSS
WV-18906	fU fC fGn001 fA fA fAn001 fA fA mA fC mA fA mAn001 fU fC fA fAn001 fA fG fA	UCGAAAAAAACAAAUCAA AGA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18907	fC fG fAn001 fA fA fAn001 fA fA mC fA mA fA mUn001 fC fA fA fAn001 fG fA fC	CGAAAAAAACAAAUCAAA GAC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18908	fG fA fAn001 fA fA fAn001 fA fC mA fA mA fU mCn001 fA fA fA fGn001 fA fC fU	GAAAAAAACAAAUCAAAG ACU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18909	fA fA fAn001 fA fA fAn001 fC fA mA fA mU fC mAn001 fA fA fG fAn001 fC fU fU	AAAAAAACAAAUCAAAGA CUU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18910	fA fA fAn001 fA fA fCn001 fA fA mA fU mC fA mAn001 fA fG fA fCn001 fU fU fA	AAAAAACAAAUCAAAGAC UUA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18911	fA fA fAn001 fA fC fAn001 fA fA mU fC mA fA mAn001 fG fA fC fUn001 fU fA fC	AAAACAAAUCAAAGACU UAC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18912	fA fA fAn001 fC fA fAn001 fA fU mC fA mA fA mGn001 fA fC fU fUn001 fA fC fC	AAACAAAUCAAAGACUU ACC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18913	fA fA fCn001 fA fA fAn001 fU fC mA fA mA fG mAn001 fC fU fU fAn001 fC fC fU	AACAAAUCAAAGACUUA CCU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18914	fA fC fAn001 fA fA fUn001 fC fA mA fA mG fA mCn001 fU fU fA fCn001 fC fU fU	ACAAAUCAAAGACUUAC CUU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18915	fC fA fAn001 fA fU fCn001 fA fA mA fG mA fC mUn001 fU fA fC fCn001 fU fU fA	CAAAUCAAAGACUUACC UUA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18916	fA fA fAn001 fU fC fAn001 fA fA mG fA mC fU mUn001 fA fC fC fUn001 fU fA fA	AAAUCAAAGACUUACCU UAA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18917	fA fA fUn001 fC fA fAn001 fA fG mA fC mU fU mAn001 fC fC fU fUn001 fA fA fG	AAUCAAAGACUUACCUU AAG	SSnXSS nXSSSS SSnXSS SnXSS
WV-18918	fA fU fCn001 fA fA fAn001 fG fA mC fU mU fA mCn001 fC fU fU fAn001 fA fG fA	AUCAAAGACUUACCUUA AGA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18919	fU fC fAn001 fA fA fGn001 fA fC mU fU mA fC mCn001 fU fU fA fAn001 fG fA fU	UCAAAGACUUACCUUAA GAU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18920	fC fA fAn001 fA fG fAn001 fC fU mU fA mC fC mUn001 fU fA fA fGn001 fA fU fA	CAAAGACUUACCUUAAG AUA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18921	fA fA fAn001 fG fA fCn001 fU fU mA fC mC fU mUn001 fA	AAAGACUUACCUUAAGA	SSnXSS nXSSSS SSnXSS

	fA fG fAn001 fU fA fC	UAC	SnXSS
WV-18922	fA fA fGn001 fA fC fUn001 fU fA mC fC mU fU mAn001 fA fG fA fUn001 fA fC fC	AAGACUUACCUUAAGAU ACC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18923	fA fG fAn001 fC fU fUn001 fA fC mC fU mU fA mAn001 fG fA fU fAn001 fC fC fA	AGACUUACCUUAAGAUA CCA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18924	fG fA fCn001 fU fU fAn001 fC fC mU fU mA fA mGn001 fA fU fA fCn001 fC fA fU	GACUUACCUUAAGAUAC CAU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18925	fA fC fUn001 fU fA fCn001 fC fU mU fA mA fG mAn001 fU fA fC fCn001 fA fU fU	ACUUACCUUAAGAUACC AUU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18926	fC fU fUn001 fA fC fCn001 fU fU mA fA mG fA mUn001 fA fC fC fAn001 fU fU fU	CUUACCUUAAGAUACCA UUU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18927	fU fU fAn001 fC fC fUn001 fU fA mA fG mA fU mAn001 fC fC fA fUn001 fU fU fG	UUACCUUAAGAUACCAU UUG	SSnXSS nXSSSS SSnXSS SnXSS
WV-18928	fU fA fCn001 fC fU fUn001 fA fA mG fA mU fA mCn001 fC fA fU fUn001 fU fG fU	UACCUUAAGAUACCAUU UGU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18929	fA fG fGn001 fC fA fAn001 fA fA mC fA mA fA mAn001 fA fU fG fAn001 fA fG fC	AGGCAAAACAAAAAUGA AGC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18930	fG fC fAn001 fA fA fAn001 fC fA mA fA mA fA mUn001 fG fA fA fGn001 fC fC fC	GCAAAACAAAAAUGAAG CCC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18931	fA fA fAn001 fA fC fAn001 fA fA mA fA mU fG mAn001 fA fG fC fCn001 fC fC fA	AAAACAAAAAUGAAGCC CCA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18932	fA fA fCn001 fA fA fAn001 fA fA mU fG mA fA mGn001 fC fC fC fCn001 fA fU fG	AACAAAAAUGAAGCCCC AUG	SSnXSS nXSSSS SSnXSS SnXSS
WV-18933	fC fA fAn001 fA fA fAn001 fU fG mA fA mG fC mCn001 fC fC fA fUn001 fG fU fC	CAAAAAUGAAGCCCCAU GUC	SSnXSS nXSSSS SSnXSS SnXSS
WV-18934	fA fA fAn001 fA fU fGn001 fA fA mG fC mC fC mCn001 fA fU fG fUn001 fC fU fU	AAAAUGAAGCCCCAUGU CUU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18935	fA fA fUn001 fG fA fAn001 fG fC mC fC mC fA mUn001 fG fU fC fUn001 fU fU fU	AAUGAAGCCCCAUGUCU UUU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18936	fA fU fGn001 fA fA fGn001 fC fC mC fC mA fU mGn001 fU fC fU fUn001 fU fU fU	AUGAAGCCCCAUGUCUU UUU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18937	fG fA fAn001 fG fC fCn001 fC fC mA fU mG fU mCn001 fU fU fU fUn001 fU fA fU	GAAGCCCCAUGUCUUUU UAU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18938	fA fG fCn001 fC fC fCn001 fA fU mG fU mC fU mUn001 fU fU fU fAn001 fU fU fU	AGCCCCAUGUCUUUUUA UUU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18939	fC fC fCn001 fC fA fUn001 fG fU mC fU mU fU mUn001 fU	CCCCAUGUCUUUUUAUU	SSnXSS nXSSSS SSnXSS

	fA fU fUn001 fU fG fA	UGA	SnXSS
WV-18940	fU fG fAn001 fA fG fCn001 fC fC mC fA mU fG mUn001 fC fU fU fUn001 fU fU fA	UGAAGCCCCAUGUCUUU UUA	SSnXSS nXSSSS SSnXSS SnXSS
WV-18941	fA fA fGn001 fC fC fCn001 fC fA mU fG mU fC mUn001 fU fU fU fUn001 fA fU fU	AAGCCCCAUGUCUUUUU AUU	SSnXSS nXSSSS SSnXSS SnXSS
WV-18942	fG fC fCn001 fC fC fAn001 fU fG mU fC mU fU mUn001 fU fU fA fUn001 fU fU fG	GCCCCAUGUCUUUUUAU UUG	SSnXSS nXSSSS SSnXSS SnXSS
WV-18944	fU fC fA fC fU fC mAn001 fG fA mU fA mGn001 mUn001 fU fG fA fA fG fC fC	UCACUCAGAUAGUUGAA GCC	XXXXX XnXXXX XnXnXXX XXXX
WV-18945	fU fC fAn001 fC fU fCn001 mA fG fA mU fA mG mU fU fG fA fAn001 fG fC fC	UCACUCAGAUAGUUGAA GCC	XXnXXX nXOXXX XOOXXX nXXX
WV-18983	fC fC fU fA fC fC fC fU mA fU mG fU mA fC fA fU fC fG fU fU	CCUACCCUAUGUACAUC GUU	SSSSS SSSSS SSSSS SSSS
WV-18984	fC fC fU fA fU fG fU fA mC fA mU fC mG fU fU fC fU fG fC fU	CCUAUGUACAUCGUUCU GCU	SSSSS SSSSS SSSSS SSSS
WV-18985	fG fU fA fC fA fU fC fG mU fU mC fU mG fC fU fU fU fC fU fG fA	GUACAUCGUUCUGCUUC UGA	SSSSS SSSSS SSSSS SSSS
WV-18986	fU fC fG fU fU fC fU fG mC fU mU fC mU fG fA fA fC fU fG fC	UCGUUCUGCUUCUGAAC UGC	SSSSS SSSSS SSSSS SSSS
WV-18987	fU fC fU fG fC fU fU fU fC mU fG mA fA mC fU fG fC fU fU fG fG fA	UCUGCUUCUGAACUGCU GGA	SSSSS SSSSS SSSSS SSSS
WV-18988	fU fU fC fU fG fA fA fC mU fG mC fU mG fG fA fA fA fG fU fC	UUCUGAACUGCUGGAAA GUC	SSSSS SSSSS SSSSS SSSS
WV-18989	fA fA fC fU fG fC fU fG mG fA mA fA mG fU fC fG fC fC fU fC	AACUGGCUGGAAAGUCGC CUC	SSSSS SSSSS SSSSS SSSS
WV-18990	fA fA fG fU fC fG fC fC mU fC mC fA mA fU fA fG fG fU fG fC	AAGUCGCCUCCCAAUAGG UGC	SSSSS SSSSS SSSSS SSSS
WV-18991	fG fC fC fU fC fC fC fA fA mU fA mG fG mU fG fC fC fU fU fG fC fC	GCCUCCCAAUAGGUGCCU GCC	SSSSS SSSSS SSSSS SSSS
WV-18992	fC fA fA fU fA fG fG fU mG fC mC fU mG fC fC fG fG fG fC fU fU	CAAUAGGUGCCUGCCGG CUU	SSSSS SSSSS SSSSS SSSS
WV-18993	fG fG fU fG fC fC fU fG mC fC mG fG mC fU fU fA fA fU fU fC	GGUGCCUGCCGGCUUAA UUC	SSSSS SSSSS SSSSS SSSS
WV-18994	fC fU fG fC fC fC fG fG fC mU fU mA fA mU fU fC fA fU fC fA fU	CUGCCGGCUUAAUUCAU CAU	SSSSS SSSSS SSSSS SSSS
WV-18995	fG fG fC fU fU fA fA fU mU fC mA fU mC fA fU fC fU fU	GGCUUAAUUCAUCAUCU	SSSSS SSSSS SSSSS SSSS

	fU fC	UUC	
WV-18996	fA fA fU fU fC fA fU fC mA fU mC fU mU fU fC fA fG fC fU fG	AAUUCAUCAUCUUUCAG CUG	SSSSS SSSSS SSSSS SSSS
WV-18997	fA fU fC fA fU fC fU fU mU fC mA fG mC fU fG fU fA fG fC fC	AUCAUCUUUCAGCUGUA GCC	SSSSS SSSSS SSSSS SSSS
WV-18998	fC fU fU fU fC fA fG fC mU fG mU fA mG fC fC fA fC fA fC fC	CUUUCAGCUGUAGCCAC ACC	SSSSS SSSSS SSSSS SSSS
WV-18999	fA fG fC fU fG fU fA fG mC fC mA fC mA fC fC fA fG fA fA fG	AGCUGUAGCCACACCAG AAG	SSSSS SSSSS SSSSS SSSS
WV-19000	fU fA fG fC fC fA fC fA mC fC mA fG mA fA fG fU fU fC fC fU	UAGCCACACCAGAAGUU CCU	SSSSS SSSSS SSSSS SSSS
WV-19001	fA fC fA fC fC fA fG fA mA fG mU fU mC fC fU fG fC fA fG fA	ACACCAGAAGUUCCUGC AGA	SSSSS SSSSS SSSSS SSSS
WV-19002	fA fG fA fA fG fU fU fC mC fU mG fC mA fG fA fG fA fA fA fG	AGAAGUUCCUGCAGAGA AAG	SSSSS SSSSS SSSSS SSSS
WV-19003	fU fC fC fU fG fC fA fG mA fG mA fA mA fG fG fU fG fC fA fG	UCCUGCAGAGAAAGGUG CAG	SSSSS SSSSS SSSSS SSSS
WV-19004	fC fA fG fA fG fA fA fA mG fG mU fG mC fA fG fA fC fG fC fU	CAGAGAAAGGUGCAGAC GCU	SSSSS SSSSS SSSSS SSSS
WV-19005	fA fA fA fG fG fU fG fC mA fG mA fC mG fC fU fU fC fC fA fC	AAAGGUGCAGACGCUUC CAC	SSSSS SSSSS SSSSS SSSS
WV-19006	fU fG fC fA fG fA fC fG mC fU mU fC mC fA fC fU fG fG fU fC	UGCAGACGCUUCCACUG GUC	SSSSS SSSSS SSSSS SSSS
WV-19007	fA fC fG fC fU fU fC fC mA fC mU fG mG fU fC fA fG fA fA fC	ACGCUUCCACUGGUCAG AAC	SSSSS SSSSS SSSSS SSSS
WV-19008	fU fC fC fA fC fU fG fG mU fC mA fG mA fA fC fU fG fG fC fU	UCCACUGGUCAGAACUG GCU	SSSSS SSSSS SSSSS SSSS
WV-19009	fU fG fG fU fC fA fG fA mA fC mU fG mG fC fU fU fC fC fA fA	UGGUCAGAACUGGCUUC CAA	SSSSS SSSSS SSSSS SSSS
WV-19010	fA fG fA fA fC fC fU fG fG mC fU mU fC mC fA fA fA fU fG fG fG	AGAACUGGCUUCCAAAU GGG	SSSSS SSSSS SSSSS SSSS
WV-19011	fU fG fG fC fU fU fC fC mA fA mA fU mG fG fG fA fC fC fU fG	UGGCUUCCAAAUGGGAC CUG	SSSSS SSSSS SSSSS SSSS
WV-19012	fA fG fG fC fA fC fG fA mG fG mC fU mU fA fA fA fA fA fU fG	AGGCACGAGGCUUAAAA AUG	SSSSS SSSSS SSSSS SSSS
WV-19013	fG fG fC fA fC fG fA fG mG fC mU fU mA fA fA fA fA fU	GGCACGAGGCUUAAAAA	SSSSS SSSSS SSSSS SSSS

	fG fU	UGU	
WV-19014	fG fC fA fC fG fA fG fG mC fU mU fA mA fA fA fA fU fG fU fC	GCACGAGGCUUAAAAAU GUC	SSSSS SSSSS SSSSS SSSS
WV-19015	fC fA fC fG fA fG fG fC mU fU mA fA mA fA fA fU fG fU fC fC	CACGAGGCUUAAAAAUG UCC	SSSSS SSSSS SSSSS SSSS
WV-19016	fA fC fG fA fG fG fC fU mU fA mA fA fA fU fG fU fC fC fU	ACGAGGCUUAAAAAUGU CCU	SSSSS SSSSS SSSSS SSSS
WV-19017	fC fG fA fG fG fC fU fU mA fA mA fA mA fU fG fU fC fC fU fA	CGAGGCUUAAAAAUGUC CUA	SSSSS SSSSS SSSSS SSSS
WV-19018	fG fA fG fG fC fU fU fA mA fA mA fA mU fG fU fC fC fU fA fC	GAGGCUUAAAAAUGUCC UAC	SSSSS SSSSS SSSSS SSSS
WV-19019	fA fG fG fC fU fU fA fA mA fA mA fU mG fU fC fC fU fA fC fC	AGGCUUAAAAAUGUCCU ACC	SSSSS SSSSS SSSSS SSSS
WV-19020	fG fG fC fU fU fU fA fA fA mA fA mU fG mU fC fC fU fA fC fC fC	GGCUUAAAAAUGUCCUA CCC	SSSSS SSSSS SSSSS SSSS
WV-19021	fG fC fU fU fU fA fA fA mA fU mG fU mC fC fU fA fC fC fC fU	GCUUAAAAAUGUCCUAC CCU	SSSSS SSSSS SSSSS SSSS
WV-19022	fC fU fU fA fA fA fA fA mU fG mU fC mC fU fA fC fC fC fU fA	CUUAAAAAUGUCCUACC CUA	SSSSS SSSSS SSSSS SSSS
WV-19023	fU fU fA fA fA fA fA fU mG fU mC fC mU fA fC fC fC fC fU fA fU	UUAAAAAUGUCCUACCC UAU	SSSSS SSSSS SSSSS SSSS
WV-19024	fU fA fA fA fA fA fA fU fG mU fC mC fU mA fC fC fC fC fU fA fU fG	UAAAAAUGUCCUACCCU AUG	SSSSS SSSSS SSSSS SSSS
WV-19025	fA fA fA fA fA fA fU fG fU mC fC mU fA mC fC fC fU fA fU fG fU	AAAAAUGUCCUACCCUA UGU	SSSSS SSSSS SSSSS SSSS
WV-19026	fA fA fA fA fA fU fG fU fC mC fU mA fC mC fC fU fA fU fG fU fA	AAAAUGUCCUACCCUAU GUA	SSSSS SSSSS SSSSS SSSS
WV-19027	fA fA fA fU fG fU fC fC mU fA mC fC mC fU fA fU fG fU fA fC	AAAUGUCCUACCCUAUG UAC	SSSSS SSSSS SSSSS SSSS
WV-19028	fA fA fU fG fU fC fC fU mA fC mC fC mU fA fU fG fU fA fC fA	AAUGUCCUACCCUAUGU ACA	SSSSS SSSSS SSSSS SSSS
WV-19029	fA fU fG fU fC fC fU fA mC fC mC fU mA fU fG fU fA fC fA fU	AUGUCCUACCCUAUGUA CAU	SSSSS SSSSS SSSSS SSSS
WV-19030	fU fG fU fC fC fU fA fC mC fC mU fA mU fG fU fA fC fA fU fC	UGUCCUACCCUAUGUAC AUC	SSSSS SSSSS SSSSS SSSS
WV-19031	fG fU fC fC fU fA fC fC mC fU mA fU mG fU fA fC fA fU	GUCCUACCCUAUGUACA	SSSSS SSSSS SSSSS SSSS

	fC fG	UCG	
WV-19032	fU fC fC fU fA fC fC fC mU fA mU fG mU fA fC fC fA fU fC fG fU	UCCUACCCUAUGUACAU CGU	SSSSS SSSSS SSSSS SSSS
WV-19033	fC fU fA fC fC fC fC fU fA mU fG mU fA mC fA fU fC fG fU fU fC	CUACCCUAUGUACAUCG UUC	SSSSS SSSSS SSSSS SSSS
WV-19034	fU fA fC fC fC fC fU fA fU mG fU mA fC mA fU fC fG fU fU fC fU	UACCCUAUGUACAUCGU UCU	SSSSS SSSSS SSSSS SSSS
WV-19801	fC fC fU fU fU fC fC mC fU fG mA fA mG mG fU fU fC fC fU fC fC	CCUUCCCUGAAGGUUCC UCC	XXXXX XOXXX XOOXX XXXX
WV-19802	fC fC fU fU fC fC mC fU fG mA fA mG mG fU fU fC fC fU fC fC	CCUUCCCUGAAGGUUCC UCC	SSSSS SOSSS SOOSS SSSS
WV-19803	fC fC fU fU fU fC fC mCn001 fU fG mA fA mGn001 mGn001 fU fU fC fC fU fU fC fC	CCUUCCCUGAAGGUUCC UCC	XXXXX XnXXXX XnXnXXX XXXX
WV-19804	fC fC fU fU fU fC fC mCn001 fU fG mA fA mGn001 mGn001 fU fU fC fC fU fU fC fC	CCUUCCCUGAAGGUUCC UCC	SSSSS SnXSSS SnXnXSS SSSS
WV-19805	fC fC fUn001 fU fC fC fCn001 mC fU fG mA fA mG mG fU fU fC fCn001 fU fC fC	CCUUCCCUGAAGGUUCC UCC	XXnXXX nXOXXX XOOXX XnXXX
WV-19806	fC fC fUn001 R fU fC fC fCn001 R mC fU fG mA fA mG mG fU fU fC fCn001 R fU fC fC	CCUUCCCUGAAGGUUCC UCC	SSnRSS nROSSS SOOSS SnRSS
WV-19886	fC fU fUn001 fC fU fGn001 fC fC mA fA mC fU mU fU fU fA fUn001 fC fA fU	CUUCUGCCAACUUUUAU CAU	SSnXSS nXSSSS SSSSS SnXSS
WV-19887	fU fU fCn001 fU fG fCn001 fC fA mA fC mU fU mU fU fA fU fCn001 fA fU fU	UUCUGCCAACUUUUAUC AUU	SSnXSS nXSSSS SSSSS SnXSS
WV-19888	fU fC fUn001 fG fC fCn001 fA fA mC fU mU fU mU fA fU fC fAn001 fU fU fU	UCUGCCAACUUUUAUCA UUU	SSnXSS nXSSSS SSSSS SnXSS
WV-19889	fC fU fGn001 fC fC fAn001 fA fC mU fU mU fU mA fU fC fA fUn001 fU fU fU	CUGCCAACUUUUAUCAU UUU	SSnXSS nXSSSS SSSSS SnXSS
WV-19890	fU fG fCn001 fC fA fAn001 fC fU mU fU mU fA mU fC fA fU fUn001 fU fU fU	UGCCAACUUUUAUCAUU UUU	SSnXSS nXSSSS SSSSS SnXSS
WV-19891	fG fC fCn001 fA fA fCn001 fU fU mU fU mA fU mC fA fU fU fUn001 fU fU fU	GCCAACUUUUAUCAUUU UUU	SSnXSS nXSSSS SSSSS SnXSS
WV-19892	fC fC fAn001 fA fC fUn001 fU fU mU fA mU fC mA fU fU fU fUn001 fU fU fC	CCAACUUUUAUCAUUUU UUC	SSnXSS nXSSSS SSSSS SnXSS
WV-19893	fC fA fAn001 fC fU fUn001 fU fU mA fU mC fA mU fU fU fU fUn001 fU fC fU	CAACUUUUAUCAUUUUU UCU	SSnXSS nXSSSS SSSSS SnXSS
WV-19894	fA fA fCn001 fU fU fUn001 fU fA mU fC mA fU mU fU fU	AACUUUUAUCAUUUUUU	SSnXSS nXSSSS SSSSS

	fU fUn001 fC fU fC	CUC	SnXSS
WV-19895	fA fC fUn001 fU fU fUn001 fA fU mC fA mU fU mU fU fU fU fCn001 fU fC fA	ACUUUUAUCAUUUUUC UCA	SSnXSS nXSSSS SSSSS SnXSS
WV-19896	fC fU fUn001 fU fU fAn001 fU fC mA fU mU fU mU fU fU fC fUn001 fC fA fU	CUUUUAUCAUUUUUCU CAU	SSnXSS nXSSSS SSSSS SnXSS
WV-19897	fU fU fUn001 fU fA fUn001 fC fA mU fU mU fU mU fU fC fU fCn001 fA fU fA	UUUUAUCAUUUUUCUC AUA	SSnXSS nXSSSS SSSSS SnXSS
WV-19898	fU fU fUn001 fA fU fCn001 fA fU mU fU mU fU mU fC fU fC fAn001 fU fA fC	UUUAUCAUUUUUCUCA UAC	SSnXSS nXSSSS SSSSS SnXSS
WV-19899	fU fU fAn001 fU fC fAn001 fU fU mU fU mU fU mC fU fC fA fUn001 fA fC fC	UUAUCAUUUUUCUCAU ACC	SSnXSS nXSSSS SSSSS SnXSS
WV-19900	fU fA fUn001 fC fA fUn001 fU fU mU fU mU fC mU fC fA fU fAn001 fC fC fU	UAUCAUUUUUCUCAUA CCU	SSnXSS nXSSSS SSSSS SnXSS
WV-19901	fA fU fCn001 fA fU fUn001 fU fU mU fU mC fU mC fA fU fA fCn001 fC fU fU	AUCAUUUUUCUCAUAC CUU	SSnXSS nXSSSS SSSSS SnXSS
WV-19902	fU fC fAn001 fU fU fUn001 fU fU mU fC mU fC mA fU fA fC fCn001 fU fU fC	UCAUUUUUCUCAUACC UUC	SSnXSS nXSSSS SSSSS SnXSS
WV-19903	fC fA fUn001 fU fU fUn001 fU fU mC fU mC fA mU fA fC fC fUn001 fU fC fU	CAUUUUUCUCAUACCU UCU	SSnXSS nXSSSS SSSSS SnXSS
WV-19904	fA fU fUn001 fU fU fUn001 fU fC mU fC mA fU mA fC fC fU fUn001 fC fU fG	AUUUUUCUCAUACCUU CUG	SSnXSS nXSSSS SSSSS SnXSS
WV-19905	fU fU fUn001 fU fU fUn001 fC fU mC fA mU fA mC fC fU fU fCn001 fU fG fC	UUUUUUCUCAUACCUUC UGC	SSnXSS nXSSSS SSSSS SnXSS
WV-19906	fU fU fUn001 fU fU fCn001 fU fC mA fU mA fC mC fU fU fC fUn001 fG fC fU	UUUUUCUCAUACCUUCU GCU	SSnXSS nXSSSS SSSSS SnXSS
WV-19907	fU fU fUn001 fU fC fUn001 fC fA mU fA mC fC mU fU fC fU fGn001 fC fU fU	UUUUCUCAUACCUUCUG CUU	SSnXSS nXSSSS SSSSS SnXSS
WV-19908	fU fU fUn001 fC fU fCn001 fA fU mA fC mC fU mU fC fU fG fCn001 fU fU fG	UUUCUCAUACCUUCUGC UUG	SSnXSS nXSSSS SSSSS SnXSS
WV-19909	fU fU fCn001 fU fC fAn001 fU fA mC fC mU fU mC fU fG fC fUn001 fU fG fA	UUCUCAUACCUUCUGCU UGA	SSnXSS nXSSSS SSSSS SnXSS
WV-19910	fU fC fUn001 fC fA fUn001 fA fC mC fU mU fC mU fG fC fU fUn001 fG fA fU	UCUCAUACCUUCUGCUU GAU	SSnXSS nXSSSS SSSSS SnXSS
WV-19911	fC fU fCn001 fA fU fAn001 fC fC mU fU mC fU mG fC fU fU fGn001 fA fU fG	CUCAUACCUUCUGCUUG AUG	SSnXSS nXSSSS SSSSS SnXSS
WV-19912	fU fC fAn001 fU fA fCn001 fC fU mU fC mU fG mC fU fU	UCAUACCUUCUGCUUGA	SSnXSS nXSSSS SSSSS

	fG fAn001 fU fG fA	UGA	SnXSS
WV-19913	fC fA fUn001 fA fC fCn001 fU fU mC fU mG fC mU fU fG fA fUn001 fG fA fU	CAUACCUUCUGCUUGAU GAU	SSnXSS nXSSSS SSSSS SnXSS
WV-19914	fA fU fAn001 fC fC fUn001 fU fC mU fG mC fU mU fG fA fU fGn001 fA fU fC	AUACCUUCUGCUUGAUG AUC	SSnXSS nXSSSS SSSSS SnXSS
WV-19915	fU fA fCn001 fC fU fUn001 fC fU mG fC mU fU mG fA fU fG fAn001 fU fC fA	UACCUUCUGCUUGAUGA UCA	SSnXSS nXSSSS SSSSS SnXSS
WV-19916	fA fC fCn001 fU fU fCn001 fU fG mC fU mU fG mA fU fG fA fUn001 fC fA fU	ACCUUCUGCUUGAUGAU CAU	SSnXSS nXSSSS SSSSS SnXSS
WV-19917	fC fC fUn001 fU fC fUn001 fG fC mU fU mG fA mU fG fA fU fCn001 fA fU fC	CCUUCUGCUUGAUGAUC AUC	SSnXSS nXSSSS SSSSS SnXSS
WV-19918	fC fU fUn001 fC fU fGn001 fC fU mU fG mA fU mG fA fU fC fAn001 fU fC fU	CUUCUGCUUGAUGAUCA UCU	SSnXSS nXSSSS SSSSS SnXSS
WV-19919	fU fU fCn001 fU fG fCn001 fU fU mG fA mU fG mA fU fC fA fUn001 fC fU fC	UUCUGCUUGAUGAUCAU CUC	SSnXSS nXSSSS SSSSS SnXSS
WV-19920	fU fC fUn001 fG fC fUn001 fU fG mA fU mG fA mU fC fA fU fCn001 fU fC fG	UCUGCUUGAUGAUCAUC UCG	SSnXSS nXSSSS SSSSS SnXSS
WV-19921	fC fU fGn001 fC fU fUn001 fG fA mU fG mA fU mC fA fU fC fUn001 fC fG fU	CUGCUUGAUGAUCAUCU CGU	SSnXSS nXSSSS SSSSS SnXSS
WV-19922	fU fG fCn001 fU fU fGn001 fA fU mG fA mU fC mA fU fC fU fCn001 fG fU fU	UGCUUGAUGAUCAUCUC GUU	SSnXSS nXSSSS SSSSS SnXSS
WV-19923	fG fC fUn001 fU fG fAn001 fU fG mA fU mC fA mU fC fU fC fGn001 fU fU fG	GCUUGAUGAUCAUCUCG UUG	SSnXSS nXSSSS SSSSS SnXSS
WV-19924	fC fU fUn001 fG fA fUn001 fG fA mU fC mA fU mC fU fC fG fUn001 fU fG fA	CUUGAUGAUCAUCUCGU UGA	SSnXSS nXSSSS SSSSS SnXSS
WV-19925	fU fU fGn001 fA fU fGn001 fA fU mC fA mU fC mU fC fG fU fUn001 fG fA fU	UUGAUGAUCAUCUCGUU GAU	SSnXSS nXSSSS SSSSS SnXSS
WV-19926	fU fG fAn001 fU fG fAn001 fU fC mA fU mC fU mC fG fU fU fGn001 fA fU fA	UGAUGAUCAUCUCGUUG AUA	SSnXSS nXSSSS SSSSS SnXSS
WV-19927	fG fA fUn001 fG fA fUn001 fC fA mU fC mU fC mG fU fU fG fAn001 fU fA fU	GAUGAUCAUCUCGUUGA UAU	SSnXSS nXSSSS SSSSS SnXSS
WV-19928	fA fU fGn001 fA fU fCn001 fA fU mC fU mC fG mU fU fG fA fUn001 fA fU fC	AUGAUCAUCUCGUUGAU AUC	SSnXSS nXSSSS SSSSS SnXSS
WV-19929	fU fG fAn001 fU fC fAn001 fU fC mU fC mG fU mU fG fA fU fAn001 fU fC fC	UGAUCAUCUCGUUGAUA UCC	SSnXSS nXSSSS SSSSS SnXSS
WV-19930	fG fA fUn001 fC fA fUn001 fC fU mC fG mU fU mG fA fU	GAUCAUCUCGUUGAUAU	SSnXSS nXSSSS SSSSS

	fA fUn001 fC fC fU	CCU	SnXSS
WV-19931	fA fU fCn001 fA fU fCn001 fU fC mG fU mU fG mA fU fA fU fCn001 fC fU fC	AUCAUCUCGUUGAUAUC CUC	SSnXSS nXSSSS SSSSS SnXSS
WV-19932	fU fC fAn001 fU fC fUn001 fC fG mU fU mG fA mU fA fU fC fCn001 fU fC fA	UCAUCUCGUUGAUAUCC UCA	SSnXSS nXSSSS SSSSS SnXSS
WV-19933	fC fA fUn001 fC fU fCn001 fG fU mU fG mA fU mA fU fC fC fUn001 fC fA fA	CAUCUCGUUGAUAUCCU CAA	SSnXSS nXSSSS SSSSS SnXSS
WV-19934	fA fU fCn001 fU fC fGn001 fU fU mG fA mU fA mU fC fC fU fCn001 fA fA fG	AUCUCGUUGAUAUCCUC AAG	SSnXSS nXSSSS SSSSS SnXSS
WV-19935	fU fC fUn001 fC fG fUn001 fU fG mA fU mA fU mC fC fU fC fAn001 fA fG fG	UCUCGUUGAUAUCCUCA AGG	SSnXSS nXSSSS SSSSS SnXSS
WV-19936	fC fU fCn001 fG fU fUn001 fG fA mU fA mU fC mC fU fC fA fAn001 fG fG fU	CUCGUUGAUAUCCUCAA GGU	SSnXSS nXSSSS SSSSS SnXSS
WV-19937	fU fC fGn001 fU fU fGn001 fA fU mA fU mC fC mU fC fA fA fGn001 fG fU fC	UCGUUGAUAUCCUCAAG GUC	SSnXSS nXSSSS SSSSS SnXSS
WV-19938	fC fG fUn001 fU fG fAn001 fU fA mU fC mC fU mC fA fA fG fGn001 fU fC fA	CGUUGAUAUCCUCAAGG UCA	SSnXSS nXSSSS SSSSS SnXSS
WV-19939	fG fU fUn001 fG fA fUn001 fA fU mC fC mU fC mA fA fG fG fUn001 fC fA fC	GUUGAUAUCCUCAAGGU CAC	SSnXSS nXSSSS SSSSS SnXSS
WV-19940	fU fU fGn001 fA fU fAn001 fU fC mC fU mC fA mA fG fG fU fCn001 fA fC fC	UUGAUAUCCUCAAGGUC ACC	SSnXSS nXSSSS SSSSS SnXSS
WV-19941	fU fG fAn001 fU fA fUn001 fC fC mU fC mA fA mG fG fU fC fAn001 fC fC fC	UGAUAUCCUCAAGGUCA CCC	SSnXSS nXSSSS SSSSS SnXSS
WV-19942	fG fA fUn001 fA fU fCn001 fC fU mC fA mA fG mG fU fC fA fCn001 fC fC fA	GAUAUCCUCAAGGUCAC CCA	SSnXSS nXSSSS SSSSS SnXSS
WV-19943	fA fU fAn001 fU fC fCn001 fU fC mA fA mG fG mU fC fA fC fCn001 fC fA fC	AUAUCCUCAAGGUCACC CAC	SSnXSS nXSSSS SSSSS SnXSS
WV-19944	fU fA fUn001 fC fC fUn001 fC fA mA fG mG fU mC fA fC fC fCn001 fA fC fC	UAUCCUCAAGGUCACCC ACC	SSnXSS nXSSSS SSSSS SnXSS
WV-19945	fA fU fCn001 fC fU fCn001 fA fA mG fG mU fC mA fC fC fC fAn001 fC fC fA	AUCCUCAAGGUCACCCA CCA	SSnXSS nXSSSS SSSSS SnXSS
WV-19946	fU fC fCn001 fU fC fAn001 fA fG mG fU mC fA mC fC fC fA fCn001 fC fA fU	UCCUCAAGGUCACCCACC AU	SSnXSS nXSSSS SSSSS SnXSS
WV-19947	fC fC fUn001 fC fA fAn001 fG fG mU fC mA fC mC fC fA fC fCn001 fA fU fC	CCUCAAGGUCACCCACCA UC	SSnXSS nXSSSS SSSSS SnXSS
WV-19948	fC fU fCn001 fA fA fGn001 fG fU mC fA mC fC mC fA fC	CUCAAGGUCACCCACCA	SSnXSS nXSSSS SSSSS

	fC fAn001 fU fC fA	UCA	SnXSS
WV-19949	fU fC fAn001 fA fG fGn001 fU fC mA fC mC fC mA fC fC fA fUn001 fC fA fC	UCAAGGUCACCCACCAU CAC	SSnXSS nXSSSS SSSSS SnXSS
WV-19950	fC fA fAn001 fG fG fUn001 fC fA mC fC mC fA mC fC fA fU fCn001 fA fC fC	CAAGGUCACCCACCAUC ACC	SSnXSS nXSSSS SSSSS SnXSS
WV-19951	fA fA fGn001 fG fU fCn001 fA fC mC fC mA fC mC fA fU fC fAn001 fC fC fC	AAGGUCACCCACCAUCA CCC	SSnXSS nXSSSS SSSSS SnXSS
WV-19952	fA fG fGn001 fU fC fAn001 fC fC mC fA mC fC mA fU fC fA fCn001 fC fC fU	AGGUCACCCACCAUCACC CU	SSnXSS nXSSSS SSSSS SnXSS
WV-19953	fG fG fUn001 fC fA fCn001 fC fC mA fC mC fA mU fC fA fC fCn001 fC fU fC	GGUCACCCACCAUCACCC UC	SSnXSS nXSSSS SSSSS SnXSS
WV-19954	fG fU fCn001 fA fC fCn001 fC fA mC fC mA fU mC fA fC fC fCn001 fU fC fU	GUCACCCACCAUCACCCU CU	SSnXSS nXSSSS SSSSS SnXSS
WV-19955	fU fC fAn001 fC fC fCn001 fA fC mC fA mU fC mA fC fC fC fUn001 fC fU fG	UCACCCACCAUCACCCUC UG	SSnXSS nXSSSS SSSSS SnXSS
WV-19956	fC fA fCn001 fC fC fAn001 fC fC mA fU mC fA mC fC fC fU fCn001 fU fG fU	CACCCACCAUCACCCUCU GU	SSnXSS nXSSSS SSSSS SnXSS
WV-19957	fA fC fCn001 fC fA fCn001 fC fA mU fC mA fC mC fC fU fC fUn001 fG fU fG	ACCCACCAUCACCCUCUG UG	SSnXSS nXSSSS SSSSS SnXSS
WV-19958	fC fC fCn001 fA fC fCn001 fA fU mC fA mC fC mC fU fC fU fGn001 fU fG fA	CCCACCAUCACCCUCUGU GA	SSnXSS nXSSSS SSSSS SnXSS
WV-19959	fC fC fAn001 fC fC fAn001 fU fC mA fC mC fC mU fC fU fG fUn001 fG fA fU	CCACCAUCACCCUCUGUG AU	SSnXSS nXSSSS SSSSS SnXSS
WV-19960	fC fA fCn001 fC fA fUn001 fC fA mC fC mC fU mC fU fG fU fGn001 fA fU fU	CACCAUCACCCUCUGUG AUU	SSnXSS nXSSSS SSSSS SnXSS
WV-19961	fA fC fCn001 fA fU fCn001 fA fC mC fC mU fC mU fG fU fG fAn001 fU fU fU	ACCAUCACCCUCUGUGA UUU	SSnXSS nXSSSS SSSSS SnXSS
WV-19962	fC fC fAn001 fU fC fAn001 fC fC mC fU mC fU mG fU fG fA fUn001 fU fU fU	CCAUCACCCUCUGUGAU UUU	SSnXSS nXSSSS SSSSS SnXSS
WV-19963	fC fA fUn001 fC fA fCn001 fC fC mU fC mU fG mU fG fA fU fUn001 fU fU fA	CAUCACCCUCUGUGAUU UUA	SSnXSS nXSSSS SSSSS SnXSS
WV-19964	fA fU fCn001 fA fC fCn001 fC fU mC fU mG fU mG fA fU fU fUn001 fU fA fU	AUCACCCUCUGUGAUUU UAU	SSnXSS nXSSSS SSSSS SnXSS
WV-19965	fU fC fAn001 fC fC fCn001 fU fC mU fG mU fG mA fU fU fU fUn001 fA fU fA	UCACCCUCUGUGAUUUU AUA	SSnXSS nXSSSS SSSSS SnXSS
WV-19966	fC fA fCn001 fC fC fUn001 fC fU mG fU mG fA mU fU fU	CACCCUCUGUGAUUUUA	SSnXSS nXSSSS SSSSS

	fU fAn001 fU fA fA	UAA	SnXSS
WV-19967	fA fC fCn001 fC fU fCn001 fU fG mU fG mA fU mU fU fU fA fU fUn001 fA fA fC	ACCCUCUGUGAUUUUAU AAC	SSnXSS nXSSSS SSSSS SnXSS
WV-19968	fC fC fCn001 fU fC fUn001 fG fU mG fA mU fU mU fU fA fU fAn001 fA fC fU	CCCUCUGUGAUUUUAUA ACU	SSnXSS nXSSSS SSSSS SnXSS
WV-19969	fC fC fUn001 fC fU fGn001 fU fG mA fU mU fU mU fA fU fA fAn001 fC fU fU	CCUCUGUGAUUUUAUAA CUU	SSnXSS nXSSSS SSSSS SnXSS
WV-19970	fC fU fCn001 fU fG fUn001 fG fA mU fU mU fU mA fU fA fA fCn001 fU fU fG	CUCUGUGAUUUUAUAAC UUG	SSnXSS nXSSSS SSSSS SnXSS
WV-19971	fU fC fUn001 fG fU fGn001 fA fU mU fU mU fA mU fA fA fC fUn001 fU fG fA	UCUGUGAUUUUAUAACU UGA	SSnXSS nXSSSS SSSSS SnXSS
WV-19972	fC fU fGn001 fU fG fAn001 fU fU mU fU mA fU mA fA fC fU fUn001 fG fA fU	CUGUGAUUUUAUAACUU GAU	SSnXSS nXSSSS SSSSS SnXSS
WV-19973	fU fG fUn001 fG fA fUn001 fU fU mU fA mU fA mA fC fU fU fGn001 fA fU fC	UGUGAUUUUAUAACUUG AUC	SSnXSS nXSSSS SSSSS SnXSS
WV-19974	fG fU fGn001 fA fU fUn001 fU fU mA fU mA fA mC fU fU fG fAn001 fU fC fA	GUGAUUUUAUAACUUGA UCA	SSnXSS nXSSSS SSSSS SnXSS
WV-19975	fU fG fAn001 fU fU fUn001 fU fA mU fA mA fC mU fU fG fA fUn001 fC fA fA	UGAUUUUAUAACUUGAU CAA	SSnXSS nXSSSS SSSSS SnXSS
WV-19976	fG fA fUn001 fU fU fUn001 fA fU mA fA mC fU mU fG fA fU fCn001 fA fA fG	GAUUUUAUAACUUGAUC AAG	SSnXSS nXSSSS SSSSS SnXSS
WV-19977	fA fU fUn001 fU fU fAn001 fU fA mA fC mU fU mG fA fU fC fAn001 fA fG fC	AUUUUAUAACUUGAUCA AGC	SSnXSS nXSSSS SSSSS SnXSS
WV-19978	fU fU fUn001 fU fA fUn001 fA fA mC fU mU fG mA fU fC fA fAn001 fG fC fA	UUUUAUAACUUGAUCAA GCA	SSnXSS nXSSSS SSSSS SnXSS
WV-19979	fU fU fUn001 fA fU fAn001 fA fC mU fU mG fA mU fC fA fA fGn001 fC fA fG	UUUAUAACUUGAUCAAG CAG	SSnXSS nXSSSS SSSSS SnXSS
WV-19980	fU fU fAn001 fU fA fAn001 fC fU mU fG mA fU mC fA fA fG fCn001 fA fG fA	UUAUAACUUGAUCAAGC AGA	SSnXSS nXSSSS SSSSS SnXSS
WV-19981	fU fA fUn001 fA fA fCn001 fU fU mG fA mU fC mA fA fG fC fAn001 fG fA fG	UAUAACUUGAUCAAGCA GAG	SSnXSS nXSSSS SSSSS SnXSS
WV-19982	fA fU fAn001 fA fC fUn001 fU fG mA fU mC fA mA fG fC fA fGn001 fA fG fA	AUAACUUGAUCAAGCAG AGA	SSnXSS nXSSSS SSSSS SnXSS
WV-19983	fU fA fAn001 fC fU fUn001 fG fA mU fC mA fA mG fC fA fG fAn001 fG fA fA	UAACUUGAUCAAGCAGA GAA	SSnXSS nXSSSS SSSSS SnXSS
WV-19984	fA fA fCn001 fU fU fGn001 fA fU mC fA mA fG mC fA fG	AACUUGAUCAAGCAGAG	SSnXSS nXSSSS SSSSS

	fA fGn001 fA fA	AAA	SnXSS
WV-19985	fA fC fUn001 fU fG fAn001 fU fC mA fA mG fC mA fG fA fG fAn001 fA fA fG	ACUUGAUCAAGCAGAGA AAG	SSnXSS nXSSSS SSSSS SnXSS
WV-19986	fC fU fUn001 fG fA fUn001 fC fA mA fG mC fA mG fA fG fA fAn001 fA fG fC	CUUGAUCAAGCAGAGAA AGC	SSnXSS nXSSSS SSSSS SnXSS
WV-19987	fU fU fGn001 fA fU fCn001 fA fA mG fC mA fG mA fG fA fA fAn001 fG fC fC	UUGAUCAAGCAGAGAAA GCC	SSnXSS nXSSSS SSSSS SnXSS
WV-19988	fU fG fAn001 fU fC fAn001 fA fG mC fA mG fA mG fA fA fA fGn001 fC fC fA	UGAUCAAGCAGAGAAAG CCA	SSnXSS nXSSSS SSSSS SnXSS
WV-19989	fG fA fUn001 fC fA fAn001 fG fC mA fG mA fG mA fA fA fG fCn001 fC fA fG	GAUCAAGCAGAGAAAGC CAG	SSnXSS nXSSSS SSSSS SnXSS
WV-19990	fA fU fCn001 fA fA fGn001 fC fA mG fA mG fA mA fA fG fC fCn001 fA fG fU	AUCAAGCAGAGAAAGCC AGU	SSnXSS nXSSSS SSSSS SnXSS
WV-19991	fU fC fAn001 fA fG fCn001 fA fG mA fG mA fA mA fG fC fC fAn001 fG fU fC	UCAAGCAGAGAAAGCCA GUC	SSnXSS nXSSSS SSSSS SnXSS
WV-19992	fC fA fAn001 fG fC fAn001 fG fA mG fA mA fA mG fC fC fA fGn001 fU fC fG	CAAGCAGAGAAAGCCAG UCG	SSnXSS nXSSSS SSSSS SnXSS
WV-19993	fA fA fGn001 fC fA fGn001 fA fG mA fA mA fG mC fC fA fG fUn001 fC fG fG	AAGCAGAGAAAGCCAGU CGG	SSnXSS nXSSSS SSSSS SnXSS
WV-19994	fA fG fCn001 fA fG fAn001 fG fA mA fA mG fC mC fA fG fU fCn001 fG fG fU	AGCAGAGAAAGCCAGUC GGU	SSnXSS nXSSSS SSSSS SnXSS
WV-19995	fG fC fAn001 fG fA fGn001 fA fA mA fG mC fC mA fG fU fC fGn001 fG fU fA	GCAGAGAAAGCCAGUCG GUA	SSnXSS nXSSSS SSSSS SnXSS
WV-19996	fC fA fGn001 fA fG fAn001 fA fA mG fC mC fA mG fU fC fG fGn001 fU fA fA	CAGAGAAAGCCAGUCGG UAA	SSnXSS nXSSSS SSSSS SnXSS
WV-19997	fA fG fAn001 fG fA fAn001 fA fG mC fC mA fG mU fC fG fU fUn001 fA fA fG	AGAGAAAGCCAGUCGGU AAG	SSnXSS nXSSSS SSSSS SnXSS
WV-19998	fG fA fGn001 fA fA fAn001 fG fC mC fA mG fU mC fG fG fU fAn001 fA fG fU	GAGAAAGCCAGUCGGUA AGU	SSnXSS nXSSSS SSSSS SnXSS
WV-19999	fA fG fAn001 fA fA fGn001 fC fC mA fG mU fC mG fG fU fA fAn001 fG fU fU	AGAAAGCCAGUCGGUAA GUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20000	fG fA fAn001 fA fG fCn001 fC fA mG fU mC fG mG fU fA fA fGn001 fU fU fC	GAAAGCCAGUCGGUAAG UUC	SSnXSS nXSSSS SSSSS SnXSS
WV-20001	fA fA fAn001 fG fC fCn001 fA fG mU fC mG fG mU fA fA fG fUn001 fU fC fU	AAAGCCAGUCGGUAAGU UCU	SSnXSS nXSSSS SSSSS SnXSS
WV-20002	fA fA fGn001 fC fC fAn001 fG fU mC fG mG fU mA fA fG	AAGCCAGUCGGUAAGUU	SSnXSS nXSSSS SSSSS

	fU fUn001 fC fU fG	CUG	SnXSS
WV-20003	fA fG fCn001 fC fA fGn001 fU fC mG fG mU fA mA fG fU fU fCn001 fU fG fU	AGCCAGUCGGUAAGUUC UGU	SSnXSS nXSSSS SSSSS SnXSS
WV-20004	fG fC fCn001 fA fG fUn001 fC fG mG fU mA fA mG fU fU fC fUn001 fG fU fC	GCCAGUCGGUAAGUUCU GUC	SSnXSS nXSSSS SSSSS SnXSS
WV-20005	fC fC fAn001 fG fU fCn001 fG fG mU fA mA fG mU fU fC fU fGn001 fU fC fC	CCAGUCGGUAAGUUCUG UCC	SSnXSS nXSSSS SSSSS SnXSS
WV-20006	fC fA fGn001 fU fC fGn001 fG fU mA fA mG fU mU fC fU fG fUn001 fC fC fA	CAGUCGGUAAGUUCUGU CCA	SSnXSS nXSSSS SSSSS SnXSS
WV-20007	fA fG fUn001 fC fG fGn001 fU fA mA fG mU fU mC fU fG fU fCn001 fC fA fA	AGUCGGUAAGUUCUGUC CAA	SSnXSS nXSSSS SSSSS SnXSS
WV-20008	fG fU fCn001 fG fG fUn001 fA fA mG fU mU fC mU fG fU fC fCn001 fA fA fG	GUCGGUAAGUUCUGUCC AAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20009	fU fC fGn001 fG fU fAn001 fA fG mU fU mC fU mG fU fC fC fAn001 fA fG fC	UCGGUAAGUUCUGUCCA AGC	SSnXSS nXSSSS SSSSS SnXSS
WV-20010	fC fG fGn001 fU fA fAn001 fG fU mU fC mU fG mU fC fC fA fAn001 fG fC fC	CGGUAAGUUCUGUCCAA GCC	SSnXSS nXSSSS SSSSS SnXSS
WV-20011	fG fG fUn001 fA fA fGn001 fU fU mC fU mG fU mC fC fA fA fGn001 fC fC fC	GGUAAGUUCUGUCCAAG CCC	SSnXSS nXSSSS SSSSS SnXSS
WV-20012	fG fU fAn001 fA fG fUn001 fU fC mU fG mU fC mC fA fA fG fG fCn001 fC fC fG	GUAAGUUCUGUCCAAGC CCG	SSnXSS nXSSSS SSSSS SnXSS
WV-20013	fU fA fAn001 fG fU fUn001 fC fU mG fU mC fC mA fA fG fC fCn001 fC fG fG	UAAGUUCUGUCCAAGCC CGG	SSnXSS nXSSSS SSSSS SnXSS
WV-20014	fA fA fGn001 fU fU fCn001 fU fG mU fC mC fA mA fG fC fC fCn001 fG fG fU	AAGUUCUGUCCAAGCCC GGU	SSnXSS nXSSSS SSSSS SnXSS
WV-20015	fA fG fUn001 fU fC fUn001 fG fU mC fC mA fA mG fC fC fC fGn001 fG fU fU	AGUUCUGUCCAAGCCCG GUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20016	fG fU fUn001 fC fU fGn001 fU fC mC fA mA fG mC fC fC fG fGn001 fU fU fG	GUUCUGUCCAAGCCCGG UUG	SSnXSS nXSSSS SSSSS SnXSS
WV-20017	fU fU fCn001 fU fG fUn001 fC fC mA fA mG fC mC fC fG fG fUn001 fU fG fA	UUCUGUCCAAGCCCGGU UGA	SSnXSS nXSSSS SSSSS SnXSS
WV-20018	fU fC fUn001 fG fU fCn001 fC fA mA fG mC fC mC fG fG fU fUn001 fG fA fA	UCUGUCCAAGCCCGGUU GAA	SSnXSS nXSSSS SSSSS SnXSS
WV-20019	fC fU fGn001 fU fC fCn001 fA fA mG fC mC fC mG fG fU fU fGn001 fA fA fA	CUGUCCAAGCCCGGUUG AAA	SSnXSS nXSSSS SSSSS SnXSS
WV-20020	fU fG fUn001 fC fC fAn001 fA fG mC fC mC fG mG fU fU	UGUCCAAGCCCGGUUGA	SSnXSS nXSSSS SSSSS

	fG fAn001 fA fA fU	AAU	SnXSS
WV-20021	fG fU fCn001 fC fA fAn001 fG fC mC fC mG fG mU fU fG fA fAn001 fA fU fC	GUCCAAGCCCGGUUGAA AUC	SSnXSS nXSSSS SSSSS SnXSS
WV-20022	fU fC fCn001 fA fA fGn001 fC fC mC fG mG fU mU fG fA fA fAn001 fU fC fU	UCCAAGCCCGGUUGAAA UCU	SSnXSS nXSSSS SSSSS SnXSS
WV-20023	fC fC fAn001 fA fG fCn001 fC fC mG fG mU fU mG fA fA fA fUn001 fC fU fG	CCAAGCCCGGUUGAAAU CUG	SSnXSS nXSSSS SSSSS SnXSS
WV-20024	fC fA fAn001 fG fC fCn001 fC fG mG fU mU fG mA fA fA fU fCn001 fU fG fC	CAAGCCCGGUUGAAAUC UGC	SSnXSS nXSSSS SSSSS SnXSS
WV-20025	fA fA fGn001 fC fC fCn001 fG fG mU fU mG fA mA fA fU fC fUn001 fG fC fC	AAGCCCGGUUGAAAUCU GCC	SSnXSS nXSSSS SSSSS SnXSS
WV-20026	fA fG fCn001 fC fC fGn001 fG fU mU fG mA fA mA fU fC fU fGn001 fC fC fA	AGCCCGGUUGAAAUCUG CCA	SSnXSS nXSSSS SSSSS SnXSS
WV-20027	fG fC fCn001 fC fG fGn001 fU fU mG fA mA fA mU fC fU fG fCn001 fC fA fG	GCCCGGUUGAAAUCUGC CAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20028	fC fC fCn001 fG fG fUn001 fU fG mA fA mA fU mC fU fG fC fCn001 fA fG fA	CCCGGUUGAAAUCUGCC AGA	SSnXSS nXSSSS SSSSS SnXSS
WV-20029	fC fC fGn001 fG fU fUn001 fG fA mA fA mU fC mU fG fC fC fAn001 fG fA fG	CCGGUUGAAAUCUGCCA GAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20030	fC fG fGn001 fU fU fU fGn001 fA fA mA fU mC fU mG fC fC fA fGn001 fA fG fC	CGGUUGAAAUCUGCCAG AGC	SSnXSS nXSSSS SSSSS SnXSS
WV-20031	fG fG fUn001 fU fG fAn001 fA fA mU fC mU fG mC fC fA fG fAn001 fG fC fA	GGUUGAAAUCUGCCAGA GCA	SSnXSS nXSSSS SSSSS SnXSS
WV-20032	fG fU fUn001 fG fA fAn001 fA fU mC fU mG fC mC fA fG fA fGn001 fC fA fG	GUUGAAAUCUGCCAGAG CAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20033	fU fU fGn001 fA fA fAn001 fU fC mU fG mC fC mA fG fA fG fCn001 fA fG fG	UUGAAAUCUGCCAGAGC AGG	SSnXSS nXSSSS SSSSS SnXSS
WV-20034	fU fG fAn001 fA fA fUn001 fC fU mG fC mC fA mG fA fG fC fAn001 fG fG fU	UGAAAUCUGCCAGAGCA GGU	SSnXSS nXSSSS SSSSS SnXSS
WV-20035	fG fA fAn001 fA fU fCn001 fU fG mC fC mA fG mA fG fC fA fGn001 fG fU fA	GAAAUCUGCCAGAGCAG GUA	SSnXSS nXSSSS SSSSS SnXSS
WV-20036	fA fA fAn001 fU fC fUn001 fG fC mC fA mG fA mG fC fA fG fGn001 fU fA fC	AAAUCUGCCAGAGCAGG UAC	SSnXSS nXSSSS SSSSS SnXSS
WV-20037	fA fA fUn001 fC fU fGn001 fC fC mA fG mA fG mC fA fG fG fUn001 fA fC fC	AAUCUGCCAGAGCAGGU ACC	SSnXSS nXSSSS SSSSS SnXSS
WV-20038	fA fU fCn001 fU fG fCn001 fC fA mG fA mG fC mA fG fG	AUCUGCCAGAGCAGGUA	SSnXSS nXSSSS SSSSS

	fU fAn001 fC fC fU	CCU	SnXSS
WV-20039	fU fC fUn001 fG fC fCn001 fA fG mA fG mC fA mG fG fU fA fCn001 fC fU fC	UCUGCCAGAGCAGGUAC CUC	SSnXSS nXSSSS SSSSS SnXSS
WV-20040	fC fU fGn001 fC fC fAn001 fG fA mG fC mA fG mG fU fA fC fCn001 fU fC fC	CUGCCAGAGCAGGUACC UCC	SSnXSS nXSSSS SSSSS SnXSS
WV-20041	fU fG fCn001 fC fA fGn001 fA fG mC fA mG fG mU fA fC fC fUn001 fC fC fA	UGCCAGAGCAGGUACCU CCA	SSnXSS nXSSSS SSSSS SnXSS
WV-20042	fG fC fCn001 fA fG fAn001 fG fC mA fG mG fU mA fC fC fU fCn001 fC fA fA	GCCAGAGCAGGUACCUC CAA	SSnXSS nXSSSS SSSSS SnXSS
WV-20043	fC fC fAn001 fG fA fGn001 fC fA mG fG mU fA mC fC fU fC fCn001 fA fA fC	CCAGAGCAGGUACCUCC AAC	SSnXSS nXSSSS SSSSS SnXSS
WV-20044	fC fA fGn001 fA fG fCn001 fA fG mG fU mA fC mC fU fC fC fAn001 fA fC fA	CAGAGCAGGUACCUCCA ACA	SSnXSS nXSSSS SSSSS SnXSS
WV-20045	fA fG fAn001 fG fC fAn001 fG fG mU fA mC fC mU fC fC fA fAn001 fC fA fU	AGAGCAGGUACCUCCAA CAU	SSnXSS nXSSSS SSSSS SnXSS
WV-20046	fG fA fGn001 fC fA fGn001 fG fU mA fC mC fU mC fC fA fA fCn001 fA fU fC	GAGCAGGUACCUCCAAC AUC	SSnXSS nXSSSS SSSSS SnXSS
WV-20047	fA fG fCn001 fA fG fGn001 fU fA mC fC mU fC mC fA fA fC fAn001 fU fC fA	AGCAGGUACCUCCAACA UCA	SSnXSS nXSSSS SSSSS SnXSS
WV-20048	fG fC fAn001 fG fG fUn001 fA fC mC fC mU mC fC mA fA fC fA fUn001 fC fA fA	GCAGGUACCUCCAACAU CAA	SSnXSS nXSSSS SSSSS SnXSS
WV-20049	fC fA fGn001 fG fU fAn001 fC fC mU fC mC fA mA fC fA fU fCn001 fA fA fG	CAGGUACCUCCAACAUC AAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20050	fA fG fGn001 fU fA fCn001 fC fU mC fC mA fA mC fA fU fC fAn001 fA fG fG	AGGUACCUCCAACAUCA AGG	SSnXSS nXSSSS SSSSS SnXSS
WV-20051	fG fG fUn001 fA fC fCn001 fU fC mC fA mA fC mA fU fC fA fAn001 fG fG fA	GGUACCUCCAACAUCAA GGA	SSnXSS nXSSSS SSSSS SnXSS
WV-20052	fG fU fAn001 fC fC fUn001 fC fC mA fA mC fA mU fC fA fA fGn001 fG fA fA	GUACCUCCAACAUCAAG GAA	SSnXSS nXSSSS SSSSS SnXSS
WV-20053	fU fA fCn001 fC fU fCn001 fC fA mA fC mA fU mC fA fA fG fGn001 fA fA fG	UACCUCCAACAUCAAGG AAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20054	fA fC fCn001 fU fC fCn001 fA fA mC fA mU fC mA fA fG fG fAn001 fA fG fA	ACCUCCAACAUCAAGGA AGA	SSnXSS nXSSSS SSSSS SnXSS
WV-20055	fC fC fUn001 fC fC fAn001 fA fC mA fU mC fA mA fG fG fA fAn001 fG fA fU	CCUCCAACAUCAAGGAA GAU	SSnXSS nXSSSS SSSSS SnXSS
WV-20056	fC fU fCn001 fC fA fAn001 fC fA mU fC mA fA mG fG fA	CUCCAACAUCAAGGAAG	SSnXSS nXSSSS SSSSS

	fA fGn001 fA fU fG	AUG	SnXSS
WV-20057	fU fC fCn001 fA fA fCn001 fA fU mC fA mA fG mG fA fA fG fAn001 fU fG fG	UCCAACAUCAAGGAAGA UGG	SSnXSS nXSSSS SSSSS SnXSS
WV-20058	fC fC fAn001 fA fC fAn001 fU fC mA fA mG fG mA fA fG fA fUn001 fG fG fC	CCAACAUCAAGGAAGAU GGC	SSnXSS nXSSSS SSSSS SnXSS
WV-20059	fC fA fAn001 fC fA fUn001 fC fA mA fG mG fA mA fG fA fU fGn001 fG fC fA	CAACAUCAAGGAAGAUG GCA	SSnXSS nXSSSS SSSSS SnXSS
WV-20060	fA fA fCn001 fA fU fCn001 fA fA mG fG mA fA mG fA fU fG fGn001 fC fA fU	AACAUCAAGGAAGAUGG CAU	SSnXSS nXSSSS SSSSS SnXSS
WV-20061	fA fC fAn001 fU fC fAn001 fA fG mG fA mA fG mA fU fG fG fCn001 fA fU fU	ACAUCAAGGAAGAUGGC AUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20062	fC fA fUn001 fC fA fAn001 fG fG mA fA mG fA mU fG fG fC fAn001 fU fU fU	CAUCAAGGAAGAUGGCA UUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20063	fA fU fCn001 fA fA fGn001 fG fA mA fG mA fU mG fG fC fA fUn001 fU fU fC	AUCAAGGAAGAUGGCAU UUC	SSnXSS nXSSSS SSSSS SnXSS
WV-20064	fU fC fAn001 fA fG fGn001 fA fA mG fA mU fG mG fC fA fU fUn001 fU fC fU	UCAAGGAAGAUGGCAUU UCU	SSnXSS nXSSSS SSSSS SnXSS
WV-20065	fC fA fAn001 fG fG fAn001 fA fG mA fU mG fG mC fA fU fU fUn001 fC fU fA	CAAGGAAGAUGGCAUUU CUA	SSnXSS nXSSSS SSSSS SnXSS
WV-20066	fA fA fGn001 fG fA fAn001 fG fA mU fG mG fC mA fU fU fU fC fCn001 fU fA fG	AAGGAAGAUGGCAUUUC UAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20067	fA fG fGn001 fA fA fGn001 fA fU mG fG mC fA mU fU fU fC fUn001 fA fG fU	AGGAAGAUGGCAUUUCU AGU	SSnXSS nXSSSS SSSSS SnXSS
WV-20068	fG fG fAn001 fA fG fAn001 fU fG mG fC mA fU mU fU fC fU fAn001 fG fU fU	GGAAGAUGGCAUUUCUA GUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20069	fG fA fAn001 fG fA fUn001 fG fG mC fA mU fU mU fC fU fA fGn001 fU fU fU	GAAGAUGGCAUUUCUAG UUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20070	fA fA fGn001 fA fU fGn001 fG fC mA fU mU fU mC fU fA fG fUn001 fU fU fG	AAGAUGGCAUUUCUAGU UUG	SSnXSS nXSSSS SSSSS SnXSS
WV-20071	fA fG fAn001 fU fG fGn001 fC fA mU fU mU fC mU fA fG fU fUn001 fU fG fG	AGAUGGCAUUUCUAGUU UGG	SSnXSS nXSSSS SSSSS SnXSS
WV-20072	fG fA fUn001 fG fG fCn001 fA fU mU fU mC fU mA fG fU fU fUn001 fG fG fA	GAUGGCAUUUCUAGUUU GGA	SSnXSS nXSSSS SSSSS SnXSS
WV-20073	fA fU fGn001 fG fC fAn001 fU fU mU fC mU fA mG fU fU fU fGn001 fG fA fG	AUGGCAUUUCUAGUUUG GAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20074	fU fG fGn001 fC fA fUn001 fU fU mC fU mA fG mU fU fU	UGGCAUUUCUAGUUUGG	SSnXSS nXSSSS SSSSS

	fG fGn001 fA fG fA	AGA	SnXSS
WV-20075	fG fG fCn001 fA fU fUn001 fU fC mU fA mG fU mU fU fG fG fAn001 fG fA fU	GGCAUUUCUAGUUUGGA GAU	SSnXSS nXSSSS SSSSS SnXSS
WV-20076	fG fC fAn001 fU fU fUn001 fC fU mA fG mU fU mU fG fG fA fGn001 fA fU fG	GCAUUUCUAGUUUGGAG AUG	SSnXSS nXSSSS SSSSS SnXSS
WV-20077	fC fA fUn001 fU fU fCn001 fU fA mG fU mU fU mG fG fA fG fAn001 fU fG fG	CAUUUCUAGUUUGGAGA UGG	SSnXSS nXSSSS SSSSS SnXSS
WV-20078	fA fU fUn001 fU fC fUn001 fA fG mU fU mU fG mG fA fG fA fUn001 fG fG fC	AUUUCUAGUUUGGAGAU GGC	SSnXSS nXSSSS SSSSS SnXSS
WV-20079	fU fU fUn001 fC fU fAn001 fG fU mU fU mG fG mA fG fA fU fGn001 fG fC fA	UUUCUAGUUUGGAGAUG GCA	SSnXSS nXSSSS SSSSS SnXSS
WV-20080	fU fU fCn001 fU fA fGn001 fU fU mU fG mG fA mG fA fU fG fGn001 fC fA fG	UUCUAGUUUGGAGAUGG CAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20081	fU fC fUn001 fA fG fUn001 fU fU mG fG mA fG mA fU fG fG fCn001 fA fG fU	UCUAGUUUGGAGAUGGC AGU	SSnXSS nXSSSS SSSSS SnXSS
WV-20082	fC fU fAn001 fG fU fUn001 fU fG mG fA mG fA mU fG fG fC fAn001 fG fU fU	CUAGUUUGGAGAUGGCA GUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20083	fU fA fGn001 fU fU fUn001 fG fG mA fG mA fU mG fG fC fA fGn001 fU fU fU	UAGUUUGGAGAUGGCAG UUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20084	fA fG fUn001 fU fU fGn001 fG fA mG fA mU fG mG fC fA fG fUn001 fU fU fC	AGUUUGGAGAUGGCAGU UUC	SSnXSS nXSSSS SSSSS SnXSS
WV-20085	fG fU fUn001 fU fG fGn001 fA fG mA fU mG fG mC fA fG fU fUn001 fU fC fC	GUUUGGAGAUGGCAGUU UCC	SSnXSS nXSSSS SSSSS SnXSS
WV-20086	fU fU fUn001 fG fG fAn001 fG fA mU fG mG fC mA fG fU fU fUn001 fC fC fU	UUUGGAGAUGGCAGUUU CCU	SSnXSS nXSSSS SSSSS SnXSS
WV-20087	fU fU fGn001 fG fA fGn001 fA fU mG fG mC fA mG fU fU fU fCn001 fC fU fU	UUGGAGAUGGCAGUUUC CUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20088	fU fG fGn001 fA fG fAn001 fU fG mG fC mA fG mU fU fU fC fCn001 fU fU fA	UGGAGAUGGCAGUUUCC UUA	SSnXSS nXSSSS SSSSS SnXSS
WV-20089	fG fG fAn001 fG fA fUn001 fG fG mC fA mG fU mU fU fC fC fUn001 fU fA fG	GGAGAUGGCAGUUUCCU UAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20090	fG fA fGn001 fA fU fGn001 fG fC mA fG mU fU mU fC fC fU fUn001 fA fG fU	GAGAUGGCAGUUUCCUU AGU	SSnXSS nXSSSS SSSSS SnXSS
WV-20091	fA fG fAn001 fU fG fGn001 fC fA mG fU mU fU mC fC fU fU fAn001 fG fU fA	AGAUGGCAGUUUCCUUA GUA	SSnXSS nXSSSS SSSSS SnXSS
WV-20092	fG fA fUn001 fG fG fCn001 fA fG mU fU mU fC mC fU fU	GAUGGCAGUUUCCUUAG	SSnXSS nXSSSS SSSSS

	fA fGn001 fU fA fA	UAA	SnXSS
WV-20093	fA fU fGn001 fG fC fAn001 fG fU mU fU mC fC mU fU fA fG fU fUn001 fA fA fC	AUGGCAGUUUCCUUAGU AAC	SSnXSS nXSSSS SSSSS SnXSS
WV-20094	fU fG fGn001 fC fA fGn001 fU fU mU fC mC fU mU fA fG fU fAn001 fA fC fC	UGGCAGUUUCCUUAGUA ACC	SSnXSS nXSSSS SSSSS SnXSS
WV-20095	fG fG fCn001 fA fG fUn001 fU fU mC fC mU fU mA fG fU fA fAn001 fC fC fA	GGCAGUUUCCUUAGUAA CCA	SSnXSS nXSSSS SSSSS SnXSS
WV-20096	fG fC fAn001 fG fU fUn001 fU fC mC fU mU fA mG fU fA fA fCn001 fC fA fC	GCAGUUUCCUUAGUAAC CAC	SSnXSS nXSSSS SSSSS SnXSS
WV-20097	fC fA fGn001 fU fU fUn001 fC fC mU fU mA fG mU fA fA fC fCn001 fA fC fA	CAGUUUCCUUAGUAACC ACA	SSnXSS nXSSSS SSSSS SnXSS
WV-20098	fA fG fUn001 fU fU fCn001 fC fU mU fA mG fU mA fA fC fC fAn001 fC fA fG	AGUUUCCUUAGUAACCA CAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20099	fG fU fUn001 fU fC fCn001 fU fU mA fG mU fA mA fC fC fA fCn001 fA fG fG	GUUUCCUUAGUAACCAC AGG	SSnXSS nXSSSS SSSSS SnXSS
WV-20100	fU fU fUn001 fC fC fUn001 fU fA mG fU mA fA mC fC fA fC fAn001 fG fG fU	UUUCCUUAGUAACCACA GGU	SSnXSS nXSSSS SSSSS SnXSS
WV-20101	fU fU fCn001 fC fU fUn001 fA fG mU fA mA fC mC fA fC fA fGn001 fG fU fU	UUCCUUAGUAACCACAG GUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20102	fU fC fCn001 fU fU fAn001 fG fU mA fA mC fC mA fC fA fG fGn001 fU fU fG	UCCUUAGUAACCACAGG UUG	SSnXSS nXSSSS SSSSS SnXSS
WV-20103	fC fC fUn001 fU fA fGn001 fU fA mA fC mC fA mC fA fG fG fUn001 fU fG fU	CCUUAGUAACCACAGGU UGU	SSnXSS nXSSSS SSSSS SnXSS
WV-20104	fC fU fUn001 fA fG fUn001 fA fA mC fC mA fC mA fG fG fU fUn001 fG fU fG	CUUAGUAACCACAGGUU GUG	SSnXSS nXSSSS SSSSS SnXSS
WV-20105	fU fU fAn001 fG fU fAn001 fA fC mC fA mC fA mG fG fU fU fGn001 fU fG fU	UUAGUAACCACAGGUUG UGU	SSnXSS nXSSSS SSSSS SnXSS
WV-20106	fU fA fGn001 fU fA fAn001 fC fC mA fC mA fG mG fU fU fG fUn001 fG fU fC	UAGUAACCACAGGUUGU GUC	SSnXSS nXSSSS SSSSS SnXSS
WV-20107	fA fG fUn001 fA fA fCn001 fC fA mC fA mG fG mU fU fG fU fGn001 fU fC fA	AGUAACCACAGGUUGUG UCA	SSnXSS nXSSSS SSSSS SnXSS
WV-20108	fG fU fAn001 fA fC fCn001 fA fC mA fG mG fU mU fG fU fG fUn001 fC fA fC	GUAACCACAGGUUGUGU CAC	SSnXSS nXSSSS SSSSS SnXSS
WV-20109	fU fA fAn001 fC fC fAn001 fC fA mG fG mU fU mG fU fG fU fCn001 fA fC fC	UAACCACAGGUUGUGUC ACC	SSnXSS nXSSSS SSSSS SnXSS
WV-20110	fA fA fCn001 fC fA fCn001 fA fG mG fU mU fG fU fU	AACCACAGGUUGUGUCA	SSnXSS nXSSSS SSSSS SnXSS

	fC fAn001 fC fC fA	CCA	SnXSS
WV-20111	fA fC fCn001 fA fC fAn001 fG fG mU fU mG fU mG fU fC fA fCn001 fC fA fG	ACCACAGGUUGUGUCAC CAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20112	fC fC fAn001 fC fA fGn001 fG fU mU fG mU fG mU fC fA fC fCn001 fA fG fA	CCACAGGUUGUGUCACC AGA	SSnXSS nXSSSS SSSSS SnXSS
WV-20113	fC fA fCn001 fA fG fGn001 fU fU mG fU mG fU mC fA fC fC fAn001 fG fA fG	CACAGGUUGUGUCACCA GAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20114	fA fC fAn001 fG fG fUn001 fU fG mU fG mU fC mA fC fC fA fGn001 fA fG fU	ACAGGUUGUGUCACCAG AGU	SSnXSS nXSSSS SSSSS SnXSS
WV-20115	fC fA fGn001 fG fU fUn001 fG fU mG fU mC fA mC fC fA fG fAn001 fG fU fA	CAGGUUGUGUCACCAGA GUA	SSnXSS nXSSSS SSSSS SnXSS
WV-20116	fA fG fGn001 fU fU fGn001 fU fG mU fC mA fC mC fA fG fA fGn001 fU fA fA	AGGUUGUGUCACCAGAG UAA	SSnXSS nXSSSS SSSSS SnXSS
WV-20117	fG fG fUn001 fU fG fUn001 fG fU mC fA mC fC mA fG fA fG fUn001 fA fA fC	GGUUGUGUCACCAGAGU AAC	SSnXSS nXSSSS SSSSS SnXSS
WV-20118	fG fU fUn001 fG fU fGn001 fU fC mA fC mC fA mG fA fG fU fAn001 fA fC fA	GUUGUGUCACCAGAGUA ACA	SSnXSS nXSSSS SSSSS SnXSS
WV-20119	fU fU fGn001 fU fG fUn001 fC fA mC fC mA fG mA fG fU fA fAn001 fC fA fG	UUGUGUCACCAGAGUAA CAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20120	fU fG fUn001 fG fU fCn001 fA fC mC fA mG fA mG fU fA fA fCn001 fA fG fU	UGUGUCACCAGAGUAAC AGU	SSnXSS nXSSSS SSSSS SnXSS
WV-20121	fG fU fGn001 fU fC fAn001 fC fC mA fG mA fG mU fA fA fC fAn001 fG fU fC	GUGUCACCAGAGUAACA GUC	SSnXSS nXSSSS SSSSS SnXSS
WV-20122	fU fG fUn001 fC fA fCn001 fC fA mG fA mG fU mA fA fC fA fGn001 fU fC fU	UGUCACCAGAGUAACAG UCU	SSnXSS nXSSSS SSSSS SnXSS
WV-20123	fG fU fCn001 fA fC fCn001 fA fG mA fG mU fA mA fC fA fG fUn001 fC fU fG	GUCACCAGAGUAACAGU CUG	SSnXSS nXSSSS SSSSS SnXSS
WV-20124	fU fC fAn001 fC fC fAn001 fG fA mG fU mA fA mC fA fG fU fCn001 fU fG fA	UCACCAGAGUAACAGUC UGA	SSnXSS nXSSSS SSSSS SnXSS
WV-20125	fC fA fCn001 fC fA fGn001 fA fG mU fA mA fC mA fG fU fC fUn001 fG fA fG	CACCAGAGUAACAGUCU GAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20126	fA fC fCn001 fA fG fAn001 fG fU mA fA mC fA mG fU fC fU fGn001 fA fG fU	ACCAGAGUAACAGUCUG AGU	SSnXSS nXSSSS SSSSS SnXSS
WV-20127	fC fC fAn001 fG fA fGn001 fU fA mA fC mA fG mU fC fU fG fAn001 fG fU fA	CCAGAGUAACAGUCUGA GUA	SSnXSS nXSSSS SSSSS SnXSS
WV-20128	fC fA fGn001 fA fG fUn001 fA fA mC fA mG fU mC fU fG	CAGAGUAACAGUCUGAG	SSnXSS nXSSSS SSSSS

	fA fGn001 fU fA fG	UAG	SnXSS
WV-20129	fA fG fAn001 fG fU fAn001 fA fC mA fG mU fC mU fG fA fG fU n001 fA fG fG	AGAGUAACAGUCUGAGU AGG	SSnXSS nXSSSS SSSSS SnXSS
WV-20130	fG fA fGn001 fU fA fAn001 fC fA mG fU mC fU mG fA fG fU fAn001 fG fG fA	GAGUAACAGUCUGAGUA GGA	SSnXSS nXSSSS SSSSS SnXSS
WV-20131	fA fG fUn001 fA fA fCn001 fA fG mU fC mU fG mA fG fU fA fGn001 fG fA fG	AGUAACAGUCUGAGUAG GAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20132	fG fU fAn001 fA fC fAn001 fG fU mC fU mG fA mG fU fA fG fGn001 fA fG fC	GUAACAGUCUGAGUAGG AGC	SSnXSS nXSSSS SSSSS SnXSS
WV-20133	fU fA fAn001 fC fA fGn001 fU fC mU fG mA fG mU fA fG fG fAn001 fG fC fU	UAACAGUCUGAGUAGGA GCU	SSnXSS nXSSSS SSSSS SnXSS
WV-20134	fA fA fCn001 fA fG fUn001 fC fU mG fA mG fU mA fG fG fA fGn001 fC fU fA	AACAGUCUGAGUAGGAG CUA	SSnXSS nXSSSS SSSSS SnXSS
WV-20135	fA fC fAn001 fG fU fCn001 fU fG mA fG mU fA mG fG fA fG fCn001 fU fA fA	ACAGUCUGAGUAGGAGC UAA	SSnXSS nXSSSS SSSSS SnXSS
WV-20136	fC fA fGn001 fU fC fUn001 fG fA mG fU mA fG mG fA fG fC fUn001 fA fA fA	CAGUCUGAGUAGGAGCU AAA	SSnXSS nXSSSS SSSSS SnXSS
WV-20137	fA fG fUn001 fC fU fGn001 fA fG mU fA mG fG mA fG fC fU fAn001 fA fA fA	AGUCUGAGUAGGAGCUA AAA	SSnXSS nXSSSS SSSSS SnXSS
WV-20138	fG fU fCn001 fU fG fAn001 fG fU mA fG mG fA mG fC fU fA fAn001 fA fA fU	GUCUGAGUAGGAGCUAA AAU	SSnXSS nXSSSS SSSSS SnXSS
WV-20139	fU fC fUn001 fG fA fGn001 fU fA mG fG mA fG mC fU fA fA fAn001 fA fU fA	UCUGAGUAGGAGCUAAA AUA	SSnXSS nXSSSS SSSSS SnXSS
WV-20140	fC fU fGn001 fA fG fUn001 fA fG mG fA mG fC mU fA fA fA fAn001 fU fA fU	CUGAGUAGGAGCUAAAA UAU	SSnXSS nXSSSS SSSSS SnXSS
WV-20141	fU fG fAn001 fG fU fAn001 fG fG mA fG mC fU mA fA fA fA fUn001 fA fU fU	UGAGUAGGAGCUAAAAU AUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20142	fG fA fGn001 fU fA fGn001 fG fA mG fC mU fA mA fA fA fU fAn001 fU fU fU	GAGUAGGAGCUAAAAUA UUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20143	fA fG fUn001 fA fG fGn001 fA fG mC fU mA fA mA fA fU fA fUn001 fU fU fU	AGUAGGAGCUAAAAUAU UUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20144	fG fU fAn001 fG fG fAn001 fG fC mU fA mA fA mA fU fA fU fUn001 fU fU fG	GUAGGAGCUAAAAUAUU UUG	SSnXSS nXSSSS SSSSS SnXSS
WV-20145	fU fA fGn001 fG fA fGn001 fC fU mA fA mA fA mU fA fU fU fUn001 fU fG fG	UAGGAGCUAAAAUAUUU UGG	SSnXSS nXSSSS SSSSS SnXSS
WV-20146	fA fG fGn001 fA fG fCn001 fU fA mA fA mA fU mA fU fU	AGGAGCUAAAAUAUUUU	SSnXSS nXSSSS SSSSS

	fU fUn001 fG fG fG	GGG	SnXSS
WV-20147	fG fG fAn001 fG fC fUn001 fA fA mA fA mU fU fU fU fG fGn001 fG fG fU	GGAGCUAAAAUAUUUUG GGU	SSnXSS nXSSSS SSSSS SnXSS
WV-20148	fG fA fGn001 fC fU fAn001 fA fA mA fU mU fU fU fG fGn001 fG fU fU	GAGCUAAAAUAUUUUGG GUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20149	fA fG fCn001 fU fA fAn001 fA fA mU fA mU fU mU fU fG fG fGn001 fU fU fU	AGCUAAAAUAUUUUGGG UUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20150	fG fC fUn001 fA fA fAn001 fA fU mA fU mU fU mU fG fG fG fUn001 fU fU fU	GCUAAAAUAUUUUGGGU UUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20151	fC fU fAn001 fA fA fAn001 fU fA mU fU mU fU mG fG fG fU fUn001 fU fU fU	CUAAAAUAUUUUGGGUU UUU	SSnXSS nXSSSS SSSSS SnXSS
WV-20152	fU fA fAn001 fA fA fUn001 fA fU mU fU mU fG mG fG fU fU fUn001 fU fU fG	UAAAAUAUUUUGGGUUU UUG	SSnXSS nXSSSS SSSSS SnXSS
WV-20153	fA fA fAn001 fA fU fAn001 fU fU mU fU mG fG mG fU fU fU fUn001 fU fG fC	AAAAUAUUUUGGGUUUU UGC	SSnXSS nXSSSS SSSSS SnXSS
WV-20154	fA fA fAn001 fU fA fUn001 fU fU mU fG mG fG mU fU fU fU fUn001 fG fC fA	AAAUAUUUUGGGUUUUU GCA	SSnXSS nXSSSS SSSSS SnXSS
WV-20155	fA fA fUn001 fA fU fUn001 fU fU mG fG mG fU mU fU fU fU fGn001 fC fA fA	AAUAUUUUGGGUUUUUG CAA	SSnXSS nXSSSS SSSSS SnXSS
WV-20156	fA fU fAn001 fU fU fUn001 fU fG mG fG mU fU mU fU fU fG fCn001 fA fA fA	AUAUUUUGGGUUUUUGC AAA	SSnXSS nXSSSS SSSSS SnXSS
WV-20157	fU fA fUn001 fU fU fUn001 fG fG mG fU mU fU mU fU fG fC fAn001 fA fA fA	UAUUUUGGGUUUUUGCA AAA	SSnXSS nXSSSS SSSSS SnXSS
WV-20158	fA fU fUn001 fU fU fGn001 fG fG mU fU mU fU mU fG fC fA fAn001 fA fA fA	AUUUUGGGUUUUUGCAA AAA	SSnXSS nXSSSS SSSSS SnXSS
WV-20159	fU fU fUn001 fU fG fGn001 fG fU mU fU mU fU mG fC fA fA fAn001 fA fA fG	UUUUGGGUUUUUGCAAA AAG	SSnXSS nXSSSS SSSSS SnXSS
WV-20160	fU fU fUn001 fG fG fGn001 fU fU mU fU mU fG mC fA fA fA fAn001 fA fG fG	UUUGGGUUUUUGCAAAA AGG	SSnXSS nXSSSS SSSSS SnXSS
WV-20314	fU fU fC fG fA fA fA fA mA fA mC fA mA fA fU fC fA fA fA fA fG	UUCGAAAAAAACAAAUCA AAG	SSSSS SSSSS SSSSS SSSS
WV-20315	fU fC fG fA fA fA fA fA mA fC mA fA mA fU fC fA fA fA fA fG fA	UCGAAAAAAACAAAUCAA AGA	SSSSS SSSSS SSSSS SSSS
WV-20316	fC fG fA fA fA fA fA fA mC fA mA fA mU fC fA fA fA fA fG fA fC	CGAAAAAAACAAAUCAAA GAC	SSSSS SSSSS SSSSS SSSS
WV-20317	fG fA fA fA fA fA fA fC mA fA mA fU mC fA fA fA fG fA	GAAAAAAACAAAUCAAAG	SSSSS SSSSS SSSSS SSSS

	fC fU	ACU	
WV-20318	fA fA fA fA fA fC fA mA fA mU fC mA fA fA fG fA fC fU fU	AAAAAACAAAUCAAAGA CUU	SSSSS SSSSS SSSSS SSSS
WV-20319	fA fA fA fA fA fC fA fA mA fU mC fA mA fA fG fA fC fU fU fA	AAAAACAAAUCAAAGAC UUA	SSSSS SSSSS SSSSS SSSS
WV-20320	fA fA fA fA fC fA fA fA mU fC mA fA mA fG fA fC fU fU fA fC	AAAACAAAUCAAAGACU UAC	SSSSS SSSSS SSSSS SSSS
WV-20321	fA fA fA fC fA fA fA fU mC fA mA fA mG fA fC fU fU fA fC fC	AAACAAAUCAAAGACUU ACC	SSSSS SSSSS SSSSS SSSS
WV-20322	fA fA fC fA fA fA fU fC mA fA mA fG mA fC fU fU fA fC fC fU	AACAAAUCAAAGACUUA CCU	SSSSS SSSSS SSSSS SSSS
WV-20323	fA fC fA fA fA fU fC fA mA fA mG fA mC fU fU fA fC fC fU fU	ACAAAUCAAAGACUUAC CUU	SSSSS SSSSS SSSSS SSSS
WV-20324	fC fA fA fA fU fC fA fA mA fG mA fC mU fU fA fC fC fU fU fA	CAAAUCAAAGACUUACC UUA	SSSSS SSSSS SSSSS SSSS
WV-20325	fA fA fA fU fC fA fA fA mG fA mC fU mU fA fC fC fU fU fU fA fA	AAAUCAAAGACUUACCU UAA	SSSSS SSSSS SSSSS SSSS
WV-20326	fA fA fU fC fA fA fA fG mA fC mU fU mA fC fC fU fU fA fA fG	AAUCAAAGACUUACCUU AAG	SSSSS SSSSS SSSSS SSSS
WV-20327	fA fU fC fA fA fA fG fA mC fU mU fA mC fC fU fU fU fA fA fG fA	AUCAAAGACUUACCUUA AGA	SSSSS SSSSS SSSSS SSSS
WV-20328	fU fC fA fA fA fG fA fC mU fU mA fC mC fU fU fA fA fG fA fU	UCAAAGACUUACCUUAA GAU	SSSSS SSSSS SSSSS SSSS
WV-20329	fC fA fA fA fG fA fC fU mU fA mC fC mU fU fA fA fG fA fU fA	CAAAGACUUACCUUAAG AUA	SSSSS SSSSS SSSSS SSSS
WV-20330	fA fA fA fG fA fC fU fU mA fC mC fU mU fA fA fG fA fU fA fC	AAAGACUUACCUUAAGA UAC	SSSSS SSSSS SSSSS SSSS
WV-20331	fA fA fG fA fC fU fU fU fA mC fC mU fU mA fA fG fA fU fA fC fC	AAGACUUACCUUAAGAU ACC	SSSSS SSSSS SSSSS SSSS
WV-20332	fA fG fA fC fU fU fA fC mC fU mU fA mA fG fA fU fA fC fC fA	AGACUUACCUUAAGAUA CCA	SSSSS SSSSS SSSSS SSSS
WV-20333	fG fA fC fU fU fA fC fC mU fU mA fA mG fA fU fA fC fC fA fU	GACUUACCUUAAGAUAC CAU	SSSSS SSSSS SSSSS SSSS
WV-20334	fA fC fU fU fA fC fC fU mU fA mA fG mA fU fA fC fC fC fA fU fU	ACUUACCUUAAGAUACC AUU	SSSSS SSSSS SSSSS SSSS
WV-20335	fC fU fU fA fC fC fU fU mA fA mG fA mU fA fC fC fA fU	CUUACCUUAAGAUACCA	SSSSS SSSSS SSSSS SSSS

	fU fU	UUU	
WV-20336	fU fU fA fC fC fU fU fA mA fG mA fU mA fC fC fA fU fU fU fG	UUACCUUAAGAUACCAU UUG	SSSSS SSSSS SSSSS SSSS
WV-20337	fU fA fC fC fU fU fA fA mG fA mU fA mC fC fA fU fU fU fG fU	UACCUUAAGAUACCAUU UGU	SSSSS SSSSS SSSSS SSSS
WV-20338	fA fG fG fC fA fA fA fA mC fA mA fA mA fA fU fG fA fA fG fC	AGGCAAAACAAAAAUGA AGC	SSSSS SSSSS SSSSS SSSS
WV-20339	fG fC fA fA fA fC fA mA fA mA fA mU fG fA fA fG fC fC fC	GCAAAACAAAAAUGAAG CCC	SSSSS SSSSS SSSSS SSSS
WV-20340	fA fA fA fA fC fA fA fA mA fA mU fG mA fA fG fC fC fC fC fA	AAAACAAAAAUGAAGCC CCA	SSSSS SSSSS SSSSS SSSS
WV-20341	fA fA fC fA fA fA fA fA mU fG mA fA mG fC fC fC fC fC fA fU fG	AACAAAAAUGAAGCCCC AUG	SSSSS SSSSS SSSSS SSSS
WV-20342	fC fA fA fA fA fA fU fG mA fA mG fC mC fC fC fA fU fG fU fC	CAAAAAUGAAGCCCCAU GUC	SSSSS SSSSS SSSSS SSSS
WV-20343	fA fA fA fA fU fG fA fA mG fC mC fC mC fA fU fG fU fC fU fU	AAAAUGAAGCCCCAUGU CUU	SSSSS SSSSS SSSSS SSSS
WV-20344	fA fA fU fG fA fA fG fC mC fC mC fA mU fG fU fC fU fU fU fU	AAUGAAGCCCCAUGUCU UUU	SSSSS SSSSS SSSSS SSSS
WV-20345	fA fU fG fA fA fG fC fC mC fC mA fU mG fU fC fU fU fU fU fU	AUGAAGCCCCAUGUCUU UUU	SSSSS SSSSS SSSSS SSSS
WV-20346	fG fA fA fG fC fC fC fC mA fU mG fU mC fU fU fU fU fU fU fA fU	GAAGCCCCAUGUCUUUU UAU	SSSSS SSSSS SSSSS SSSS
WV-20347	fA fG fC fC fC fC fA fU mG fU mC fU mU fU fU fU fA fU fU fU	AGCCCCAUGUCUUUUUA UUU	SSSSS SSSSS SSSSS SSSS
WV-20348	fC fC fC fC fA fU fG fU mC fU mU fU mU fU fA fU fU fU fG fA	CCCCAUGUCUUUUUAUU UGA	SSSSS SSSSS SSSSS SSSS
WV-20349	fU fG fA fA fG fC fC fC mC fA mU fG mU fC fU fU fU fU fU fA	UGAAGCCCCAUGUCUUU UUA	SSSSS SSSSS SSSSS SSSS
WV-20350	fA fA fG fC fC fC fC fA mU fG mU fC mU fU fU fU fU fA fU fU	AAGCCCCAUGUCUUUUU AUU	SSSSS SSSSS SSSSS SSSS
WV-20351	fG fC fC fC fC fA fU fG mU fC mU fU fU fU fA fU fU fU fG	GCCCCAUGUCUUUUUAU UUG	SSSSS SSSSS SSSSS SSSS
WV-20352	fC fU fG fC fA fU mA mU mU mC mA mA mA mG fG fA fC fA fC fC	CUGCAUAUUCAAAGGAC ACC	SSSSS SSSSS SSSSS SSSS
WV-20353	fC fU fG fC fA fU mU mG mU mU mU mG mG fC fC fU	CUGCAUUGUUUUGGCCU	SSSSS SSSSS SSSSS SSSS

	fC fU fG	CUG	
WV-20354	fA fU fA fA fA fG mC mC mG mA mA mA mU mA fC fA fC fA fC fU	AUAAAGCCGAAAUACAC ACU	SSSSS SSSSS SSSSS SSSS
WV-20355	fG fC fU fG fU fU mA mC mG mA mU mG mC mU fU fC fC fC fU fC	GCUGUUACGAUGCUUCC CUC	SSSSS SSSSS SSSSS SSSS
WV-20356	fC fU fU fU fC fC fC mU mC mU mG mU mC mA mC fA fG fA fU fU fC	CUUCCCUCUGUCACAGA UUC	SSSSS SSSSS SSSSS SSSS
WV-20357	fC fA fG fA fU fA mA mA mC mC mA mG mC mU fC fC fG fU fC fC	CAGAUAAACCAGCUCCG UCC	SSSSS SSSSS SSSSS SSSS
WV-20358	fC fU fC fC fG fU mC mC mA mG mG mC mA mA fA fC fU fC fU fC	CUCCGUCCAGGCAAACU CUC	SSSSS SSSSS SSSSS SSSS
WV-20359	fG fG fC fA fA fA mC mU mC mU mC mC mA fU fC fC fU fG fA	GGCAAACUCUCUCAUCC UGA	SSSSS SSSSS SSSSS SSSS
WV-20360	fC fU fC fU fC fU mC mA mU mC mC mU mG mA fC fA fC fA fA fA	CUCUCUCAUCCUGACAC AAA	SSSSS SSSSS SSSSS SSSS
WV-20361	fC fA fA fA fC fU mC mU mC mU mC mA mU mC fC fU fG fA fC fA	CAAACUCUCUCAUCCUG ACA	SSSSS SSSSS SSSSS SSSS
WV-20362	fG fC fU fC fU fA mA mU mA mU mU mA mU mC fA fU fU fA fU fG	GCUCUAAUAUUAUCAUU AUG	SSSSS SSSSS SSSSS SSSS
WV-20363	fA fU fA fG fC fA mC mC mG mU mG mC mU mC fU fA fA fU fA fU	AUAGCACCGUGCUCUAA UAU	SSSSS SSSSS SSSSS SSSS
WV-20364	fC fC fG fU fG fC mU mC mU mA mA mU mA mU fU fA fU fC fA fU	CCGUGCUCUAAUAUUAU CAU	SSSSS SSSSS SSSSS SSSS
WV-20365	fU fA fU fG fA fU mA mA mU mU mU mC mU fU fU fC fU fA fG	UAUGAUAAUUUUCUUUC UAG	SSSSS SSSSS SSSSS SSSS
WV-20366	fC fU fU fU fC fU mA mG mU mA mA mU mA mU fA fA fU fG fA fU	CUUUCUAGUAAUAUAAU GAU	SSSSS SSSSS SSSSS SSSS
WV-20367	fU fA fA fU fU fU mU mC mU mU mU mC mU mA fG fU fA fA fU fA	UAAUUUUCUUUCUAGUA AUA	SSSSS SSSSS SSSSS SSSS
WV-20368	fA fC fA fA fC fA mA mC mA mG mU mC mA mA fA fA fG fU fA fA	ACAACAACAGUCAAAAG UAA	SSSSS SSSSS SSSSS SSSS
WV-20369	fA fA fU fA fU fA mA mU mG mA mA mC fA fA fC fA fA fC	AAUAUAAUGAUGACAAC AAC	SSSSS SSSSS SSSSS SSSS
WV-20370	fU fG fA fU fG fA mC mA mA mC mA mC mA fG fU fU fC fA fA fA	UGAUGACAACAACAGUC AAA	SSSSS SSSSS SSSSS SSSS
WV-20371	fU fA fA fU fU fU mC mC mA mU mC mA mC mC fC fU fU	UAAUUUCCAUCACCCUU	SSSSS SSSSS SSSSS SSSS

	fC fA fG	CAG	
WV-20372	fC fA fC fC fC fU mU mC mA mG mA mA mC mC fU fG fA fU fC fU	CACCCUUCAGAACCUGA UCU	SSSSS SSSSS SSSSS SSSS
WV-20373	fU fC fC fC fA fU fC mA mC mC mC mU mU mC mA fG fA fA fC fC fU	UCCAUCACCCUUCAGAA CCU	SSSSS SSSSS SSSSS SSSS
WV-20374	fA fC fC fC fU fG fA mU mC mU mU mU mA mA mG fA fA fG fU fU fU fA	ACCUGAUCUUUAAGAAG UUA	SSSSS SSSSS SSSSS SSSS
WV-20375	fC fA fC fC fC fU mU mC mA mG mA mA mC mC mC fU fG fA fU fC	CACCCUUCAGAACCUGA UC	SSSSS SSSSS SSSSS SSS
WV-20376	fC fA fG fA fA fC mC mU mG mA mA mU mC mU mU fU fA fA fG fA fA	CAGAACCUGAUCUUUAA GAA	SSSSS SSSSS SSSSS SSSS
WV-20377	fA fG fA fG fU fC mC mA mG mA mU mU mG mU mG fC fU fG fA fA	AGAGUCCAGAUGUGCUG AA	SSSSS SSSSS SSSSS SSS
WV-20378	fC fU fG fA fA fG mA mU mA mA mA mU mA mC fA fA fU fU fU fC	CUGAAGAUAAAUACAAU UUC	SSSSS SSSSS SSSSS SSSS
WV-20379	fU fG fU fG fC fU mG mA mA mG mA mU mA mA fA fU fA fC fA fA	UGUGCUGAAGAUAAAUA CAA	SSSSS SSSSS SSSSS SSSS
WV-20380	fA fC fA fA fU fU mU mC mG mA mA mA mA fA fC fA fA fA	ACAAUUUCGAAAAAACA AA	SSSSS SSSSS SSSSS SSS
WV-20381	fC fU fG fA fA fG mA mU mA mA mA mU mA mC fA fA fU fU fU fU	CUGAAGAUAAAUACAAU UU	SSSSS SSSSS SSSSS SSS
WV-20382	fU fA fA fA fU fA mC mA mA mU mU mC mG fA fA fA fA fA fA	UAAAUACAAUUUCGAAA AA	SSSSS SSSSS SSSSS SSS
WV-20383	fA fC fU fU fU fA fC mC mU mU mA mA mG mA mU fA fC fC fA fU fU	ACUUACCUUAAGAUACC AUU	SSSSS SSSSS SSSSS SSSS
WV-20384	fA fA fU fC fA fA mA mG mA mC mU mU mA mC fC fU fU fA fA fG	AAUCAAAGACUUACCUU AAG	SSSSS SSSSS SSSSS SSSS
WV-20385	fA fA fG fA fC fU mU mA mC mC mU mU mA mA fG fA fU fA fC fC	AAGACUUACCUUAAGAU ACC	SSSSS SSSSS SSSSS SSSS
WV-20386	fA fU fU fC fU fC mA mG mG mA mA mU mU mU fG fU fG fU fC fU	AUUCUCAGGAAUUUGUG UCU	SSSSS SSSSS SSSSS SSSS
WV-20387	fC fA fU fG fU fU mC mC mC mA mA mU mU mC fU fC fA fG fG	CAUGUUCCCAAUUCUCA GG	SSSSS SSSSS SSSSS SSS
WV-20388	fC fC fC fC fA fA fU mU mC mU mC mA mG mG mA fA fU fU fU fG	CCCAAUUCUCAGGAAUU UG	SSSSS SSSSS SSSSS SSS
WV-20389	fC fU fU fU fU fC fU mG mA mA mA mA mC mU fG fU fU	CUUUCUGAGAAACUGUU	SSSSS SSSSS SSSSS SSSS

	fC fA fG	CAG	
WV-20390	fA fG fG fA fA fU mU mU mG mU mC mU fU fU fC fU fG fA	AGGAAUUUGUGUCUUUC UGA	SSSSS SSSSS SSSSS SSSS
WV-20391	fU fG fU fG fU fC mU mU mU mC mU mG mA mG fA fA fA fC fU fG	UGUGUCUUUCUGAGAAA CUG	SSSSS SSSSS SSSSS SSSS
WV-20392	fC fU fU fU fA fU mA mU mC mA mU mA mA mU fG fA fA fA fA fC	CUUUAUAUCAUAAUGAA AAC	SSSSS SSSSS SSSSS SSSS
WV-20393	fC fA fC fU fG fA mU mU mA mA mA mU mA mU fC fU fU fU fA fU	CACUGAUUAAAUAUCUU UAU	SSSSS SSSSS SSSSS SSSS
WV-20789	L001 fU fC fA fA fG fG mA fA mG fA mU fG mG fC fA fU fU fU fC fU	UCAAGGAAGAUGGCAUU UCU	ORRRR RRORO RORORRRRRR
WV-20790	Mod012L001 fU fC fA fA fG fG mA fA mG fA mU fG mG fC fA fU fU fU fC fU	UCAAGGAAGAUGGCAUU UCU	ORRRR RRORO RORORRRRRR
WV-21210	Mod118L001 fU fC fA fC fU fC mAn001 fG fA mU fA mGn001 mUn001 fU fG fA fA fG fC fC	UCACUCAGAUAGUUGAA GCC	OSSSS SSnXSS SSnXnXSSSSSS
WV-21211	Mod119L001 fU fC fA fC fU fC mAn001 fG fA mU fA mGn001 mUn001 fU fG fA fA fG fC fC	UCACUCAGAUAGUUGAA GCC	OSSSS SSnXSS SSnXnXSSSSS
WV-21212	Mod120L001 fU fC fA fC fU fC mAn001 fG fA mU fA mGn001 mUn001 fU fG fA fA fG fC fC	UCACUCAGAUAGUUGAA GCC	OSSSS SSnXSS SSnXnXSSSSS
WV-21217	fC fU fCn001 R fC fG fGn001 R fU fU mC	CUCCGGUUC	SSnRSS nRSS
WV-21218	fU fC fAn001 R fC fU fCn001 R mA fG fA mU fA mG mU fU fG fA fAn001 R fG fC fC	UCACUCAGAUAGUUGAA GCC	SSnRSS nROSSS SOSSSnRSS
WV-21245	fU fC fAn001 R fC fU fCn001 R mA fG fA mU fA mG mU fU fG fA fAn001 R fG fC fC	UCACUCAGAUAGUUGAA GCC	SSnRSS nROSSS SSOSSnRSS
WV-21257	fC fG fGn001 R fU fU mC fU mG fA mA fG fG fU fGn001 R fU fU fC	CGGUUCUGAAGGUGUUC	SSnRSS OSSSO SSSnRS S

WV-24310	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SmG	UCAAGGAAGAUGGCAUUUCG	SSSSSSOSOSSOOSSSSSS
WV-24311	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfC * SfC * SfC * SfC * SfG	UCAAGGAAGAUGGCACCCCG	SSSSSSOSOSSOOSSSSSS
WV-24463	fU * SfC * SfG * SfA * SfG * SfA * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC *	UCGAGAAAGAUGGCAUUUCU	SSSSSSOSOSSOOSSSSSS

	SfU		
WV-24464	fU * SfU * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfC * SfC * SfU	UUAAGGAAGAUGGCAUUCCU	SSSSSSOSOSSOOSSSSSS
WV-25439	fU * RfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUCUGAAGGUGUUCU	RSSSSSSOSSSOOSSSSSS
WV-25440	fU * SfC * RfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUCUGAAGGUGUUCU	SRSSSSSOSSSOOSSSSSS
WV-25441	fU * SfC * SfC * RfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUCUGAAGGUGUUCU	SSRSSSSOSSSOOSSSSSS
WV-25442	fU * SfC * SfC * SfG * RfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUCUGAAGGUGUUCU	SSSRSSSOSSSOOSSSSSS
WV-25443	fU * SfC * SfC * SfG * SfG * RfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUCUGAAGGUGUUCU	SSSSRSSOSSSOOSSSSSS
WV-25444	fU * SfC * SfC * SfG * SfG * SfU * RfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUCUGAAGGUGUUCU	SSSSSRSOSSSOOSSSSSS
WV-25445	fU * SfC * SfC * SfG * SfG * SfU * SfU * RmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUCUGAAGGUGUUCU	SSSSSSROSSSOOSSSSSS
WV-25446	fU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * RmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUCUGAAGGUGUUCU	SSSSSSSORSSOOSSSSSS
WV-25447	fU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * RfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUCUGAAGGUGUUCU	SSSSSSSOSRSOOSSSSSS
WV-25448	fU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * RmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUCUGAAGGUGUUCU	SSSSSSSOSSROOSSSSSS
WV-25449	fU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * RfU * SfG * SfU * SfU * SfU *	UCCGGUUCUGAAGGUGUUCU	SSSSSSSOSSSOORSSSSS

	SfC * SfU		
WV-25450	fU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * RfG * SfU * SfU * SfC * SfU	UCCGGUUCUGAAGGUGUUCU	SSSSSSOSSSOOSRSSSS
WV-25451	fU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * RfU * SfU * SfC * SfU	UCCGGUUCUGAAGGUGUUCU	SSSSSSOSSSOOSSRSSS
WV-25452	fU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * RfU * SfC * SfU	UCCGGUUCUGAAGGUGUUCU	SSSSSSOSSSOOSSSRSS
WV-25453	fU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * RfC * SfU	UCCGGUUCUGAAGGUGUUCU	SSSSSSOSSSOOSSSSRS
WV-25454	fU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * RfU	UCCGGUUCUGAAGGUGUUCU	SSSSSSOSSSOOSSSSSR
WV-25455	fC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	CGGUUCUGAAGGUGUUCU	SSSSSOSSSSOOSSSSSS
WV-25456	fU * SfU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UUCCGGUUCUGAAGGUGUUCU	SSSSSSSOSSSOOSSSSSS
WV-25457	fU * SfC * SfC * SfG * SfG * SfU * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUUUCUGAAGGUGUUCU	SSSSSSSSOSSSOOSSSSSS
WV-25458	fU * SfC * SfC * SfG * SfG * SfU * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfU * SfC * SfU	UCCGGUUCUGAAGGUGUUUCU	SSSSSSOSSSOOSSSSSSS
WV-25459	fU * SfC * SfC * SfG * SfG * SfU * SmCfU * SmG * SfA * SmAmGfG * SfU * SfG * SfU * SfU * SfC * SfU	UCCGGUCUGAAGGUGUUCU	SSSSSOSSSOOSSSSSS
WV-25536	lT * SfC * SlA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	TCACUCAGAUAGUUGAAGCC	SSSSSOSSSSOOSSSSSS
WV-25537	fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SlG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	SSSSSOSSSSOOSSSSSS
WV-	lT * SfC * SlA * SfC * SfU * SfC * SmAfG * SfA *	TCACUCAGAUAGUUGAAGCC	SSSSSOSSSSOOSSSSSS

25538	SmU * SfA * SmGmUfU * SfG * SfA * SfA * SlG * SfC * SfC		
WV-25539	fU * SfC * SfA * SfC * SfU * SfC * SlAfG * SfA * SmU * SfA * SlGlTfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGTUGAAGCC	SSSSSSOSSSSOOSSSSSS
WV-25540	fU * SfC * SfA * SfC * SfU * SfC * SlAfG * SfA * SmU * SfA * SlGlTlT * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGTTGAAGCC	SSSSSSOSSSSOOSSSSSS
WV-25541	fU * SfC * SfA * SfC * SfU * SfC * SlAn001RfG * SfA * SmU * SfA * SlGn001RlTn001RlT * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGTTGAAGCC	SSSSSSnRSSSSnRnRSSSSSS
WV-25542	lT * SfC * SlA * SfC * SfU * SfC * SmAn001RfG * SfA * SmU * SfA * SmGn001RmUn001RfU * SfG * SfA * SfA * SfG * SfC * SfC	TCACUCAGAUAGUUGAAGCC	SSSSSSnRSSSSnRnRSSSSSS
WV-25543	fU * SfC * SfA * SfC * SfU * SfC * SmAn001RfG * SfA * SmU * SfA * SmGn001RmUn001RfU * SfG * SfA * SfA * SlG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	SSSSSSnRSSSSnRnRSSSSSS
WV-25544	lT * SfC * SlA * SfC * SfU * SfC * SmAn001RfG * SfA * SmU * SfA * SmGn001RmUn001RfU * SfG * SfA * SfA * SlG * SfC * SfC	TCACUCAGAUAGUUGAAGCC	SSSSSSnRSSSSnRnRSSSSSS
WV-27163	L001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmU * SfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	OSSSSSSOSSSSOSSSSSSS
WV-27164	L001fU * SfC * SfAn001RfC * SfU * SfCn001RmAfG * SfA * SmU * SfA * SmGmU * SfU * SfG * SfA * SfAn001RfG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	OSSnRSSnROSSSSOSSSSnRSS

WV-19790	Mod020L001 fU fC fA fC fU fC mAn001 fG fA mU fA mGn001 mUn001 fU fG fA fA fG fC fC	UCACUCAGAUAGUUGAA GCC	OSSSS SSnXSS SSnXnXS SSSSS
WV-19791	Mod015L001 fU fC fA fC fU fC mAn001 fG fA mU fA mGn001 mUn001 fU fG fA fA fG fC fC	UCACUCAGAUAGUUGAA GCC	OSSSS SSnXSS SSnXnXS SSSSS
WV-19792	Mod109L001 fU fC fA fC fU fC mAn001 fG fA mU fA mGn001 mUn001 fU fG fA fA fG fC fC	UCACUCAGAUAGUUGAA GCC	OSSSS SSnXSS SSnXnXS SSSSS
WV-19793	Mod110L001 fU fC fA fC fU fC mAn001 fG fA mU fA mGn001 mUn001 fU fG fA fA fG fC fC	UCACUCAGAUAGUUGAA GCC	OSSSS SSnXSS SSnXnXS SSSSS
WV-19794	Mod111L001 fU fC fA fC fU fC mAn001 fG fA mU fA mGn001 mUn001 fU fG fA fA fG fC fC	UCACUCAGAUAGUUGAA GCC	OSSSS SSnXSS SSnXnXS SSSSS

WV-19795	Mod112L001 fU fC fA fC fU fC mAn001 fG fA mU fA mGn001 mUn001 fU fG fA fA fG fC fC	UCACUCAGAUAGUUGAA GCC	OSSSS SSnXSS SSnXnXS SSSSS
WV-19796	Mod113L001 fU fC fA fC fU fC mAn001 fG fA mU fA mGn001 mUn001 fU fG fA fA fG fC fC	UCACUCAGAUAGUUGAA GCC	OSSSS SSnXSS SSnXnXS SSSSS
WV-19797	Mod114L001 fU fC fA fC fU fC mAn001 fG fA mU fA mGn001 mUn001 fU fG fA fA fG fC fC	UCACUCAGAUAGUUGAA GCC	OSSSS SSnXSS SSnXnXS SSSSS
WV-19798	Mod115L001 fU fC fA fC fU fC mAn001 fG fA mU fA mGn001 mUn001 fU fG fA fA fG fC fC	UCACUCAGAUAGUUGAA GCC	OSSSS SSnXSS SSnXnXS SSSSS
WV-15883	fC * SfU * SfCn002RfC * SfG * SfGn002RfU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn002RfU * SfU * SfC	CUCCGGUUCUGAAGGUG UUC	SSnR SSnR SSOSSS OOSSnR SS
WV-15884	mU * SGeon002m5Ceon002m5Ceon002mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGAC UC	SnX nX nX SSRSSR SSRSSSSSS
WV-15885	mU * SGeon002Rm5Ceon002Rm5Ceon002RmA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGAC UC	SnR nR nR SSRSSR SSRSSSSSS
WV-15886	fC * SfU * SfCn002fC * SfG * SfGn002fU * SfU * SmCfU * SmG * SfA * SmAfGfG * SfU * SfGn002fU * SfU * SfC	CUCCGGUUCUGAAGGUG UUC	SSnX SSnX SSOSSS OOSSnX SS
WV-15887	mU * SGeon002Sm5Ceon002Sm5Ceon002SmA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGAC UC	SnS nS nS SSRSSR SSRSSSSSS
WV-16006	fCfUfCn003RfCfGfGn003RfUfUmCfUmGfAmAfGfGfUfGn003RfUfUfC	CUCCGGUUCUGAAGGUG UUC	SSnR SSnR SSOSSS OOSSnR SS
WV-16008	fUfCfAfCfUfCmAn003fGfAmUfAmGn003mUn003fUfGfAfA fGfCfC	UCACUCAGAUAGUUGAA GCC	SSSSSSnX SSSSnX nX SSSSSS
WV-16007	fCfUfCn004RfCfGfGn004RfUfUmCfU mGfAmAfGfGfUfGn004RfUfUfC	CUCCGGUUCUGAAGGUG UUC	SSnR SSnR SSOSSS OOSSnR SS
WV-16009	fUfCfAfCfUfCmAn004fGfAmUfAmG n004mUn004fUfGfAfAfGfCfC	UCACUCAGAUAGUUGAA GCC	SSSSSS nX SSSSnX nX SSSSSS
WV-24088	fU * SfC * SfA * SfC * SfU * SfC * SmAn005fG * SfA * SmU * SfA * SmGn005mUn005fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAA GCC	SSSSS S nX SSSS nX nX SSSSS S	
WV-24089	fU * SfC * SfA * SfC * SfU * SfC * SmAn005RfG * SfA * SmU * SfA * SmGn005RmUn005RfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAA GCC	SSSSS S nR SSSS nR nR SSSSS S	
WV-24090	fU * SfC * SfA * SfC * SfU * SfC * SmAn005SfG * SfA *	UCACUCAGAUAGUUGAA	SSSSS S nS SSSS nS nS	

	SmU * SfA * SmGn005SmUn005SfU * SfG * SfA * SfA * SfG * SfC * SfC	GCC	SSSSS S
WV-24100	mU * SGeon005m5Ceon005m5Ceon005mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGAC UC	S nX nX nX SSRSS RSSRSS SSSS
WV-24101	mU * SGeon005Rm5Ceon005Rm5Ceon005RmA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGAC UC	S nR nR nR SSRSS RSSRSS SSSS
WV-24102	mU * SGeon005Sm5Ceon005Sm5Ceon005SmA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGAC UC	S nS nS nS SSRSS RSSRSS SSSS
WV-24091	fU * SfC * SfA * SfC * SfU * SfC * SmAn006fG * SfA * SmU * SfA * SmGn006mUn006fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAA GCC	SSSSS S nX SSSS nX nX SSSSS S
WV-24092	fU * SfC * SfA * SfC * SfU * SfC * SmAn006RfG * SfA * SmU * SfA * SmGn006RmUn006RfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAA GCC	SSSSS S nR SSSS nR nR SSSSS S
WV-24093	fU * SfC * SfA * SfC * SfU * SfC * SmAn006SfG * SfA * SmU * SfA * SmGn006SmUn006SfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAA GCC	SSSSS S nS SSSS nS nS SSSSS S
WV-24103	mU * SGeon006m5Ceon006m5Ceon006mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGAC UC	S nX nX nX SSRSS RSSRSS SSSS
WV-24104	mU * SGeon006Rm5Ceon006Rm5Ceon006RmA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGAC UC	S nR nR nR SSRSS RSSRSS SSSS
WV-24105	mU * SGeon006Sm5Ceon006Sm5Ceon006SmA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGAC UC	S nS nS nS SSRSS RSSRSS SSSS
WV-24094	fU * SfC * SfA * SfC * SfU * SfC * SmAn007fG * SfA * SmU * SfA * SmGn007mUn007fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAA GCC	SSSSS S nX SSSS nX nX SSSSS S
WV-24095	fU * SfC * SfA * SfC * SfU * SfC * SmAn007RfG * SfA * SmU * SfA * SmGn007RmUn007RfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAA GCC	SSSSS S nR SSSS nR nR SSSSS S
WV-24096	fU * SfC * SfA * SfC * SfU * SfC * SmAn007SfG * SfA *	UCACUCAGAUAGUUGAA	SSSSS S nS SSSS nS nS

	SmU * SfA * SmGn007SmUn007SfU * SfG * SfA * SfA * SfG * SfC * SfC	GCC	SSSSS S
WV-24106	mU * SGeon007Rm5Ceon007Rm5Ceon007RmA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGAC UC	S nR nR nR SSRSS RSSRSS SSSS
WV-24107	mU * SGeon007Sm5Ceon007Sm5Ceon007SmA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGAC UC	S nS nS nS SSRSS RSSRSS SSSS
WV-24097	fU * SfC * SfA * SfC * SfU * SfC * SmAn008fG * SfA * SmU * SfA * SmGn008mUn008fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAA GCC	SSSSS S nX SSSS nX nX SSSSS S
WV-24098	fU * SfC * SfA * SfC * SfU * SfC * SmAn008RfG * SfA * SmU * SfA * SmGn008RmUn008RfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAA GCC	SSSSS S nR SSSS nR nR SSSSS S
WV-24099	fU * SfC * SfA * SfC * SfU * SfC * SmAn008SfG * SfA * SmU * SfA * SmGn008SmUn008SfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAA GCC	SSSSS S nS SSSS nS nS SSSSS S
WV-24108	mU * SGeon008m5Ceon008m5Ceon008mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGAC UC	S nX nX nX SSRSS RSSRSS SSSS
WV-24109	mU * SGeon008Rm5Ceon008Rm5Ceon008RmA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGAC UC	S nR nR nR SSRSS RSSRSS SSSS
WV-24110	mU * SGeon008Sm5Ceon008Sm5Ceon008SmA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGAC UC	S nS nS nS SSRSS RSSRSS SSSS

WV-12880	fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001fU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnX SSnX SSOSS SOSSSnX SS
WV-12880	fC * SfU * SfCn001fC * SfG * SfGn001fU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001fU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnX SSnX SSOSS SOSSSnX SS
WV-21219	fGm001RfU	GU	nR
WV-21226	fCn001RfC	CC	nR
WV-	fGm001SfU	GU	nS

21252			
WV-21253	fCn001SfC	CC	nS
WV-21258	fGn001RmA	GA	nR
WV-21374	fC * RfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	RSnR SSnR SSOSS SOSSSnR SS
WV-21375	fC * SfU * RfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SRnR SSnR SSOSS SOSSSnR SS
WV-21376	fC * SfU * SfCn001SfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnS SSnR SSOSS SOSSSnR SS
WV-21377	fC * SfU * SfCn001RfC * RfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnR RSnR SSOSS SOSSSnR SS
WV-21378	fC * SfU * SfCn001RfC * SfG * RfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnR SRnR SSOSS SOSSSnR SS
WV-21379	fC * SfU * SfCn001RfC * SfG * SfGn001SfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnR SSnS SSOSS SOSSSnR SS
WV-21380	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * RfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnR SSnR RSOSSSO SS SnR SS
WV-21381	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * RmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnR SSnR SROSSSO SS SnR SS
WV-21382	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * RmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnR SSnR SSORSSOSS SnR SS
WV-21383	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * RfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnR SSnR SSOSRSOSSSnR SS
WV-21384	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * RmAfG * SfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnR SSnR SSOSS ROSSSnR SS
WV-21385	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * RfG * SfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnR SSnR SSOSS SORSSnR SS
WV-21386	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * RfU * SfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnR SSnR SSOSS SOSRSnR SS
WV-21387	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * RfGn001RfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnR SSnR SSOSS SOSSRnR SS

WV-21388	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001SfU * SfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnR SSnR SSOSS SOSSSnS SS
WV-21389	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * RfU * SfC	CUCCGGUUCUGAAGGUGUUC	SSnR SSnR SSOSS SOSSSnR RS
WV-21390	fC * SfU * SfCn001RfC * SfG * SfGn001RfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGn001RfU * SfU * RfC	CUCCGGUUCUGAAGGUGUUC	SSnR SSnR SSOSS SOSSSnR SR
WV-21578	fC * SfU * SfUn001fA * SfA * SfGn001fA * SfU * SmA * SfC * SmC * SfA * SmU * SfU * SfU * SfG * SfUn001fA * SfU * SfU	CUUAAGAUACCAUUUGUAUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21579	fU * SfU * SfAn001fA * SfG * SfAn001fU * SfA * SmC * SfC * SmA * SfU * SmU * SfU * SfG * SfU * SfAn001fU * SfU * SfU	UUAAGAUACCAUUUGUAUUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21580	fU * SfA * SfAn001fG * SfA * SfUn001fA * SfC * SmC * SfA * SmU * SfU * SmU * SfG * SfU * SfA * SfUn001fU * SfU * SfA	UAAGAUACCAUUUGUAUUUA	SSnX SSnX SSSSS SSSSS nX SS
WV-21581	fA * SfA * SfGn001fA * SfU * SfAn001fC * SfC * SmA * SfU * SmU * SfU * SmG * SfU * SfA * SfU * SfUn001fU * SfA * SfG	AAGAUACCAUUUGUAUUUAG	SSnX SSnX SSSSS SSSSS nX SS
WV-21582	fA * SfG * SfAn001fU * SfA * SfCn001fC * SfA * SmU * SfU * SmU * SfG * SmU * SfA * SfU * SfUn001fA * SfG * SfC	AGAUACCAUUUGUAUUUAGC	SSnX SSnX SSSSS SSSSS nX SS
WV-21583	fG * SfA * SfUn001fA * SfC * SfCn001fA * SfU * SmU * SfU * SmG * SfU * SmA * SfU * SfU * SfAn001fG * SfC * SfA	GAUACCAUUUGUAUUUAGCA	SSnX SSnX SSSSS SSSSS nX SS
WV-21584	fA * SfU * SfAn001fC * SfC * SfAn001fU * SfU * SmU * SfG * SmU * SfA * SmU * SfU * SfU * SfA * SfGn001fC * SfA * SfU	AUACCAUUUGUAUUUAGCAU	SSnX SSnX SSSSS SSSSS nX SS
WV-21585	fU * SfA * SfCn001fC * SfA * SfUn001fU * SfU * SmG * SfU * SmA * SfU * SmU * SfU * SfA * SfG * SfCn001fA * SfU * SfG	UACCAUUUGUAUUUAGCAUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21586	fA * SfC * SfCn001fA * SfU * SfUn001fU * SfG * SmU * SfA * SmU * SfU * SmU * SfA * SfG * SfC * SfAn001fU * SfG * SfU	ACCAUUUGUAUUUAGCAUGU	SSnX SSnX SSSSS SSSSS nX SS
WV-21587	fC * SfC * SfAn001fU * SfU * SfUn001fG * SfU * SmA * SfU * SmU * SfU * SmA * SfG * SfC * SfA * SfUn001fG * SfU * SfU	CCAUUUGUAUUUAGCAUGUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21588	fC * SfA * SfUn001fU * SfU * SfGn001fU * SfA * SmU * SfU * SmU * SfA * SmG * SfC * SfA * SfU * SfGn001fU * SfU * SfC	CAUUUGUAUUUAGCAUGUUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21589	fA * SfU * SfUn001fU * SfG * SfUn001fA * SfU * SmU * SfU * SmA * SfG * SmC * SfA * SfU * SfG * SfUn001fU * SfC * SfC	AUUUGUAUUUAGCAUGUUCC	SSnX SSnX SSSSS SSSSS nX SS
WV-21590	fU * SfU * SfUn001fG * SfU * SfAn001fU * SfU * SmU * SfA * SmG * SfC * SmA * SfU * SfG * SfU * SfUn001fC * SfC * SfC	UUUGUAUUUAGCAUGUUCCC	SSnX SSnX SSSSS SSSSS nX SS
WV-21591	fU * SfU * SfGn001fU * SfA * SfUn001fU * SfU * SmA * SfG * SmC * SfA * SmU * SfG * SfU * SfU * SfCn001fC * SfC * SfA	UUGUAUUUAGCAUGUUCCCA	SSnX SSnX SSSSS SSSSS nX SS
WV-21592	fU * SfG * SfUn001fA * SfU * SfUn001fU * SfA * SmG * SfC * SmA * SfU * SmG * SfU * SfU * SfC * SfCn001fC * SfA * SfA	UGUAUUUAGCAUGUUCCCAA	SSnX SSnX SSSSS SSSSS nX SS

WV-21593	fG * SfU * SfAn001fU * SfU * SfUn001fA * SfG * SmC * SfA * SmU * SfG * SmU * SfU * SfC * SfCn001fA * SfA * SfU	GUAUUUAGCAUGUUCCCAAU	SSnX SSnX SSSSS SSSSS nX SS
WV-21594	fU * SfA * SfUn001fU * SfU * SfAn001fG * SfC * SmA * SfU * SmG * SfU * SmU * SfC * SfC * SfAn001fA * SfU * SfU	UAUUUAGCAUGUUCCCAAUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21595	fU * SfU * SfUn001fA * SfG * SfCn001fA * SfU * SmG * SfU * SmU * SfC * SmC * SfC * SfA * SfA * SfUn001fU * SfC * SfU	UUUAGCAUGUUCCCAAUUCU	SSnX SSnX SSSSS SSSSS nX SS
WV-21596	fU * SfU * SfAn001fG * SfC * SfAn001fU * SfG * SmU * SfU * SmC * SfC * SmC * SfA * SfA * SfU * SfUn001fC * SfU * SfC	UUAGCAUGUUCCCAAUUCUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21597	fU * SfA * SfGn001fC * SfA * SfUn001fG * SfU * SmU * SfC * SmC * SfC * SmA * SfA * SfU * SfU * SfCn001fU * SfC * SfA	UAGCAUGUUCCCAAUUCUCA	SSnX SSnX SSSSS SSSSS nX SS
WV-21598	fA * SfG * SfCn001fA * SfU * SfGn001fU * SfU * SmC * SfC * SmC * SfA * SmA * SfU * SfU * SfC * SfUn001fC * SfA * SfG	AGCAUGUUCCCAAUUCUCAG	SSnX SSnX SSSSS SSSSS nX SS
WV-21599	fG * SfC * SfAn001fU * SfG * SfUn001fU * SfC * SmC * SfC * SmA * SfA * SmU * SfU * SfC * SfU * SfCn001fA * SfG * SfG	GCAUGUUCCCAAUUCUCAGG	SSnX SSnX SSSSS SSSSS nX SS
WV-21600	fC * SfA * SfUn001fG * SfU * SfUn001fC * SfC * SmC * SfA * SmA * SfU * SmU * SfC * SfU * SfC * SfAn001fG * SfG * SfA	CAUGUUCCCAAUUCUCAGGA	SSnX SSnX SSSSS SSSSS nX SS
WV-21601	fA * SfU * SfGn001fU * SfU * SfCn001fC * SfC * SmA * SfA * SmU * SfU * SmC * SfU * SfC * SfA * SfGn001fG * SfA * SfA	AUGUUCCCAAUUCUCAGGAA	SSnX SSnX SSSSS SSSSS nX SS
WV-21602	fU * SfG * SfUn001fU * SfC * SfCn001fC * SfA * SmA * SfU * SmU * SfC * SmU * SfC * SfA * SfG * SfGn001fA * SfA * SfU	UGUUCCCAAUUCUCAGGAAU	SSnX SSnX SSSSS SSSSS nX SS
WV-21603	fG * SfU * SfUn001fC * SfC * SfCn001fA * SfA * SmU * SfU * SmC * SfU * SmC * SfA * SfG * SfG * SfAn001fA * SfU * SfU	GUUCCCAAUUCUCAGGAAUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21604	fU * SfU * SfCn001fC * SfC * SfAn001fA * SfU * SmU * SfC * SmU * SfC * SmA * SfG * SfG * SfA * SfAn001fU * SfU * SfU	UUCCCAAUUCUCAGGAAUUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21605	fU * SfC * SfCn001fC * SfA * SfAn001fU * SfU * SmC * SfU * SmC * SfA * SmG * SfG * SfA * SfA * SfUn001fU * SfU * SfG	UCCCAAUUCUCAGGAAUUUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21606	fC * SfC * SfCn001fA * SfA * SfUn001fU * SfC * SmU * SfC * SmA * SfG * SmG * SfA * SfA * SfU * SfUn001fU * SfG * SfU	CCCAAUUCUCAGGAAUUUGU	SSnX SSnX SSSSS SSSSS nX SS
WV-21607	fC * SfC * SfAn001fA * SfU * SfUn001fC * SfU * SmC * SfA * SmG * SfG * SmA * SfA * SfU * SfU * SfUn001fG * SfU * SfG	CCAAUUCUCAGGAAUUUGUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21608	fC * SfA * SfAn001fU * SfU * SfCn001fU * SfC * SmA * SfG * SmG * SfA * SmA * SfU * SfU * SfU * SfGn001fU * SfG * SfU	CAAUUCUCAGGAAUUUGUGU	SSnX SSnX SSSSS SSSSS nX SS
WV-21609	fA * SfA * SfUn001fU * SfC * SfUn001fC * SfA * SmG * SfG * SmA * SfA * SmU * SfU * SfU * SfG * SfUn001fG * SfU * SfC	AAUUCUCAGGAAUUUGUGUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21610	fA * SfU * SfUn001fC * SfU * SfCn001fA * SfG * SmG * SfA * SmA * SfU * SmU * SfU * SfG * SfU * SfGn001fU * SfC * SfU	AUUCUCAGGAAUUUGUGUCU	SSnX SSnX SSSSS SSSSS nX SS

WV-21611	fU * SfU * SfCn001fU * SfC * SfAn001fG * SfG * SmA * SfA * SmU * SfU * SmU * SfG * SfU * SfG * SfUn001fC * SfU * SfU	UUCUCAGGAAUUUGUGUCUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21612	fU * SfC * SfUn001fC * SfA * SfGn001fG * SfA * SmA * SfU * SmU * SfU * SmG * SfU * SfG * SfU * SfCn001fU * SfU * SfU	UCUCAGGAAUUUGUGUCUUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21613	fC * SfU * SfCn001fA * SfG * SfGn001fA * SfA * SmU * SfU * SmU * SfG * SmU * SfG * SfU * SfC * SfUn001fU * SfU * SfC	CUCAGGAAUUUGUGUCUUUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21614	fU * SfC * SfAn001fG * SfG * SfAn001fA * SfU * SmU * SfU * SmG * SfU * SmG * SfU * SfC * SfU * SfUn001fU * SfC * SfU	UCAGGAAUUUGUGUCUUUCU	SSnX SSnX SSSSS SSSSS nX SS
WV-21615	fC * SfA * SfGn001fG * SfA * SfAn001fU * SfU * SmU * SfG * SmU * SfG * SmU * SfC * SfU * SfU * SfUn001fC * SfU * SfG	CAGGAAUUUGUGUCUUUCUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21616	fA * SfG * SfGn001fA * SfA * SfUn001fU * SfU * SmG * SfU * SmG * SfU * SmC * SfU * SfU * SfCn001fU * SfG * SfA	AGGAAUUUGUGUCUUUCUGA	SSnX SSnX SSSSS SSSSS nX SS
WV-21617	fG * SfG * SfAn001fA * SfU * SfUn001fU * SfG * SmU * SfG * SmU * SfC * SmU * SfU * SfC * SfUn001fG * SfA * SfG	GGAAUUUGUGUCUUUCUGAG	SSnX SSnX SSSSS SSSSS nX SS
WV-21618	fG * SfA * SfAn001fU * SfU * SfUn001fG * SfU * SmG * SfU * SmC * SfU * SmU * SfU * SfC * SfU * SfGn001fA * SfG * SfA	GAAUUUGUGUCUUUCUGAGA	SSnX SSnX SSSSS SSSSS nX SS
WV-21619	fA * SfA * SfUn001fU * SfU * SfGn001fU * SfG * SmU * SfC * SmU * SfU * SmU * SfC * SfU * SfG * SfAn001fG * SfA * SfA	AAUUUGUGUCUUUCUGAGAA	SSnX SSnX SSSSS SSSSS nX SS
WV-21620	fA * SfU * SfUn001fU * SfG * SfUn001fG * SfU * SmC * SfU * SmU * SfU * SmC * SfU * SfG * SfA * SfGn001fA * SfA * SfA	AUUUGUGUCUUUCUGAGAAA	SSnX SSnX SSSSS SSSSS nX SS
WV-21621	fU * SfU * SfUn001fG * SfU * SfGn001fU * SfC * SmU * SfU * SmU * SfC * SmU * SfG * SfA * SfG * SfAn001fA * SfA * SfC	UUUGUGUCUUUCUGAGAAAC	SSnX SSnX SSSSS SSSSS nX SS
WV-21622	fU * SfU * SfGn001fU * SfG * SfUn001fC * SfU * SmU * SfU * SmC * SfU * SmG * SfA * SfG * SfA * SfAn001fA * SfC * SfU	UUGUGUCUUUCUGAGAAACU	SSnX SSnX SSSSS SSSSS nX SS
WV-21623	fU * SfG * SfUn001fG * SfU * SfCn001fU * SfU * SmU * SfC * SmU * SfG * SmA * SfG * SfA * SfA * SfAn001fC * SfU * SfG	UGUGUCUUUCUGAGAAACUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21624	fG * SfU * SfGn001fU * SfC * SfUn001fU * SfU * SmC * SfU * SmG * SfA * SmG * SfA * SfA * SfA * SfCn001fU * SfG * SfU	GUGUCUUUCUGAGAAACUGU	SSnX SSnX SSSSS SSSSS nX SS
WV-21625	fU * SfG * SfUn001fC * SfU * SfUn001fU * SfC * SmU * SfG * SmA * SfG * SmA * SfA * SfA * SfC * SfUn001fG * SfU * SfU	UGUCUUUCUGAGAAACUGUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21626	fG * SfU * SfCn001fU * SfU * SfUn001fC * SfU * SmG * SfA * SmG * SfA * SmA * SfA * SfC * SfU * SfGn001fU * SfU * SfC	GUCUUUCUGAGAAACUGUUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21627	fU * SfC * SfUn001fU * SfU * SfCn001fU * SfG * SmA * SfG * SmA * SfA * SmA * SfC * SfU * SfG * SfUn001fU * SfC * SfA	UCUUUCUGAGAAACUGUUCA	SSnX SSnX SSSSS SSSSS nX SS
WV-21628	fC * SfU * SfUn001fU * SfC * SfUn001fG * SfA * SmG * SfA * SmA * SfA * SmC * SfU * SfG * SfU * SfUn001fC * SfA * SfG	CUUUCUGAGAAACUGUUCAG	SSnX SSnX SSSSS SSSSS nX SS

WV-21629	fU * SfU * SfUn001fC * SfU * SfGn001fA * SfG * SmA * SfA * SmA * SfC * SmU * SfG * SfU * SfU * SfCn001fA * SfG * SfC	UUUCUGAGAAACUGUUCAGC	SSnX SSnX SSSSS SSSSS nX SS
WV-21630	fU * SfU * SfCn001fU * SfG * SfAn001fG * SfA * SmA * SfA * SmC * SfU * SmG * SfU * SfU * SfC * SfAn001fG * SfC * SfU	UUCUGAGAAACUGUUCAGCU	SSnX SSnX SSSSS SSSSS nX SS
WV-21631	fU * SfC * SfUn001fG * SfA * SfGn001fA * SfA * SmA * SfC * SmU * SfG * SmU * SfU * SfC * SfA * SfGn001fC * SfU * SfU	UCUGAGAAACUGUUCAGCUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21632	fC * SfU * SfGn001fA * SfG * SfAn001fA * SfA * SmC * SfU * SmG * SfU * SmU * SfC * SfA * SfG * SfCn001fU * SfU * SfC	CUGAGAAACUGUUCAGCUUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21633	fU * SfG * SfAn001fG * SfA * SfAn001fA * SfC * SmU * SfG * SmU * SfU * SmC * SfA * SfG * SfC * SfUn001fU * SfC * SfU	UGAGAAACUGUUCAGCUUCU	SSnX SSnX SSSSS SSSSS nX SS
WV-21634	fG * SfA * SfGn001fA * SfA * SfAn001fC * SfU * SmG * SfU * SmU * SfC * SmA * SfG * SfC * SfU * SfUn001fC * SfU * SfG	GAGAAACUGUUCAGCUUCUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21635	fA * SfG * SfAn001fA * SfA * SfCn001fU * SfG * SmU * SfU * SmC * SfA * SmG * SfC * SfU * SfU * SfCn001fU * SfG * SfU	AGAAACUGUUCAGCUUCUGU	SSnX SSnX SSSSS SSSSS nX SS
WV-21636	fG * SfA * SfAn001fA * SfC * SfUn001fG * SfU * SmU * SfC * SmA * SfG * SmC * SfU * SfU * SfC * SfUn001fG * SfU * SfU	GAAACUGUUCAGCUUCUGUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21637	fA * SfA * SfAn001fC * SfU * SfGn001fU * SfU * SmC * SfA * SmG * SfC * SmU * SfU * SfC * SfU * SfGn001fU * SfU * SfA	AAACUGUUCAGCUUCUGUUA	SSnX SSnX SSSSS SSSSS nX SS
WV-21638	fA * SfA * SfCn001fU * SfG * SfUn001fU * SfC * SmA * SfG * SmC * SfU * SmU * SfC * SfU * SfG * SfUn001fU * SfA * SfG	AACUGUUCAGCUUCUGUUAG	SSnX SSnX SSSSS SSSSS nX SS
WV-21639	fA * SfC * SfUn001fG * SfU * SfUn001fC * SfA * SmG * SfC * SmU * SfU * SmC * SfU * SfG * SfU * SfUn001fA * SfG * SfC	ACUGUUCAGCUUCUGUUAGC	SSnX SSnX SSSSS SSSSS nX SS
WV-21640	fC * SfU * SfGn001fU * SfU * SfCn001fA * SfG * SmC * SfU * SmU * SfC * SmU * SfG * SfU * SfU * SfAn001fG * SfC * SfC	CUGUUCAGCUUCUGUUAGCC	SSnX SSnX SSSSS SSSSS nX SS
WV-21641	fU * SfG * SfUn001fU * SfC * SfAn001fG * SfC * SmU * SfU * SmC * SfU * SmG * SfU * SfU * SfA * SfGn001fC * SfC * SfA	UGUUCAGCUUCUGUUAGCCA	SSnX SSnX SSSSS SSSSS nX SS
WV-21642	fG * SfU * SfUn001fC * SfA * SfGn001fC * SfU * SmU * SfC * SmU * SfG * SmU * SfU * SfA * SfG * SfCn001fC * SfA * SfC	GUUCAGCUUCUGUUAGCCAC	SSnX SSnX SSSSS SSSSS nX SS
WV-21643	fU * SfU * SfCn001fA * SfG * SfCn001fU * SfU * SmC * SfU * SmG * SfU * SmU * SfA * SfG * SfC * SfCn001fA * SfC * SfU	UUCAGCUUCUGUUAGCCACU	SSnX SSnX SSSSS SSSSS nX SS
WV-21644	fU * SfC * SfAn001fG * SfC * SfUn001fU * SfC * SmU * SfG * SmU * SfU * SmA * SfG * SfC * SfC * SfAn001fC * SfU * SfG	UCAGCUUCUGUUAGCCACUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21645	fC * SfA * SfGn001fC * SfU * SfUn001fC * SfU * SmG * SfU * SmU * SfA * SmG * SfC * SfC * SfA * SfCn001fU * SfG * SfA	CAGCUUCUGUUAGCCACUGA	SSnX SSnX SSSSS SSSSS nX SS
WV-21646	fA * SfG * SfCn001fU * SfU * SfCn001fU * SfG * SmU * SfU * SmA * SfG * SmC * SfC * SfA * SfC * SfUn001fG * SfA * SfU	AGCUUCUGUUAGCCACUGAU	SSnX SSnX SSSSS SSSSS nX SS

WV-21647	fG * SfC * SfUn001fU * SfC * SfUn001fG * SfU * SmU * SfA * SmG * SfC * SmC * SfA * SfC * SfU * SfGn001fA * SfU * SfU	GCUUCUGUUAGCCACUGAUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21648	fC * SfU * SfUn001fC * SfU * SfGn001fU * SfU * SmA * SfG * SmC * SfC * SmA * SfC * SfU * SfG * SfAn001fU * SfU * SfA	CUUCUGUUAGCCACUGAUUA	SSnX SSnX SSSSS SSSSS nX SS
WV-21649	fU * SfU * SfCn001fU * SfG * SfUn001fU * SfA * SmG * SfC * SmC * SfA * SmC * SfU * SfG * SfA * SfUn001fU * SfA * SfA	UUCUGUUAGCCACUGAUUAA	SSnX SSnX SSSSS SSSSS nX SS
WV-21650	fU * SfC * SfUn001fG * SfU * SfUn001fA * SfG * SmC * SfC * SmA * SfC * SmU * SfG * SfA * SfU * SfUn001fA * SfA * SfA	UCUGUUAGCCACUGAUUAAA	SSnX SSnX SSSSS SSSSS nX SS
WV-21651	fC * SfU * SfGn001fU * SfU * SfAn001fG * SfC * SmC * SfA * SmC * SfU * SmG * SfA * SfU * SfU * SfAn001fA * SfA * SfU	CUGUUAGCCACUGAUUAAAU	SSnX SSnX SSSSS SSSSS nX SS
WV-21652	fU * SfG * SfUn001fU * SfA * SfGn001fC * SfC * SmA * SfC * SmU * SfG * SmA * SfU * SfU * SfA * SfAn001fA * SfU * SfA	UGUUAGCCACUGAUUAAAUA	SSnX SSnX SSSSS SSSSS nX SS
WV-21653	fG * SfU * SfUn001fA * SfG * SfCn001fC * SfA * SmC * SfU * SmG * SfA * SmU * SfU * SfA * SfA * SfAn001fU * SfA * SfU	GUUAGCCACUGAUUAAAUAU	SSnX SSnX SSSSS SSSSS nX SS
WV-21654	fU * SfU * SfAn001fG * SfC * SfCn001fA * SfC * SmU * SfG * SmA * SfU * SmU * SfA * SfA * SfA * SfUn001fA * SfU * SfC	UUAGCCACUGAUUAAAUAUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21655	fU * SfA * SfGn001fC * SfC * SfAn001fC * SfU * SmG * SfA * SmU * SfU * SmA * SfA * SfA * SfU * SfAn001fU * SfC * SfU	UAGCCACUGAUUAAAUAUCU	SSnX SSnX SSSSS SSSSS nX SS
WV-21656	fA * SfG * SfCn001fC * SfA * SfCn001fU * SfG * SmA * SfU * SmU * SfA * SmA * SfA * SfU * SfA * SfUn001fC * SfU * SfU	AGCCACUGAUUAAAUAUCUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21657	fG * SfC * SfCn001fA * SfC * SfUn001fG * SfA * SmU * SfU * SmA * SfA * SmA * SfU * SfA * SfU * SfCn001fU * SfU * SfU	GCCACUGAUUAAAUAUCUUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21658	fC * SfC * SfAn001fC * SfU * SfGn001fA * SfU * SmU * SfA * SmA * SfA * SmU * SfA * SfU * SfC * SfUn001fU * SfU * SfA	CCACUGAUUAAAUAUCUUUA	SSnX SSnX SSSSS SSSSS nX SS
WV-21659	fC * SfA * SfCn001fU * SfG * SfAn001fU * SfU * SmA * SfA * SmA * SfU * SmA * SfU * SfC * SfU * SfUn001fU * SfA * SfU	CACUGAUUAAAUAUCUUUAU	SSnX SSnX SSSSS SSSSS nX SS
WV-21660	fA * SfC * SfUn001fG * SfA * SfUn001fU * SfA * SmA * SfA * SmU * SfA * SmU * SfC * SfU * SfU * SfUn001fA * SfU * SfA	ACUGAUUAAAUAUCUUUAUA	SSnX SSnX SSSSS SSSSS nX SS
WV-21661	fC * SfU * SfGn001fA * SfU * SfUn001fA * SfA * SmA * SfU * SmA * SfU * SmC * SfU * SfU * SfU * SfAn001fU * SfA * SfU	CUGAUUAAAUAUCUUUAUAU	SSnX SSnX SSSSS SSSSS nX SS
WV-21662	fU * SfG * SfAn001fU * SfU * SfAn001fA * SfA * SmU * SfA * SmU * SfC * SmU * SfU * SfU * SfA * SfUn001fA * SfU * SfC	UGAUUAAAUAUCUUUAUAUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21663	fG * SfA * SfUn001fU * SfA * SfAn001fA * SfU * SmA * SfU * SmC * SfU * SmU * SfU * SfA * SfU * SfAn001fU * SfC * SfA	GAUUAAAUAUCUUUAUAUCA	SSnX SSnX SSSSS SSSSS nX SS
WV-21664	fA * SfU * SfUn001fA * SfA * SfAn001fU * SfA * SmU * SfC * SmU * SfU * SmU * SfA * SfU * SfA * SfUn001fC * SfA * SfU	AUUAAAUAUCUUUAUAUCAU	SSnX SSnX SSSSS SSSSS nX SS

WV-21665	fU * SfU * SfAn001fA * SfA * SfUn001fA * SfU * SmC * SfU * SmU * SfU * SmA * SfU * SfA * SfU * SfCn001fA * SfU * SfA	UUAAAUAUCUUUAUAUCAUA	SSnX SSnX SSSSS SSSSS nX SS
WV-21666	fU * SfA * SfAn001fA * SfU * SfAn001fU * SfC * SmU * SfU * SmU * SfA * SmU * SfA * SfU * SfC * SfAn001fU * SfA * SfA	UAAAUAUCUUUAUAUCAUAA	SSnX SSnX SSSSS SSSSS nX SS
WV-21667	fA * SfA * SfAn001fU * SfA * SfUn001fC * SfU * SmU * SfU * SmA * SfU * SmA * SfU * SfC * SfA * SfUn001fA * SfA * SfU	AAAUAUCUUUAUAUCAUAAU	SSnX SSnX SSSSS SSSSS nX SS
WV-21668	fA * SfA * SfUn001fA * SfU * SfCn001fU * SfU * SmU * SfA * SmU * SfA * SmU * SfC * SfA * SfU * SfAn001fA * SfU * SfG	AAUAUCUUUAUAUCAUAAUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21669	fA * SfU * SfAn001fU * SfC * SfUn001fU * SfU * SmA * SfU * SmA * SfU * SmC * SfA * SfU * SfA * SfAn001fU * SfG * SfA	AUAUCUUUAUAUCAUAAUGA	SSnX SSnX SSSSS SSSSS nX SS
WV-21670	fU * SfA * SfUn001fC * SfU * SfUn001fU * SfA * SmU * SfA * SmU * SfC * SmA * SfU * SfA * SfUn001fG * SfA * SfA	UAUCUUUAUAUCAUAAUGAA	SSnX SSnX SSSSS SSSSS nX SS
WV-21671	fA * SfU * SfCn001fU * SfU * SfUn001fA * SfU * SmA * SfU * SmC * SfA * SmU * SfA * SfU * SfGn001fA * SfA * SfA	AUCUUUAUAUCAUAAUGAAA	SSnX SSnX SSSSS SSSSS nX SS
WV-21672	fU * SfC * SfUn001fU * SfU * SfAn001fU * SfA * SmU * SfC * SmA * SfU * SmA * SfA * SfU * SfG * SfAn001fA * SfA * SfA	UCUUUAUAUCAUAAUGAAAA	SSnX SSnX SSSSS SSSSS nX SS
WV-21673	fC * SfU * SfUn001fU * SfA * SfUn001fA * SfU * SmC * SfA * SmU * SfA * SmA * SfU * SfG * SfA * SfAn001fA * SfA * SfC	CUUUAUAUCAUAAUGAAAAC	SSnX SSnX SSSSS SSSSS nX SS
WV-21723	fC * SfU * SfGn001fA * SfA * SfUn001fU * SfA * SmU * SfU * SmU * SfC * SmU * SfU * SfC * SfC * SfCn001fC * SfA * SfG	CUGAAUUAUUUCUUCCCCAG	SSnX SSnX SSSSS SSSSS nX SS
WV-21724	fU * SfG * SfAn001fA * SfU * SfUn001fA * SfU * SmU * SfU * SmC * SfU * SmU * SfC * SfC * SfCn001fA * SfG * SfU	UGAAUUAUUUCUUCCCCAGU	SSnX SSnX SSSSS SSSSS nX SS
WV-21725	fG * SfA * SfAn001fU * SfU * SfAn001fU * SfU * SmU * SfC * SmU * SfU * SmC * SfC * SfC * SfAn001fG * SfU * SfU	GAAUUAUUUCUUCCCCAGUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21726	fA * SfA * SfUn001fU * SfA * SfUn001fU * SfU * SmC * SfU * SmU * SfC * SmC * SfC * SfC * SfA * SfGn001fU * SfU * SfG	AAUUAUUUCUUCCCCAGUUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21727	fA * SfU * SfUn001fA * SfU * SfUn001fU * SfC * SmU * SfU * SmC * SfC * SmC * SfC * SfA * SfG * SfUn001fU * SfG * SfC	AUUAUUUCUUCCCCAGUUGC	SSnX SSnX SSSSS SSSSS nX SS
WV-21728	fU * SfU * SfAn001fU * SfU * SfUn001fC * SfU * SmU * SfC * SmC * SfC * SmC * SfA * SfG * SfU * SfUn001fG * SfC * SfA	UUAUUUCUUCCCCAGUUGCA	SSnX SSnX SSSSS SSSSS nX SS
WV-21729	fU * SfA * SfUn001fU * SfU * SfCn001fU * SfU * SmC * SfC * SmC * SfC * SmA * SfG * SfU * SfU * SfGn001fC * SfA * SfU	UAUUUCUUCCCCAGUUGCAU	SSnX SSnX SSSSS SSSSS nX SS
WV-21730	fA * SfU * SfUn001fU * SfC * SfUn001fU * SfC * SmC * SfC * SmC * SfA * SmG * SfU * SfU * SfG * SfCn001fA * SfU * SfU	AUUUCUUCCCCAGUUGCAUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21731	fU * SfU * SfUn001fC * SfU * SfUn001fC * SfC * SmC * SfC * SmA * SfG * SmU * SfU * SfG * SfC * SfAn001fU * SfU * SfC	UUUCUUCCCCAGUUGCAUUC	SSnX SSnX SSSSS SSSSS nX SS

WV-21732	fU * SfU * SfCn001fU * SfU * SfCn001fC * SfC * SmC * SfA * SmG * SfU * SmU * SfG * SfC * SfA * SfUn001fU * SfC * SfA	UUCUUCCCCCAGUUGCAUUCA	SSnX SSnX SSSSS SSSSS nX SS
WV-21733	fU * SfC * SfUn001fU * SfC * SfCn001fC * SfC * SmA * SfG * SmU * SfU * SmG * SfC * SfA * SfU * SfUn001fC * SfA * SfA	UCUUCCCCCAGUUGCAUUCAA	SSnX SSnX SSSSS SSSSS nX SS
WV-21734	fC * SfU * SfUn001fC * SfC * SfCn001fC * SfA * SmG * SfU * SmU * SfG * SmC * SfA * SfU * SfU * SfCn001fA * SfA * SfU	CUUCCCCCAGUUGCAUUCAAU	SSnX SSnX SSSSS SSSSS nX SS
WV-21735	fU * SfU * SfCn001fC * SfC * SfCn001fA * SfG * SmU * SfU * SmG * SfC * SmA * SfU * SfU * SfC * SfAn001fA * SfU * SfG	UUCCCCAGUUGCAUUCAAUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21736	fU * SfC * SfCn001fC * SfC * SfAn001fG * SfU * SmU * SfG * SmC * SfA * SmU * SfU * SfC * SfA * SfAn001fU * SfG * SfU	UCCCCAGUUGCAUUCAAUGU	SSnX SSnX SSSSS SSSSS nX SS
WV-21737	fC * SfC * SfCn001fC * SfA * SfGn001fU * SfU * SmG * SfC * SmA * SfU * SmU * SfC * SfA * SfA * SfUn001fG * SfU * SfU	CCCCAGUUGCAUUCAAUGUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21738	fC * SfC * SfCn001fA * SfG * SfUn001fU * SfG * SmC * SfA * SmU * SfU * SmC * SfA * SfA * SfU * SfGn001fU * SfU * SfC	CCCAGUUGCAUUCAAUGUUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21739	fC * SfC * SfAn001fG * SfU * SfUn001fG * SfC * SmA * SfU * SmU * SfC * SmA * SfA * SfU * SfG * SfUn001fU * SfC * SfU	CCAGUUGCAUUCAAUGUUCU	SSnX SSnX SSSSS SSSSS nX SS
WV-21740	fC * SfA * SfGn001fU * SfU * SfGn001fC * SfA * SmU * SfU * SmC * SfA * SmA * SfU * SfG * SfU * SfUn001fC * SfU * SfG	CAGUUGCAUUCAAUGUUCUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21741	fA * SfG * SfUn001fU * SfG * SfCn001fA * SfU * SmU * SfC * SmA * SfA * SmU * SfG * SfU * SfU * SfCn001fU * SfG * SfA	AGUUGCAUUCAAUGUUCUGA	SSnX SSnX SSSSS SSSSS nX SS
WV-21742	fG * SfU * SfUn001fG * SfC * SfAn001fU * SfU * SmC * SfA * SmA * SfU * SmG * SfU * SfU * SfC * SfUn001fG * SfA * SfC	GUUGCAUUCAAUGUUCUGAC	SSnX SSnX SSSSS SSSSS nX SS
WV-21743	fU * SfU * SfGn001fC * SfA * SfUn001fU * SfC * SmA * SfA * SmU * SfG * SmU * SfU * SfC * SfU * SfGn001fA * SfC * SfA	UUGCAUUCAAUGUUCUGACA	SSnX SSnX SSSSS SSSSS nX SS
WV-21744	fU * SfG * SfCn001fA * SfU * SfUn001fC * SfA * SmA * SfU * SmG * SfU * SmU * SfC * SfU * SfG * SfAn001fC * SfA * SfA	UGCAUUCAAUGUUCUGACAA	SSnX SSnX SSSSS SSSSS nX SS
WV-21745	fG * SfC * SfAn001fU * SfU * SfCn001fA * SfA * SmU * SfG * SmU * SfU * SmC * SfU * SfG * SfA * SfCn001fA * SfA * SfC	GCAUUCAAUGUUCUGACAAC	SSnX SSnX SSSSS SSSSS nX SS
WV-21746	fC * SfA * SfUn001fU * SfC * SfAn001fA * SfU * SmG * SfU * SmU * SfC * SmU * SfG * SfA * SfC * SfAn001fA * SfC * SfA	CAUUCAAUGUUCUGACAACA	SSnX SSnX SSSSS SSSSS nX SS
WV-21747	fA * SfU * SfUn001fC * SfA * SfAn001fU * SfG * SmU * SfU * SmC * SfU * SmG * SfA * SfC * SfA * SfAn001fC * SfA * SfG	AUUCAAUGUUCUGACAACAG	SSnX SSnX SSSSS SSSSS nX SS
WV-21748	fU * SfU * SfCn001fA * SfA * SfUn001fG * SfU * SmU * SfC * SmU * SfG * SmA * SfC * SfA * SfA * SfCn001fA * SfG * SfU	UUCAAUGUUCUGACAACAGU	SSnX SSnX SSSSS SSSSS nX SS
WV-21749	fU * SfC * SfAn001fA * SfU * SfGn001fU * SfU * SmC * SfU * SmG * SfA * SmC * SfA * SfA * SfC * SfAn001fG * SfU * SfU	UCAAUGUUCUGACAACAGUU	SSnX SSnX SSSSS SSSSS nX SS

WV-21750	fC * SfA * SfAn001fU * SfG * SfUn001fU * SfC * SmU * SfG * SmA * SfC * SmA * SfA * SfC * SfA * SfGn001fU * SfU * SfU	CAAUGUUCUGACAACAGUUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21751	fA * SfA * SfUn001fG * SfU * SfUn001fC * SfU * SmG * SfA * SmC * SfA * SmA * SfC * SfA * SfG * SfUn001fU * SfU * SfG	AAUGUUCUGACAACAGUUUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21752	fA * SfU * SfGn001fU * SfU * SfCn001fU * SfG * SmA * SfC * SmA * SfA * SmC * SfA * SfG * SfU * SfUn001fU * SfG * SfC	AUGUUCUGACAACAGUUUGC	SSnX SSnX SSSSS SSSSS nX SS
WV-21753	fU * SfG * SfUn001fU * SfC * SfUn001fG * SfA * SmC * SfA * SmA * SfC * SmA * SfG * SfU * SfU * SfUn001fG * SfC * SfC	UGUUCUGACAACAGUUUGCC	SSnX SSnX SSSSS SSSSS nX SS
WV-21754	fG * SfU * SfUn001fC * SfU * SfGn001fA * SfC * SmA * SfA * SmC * SfA * SmG * SfU * SfU * SfUn001fC * SfC * SfG	GUUCUGACAACAGUUUGCCG	SSnX SSnX SSSSS SSSSS nX SS
WV-21755	fU * SfU * SfCn001fU * SfG * SfAn001fC * SfA * SmA * SfC * SmA * SfG * SmU * SfU * SfU * SfG * SfCn001fC * SfG * SfC	UUCUGACAACAGUUUGCCGC	SSnX SSnX SSSSS SSSSS nX SS
WV-21756	fU * SfC * SfUn001fG * SfA * SfCn001fA * SfA * SmC * SfA * SmG * SfU * SmU * SfU * SfG * SfC * SfCn001fG * SfC * SfU	UCUGACAACAGUUUGCCGCU	SSnX SSnX SSSSS SSSSS nX SS
WV-21757	fC * SfU * SfGn001fA * SfC * SfAn001fA * SfC * SmA * SfG * SmU * SfU * SmU * SfG * SfC * SfC * SfGn001fC * SfU * SfG	CUGACAACAGUUUGCCGCUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21758	fU * SfG * SfAn001fC * SfA * SfAn001fC * SfA * SmG * SfU * SmU * SfU * SmG * SfC * SfC * SfG * SfCn001fU * SfG * SfC	UGACAACAGUUUGCCGCUGC	SSnX SSnX SSSSS SSSSS nX SS
WV-21759	fG * SfA * SfCn001fA * SfA * SfCn001fA * SfG * SmU * SfU * SmU * SfG * SmC * SfC * SfG * SfC * SfUn001fG * SfC * SfC	GACAACAGUUUGCCGCUGCC	SSnX SSnX SSSSS SSSSS nX SS
WV-21760	fA * SfC * SfAn001fA * SfC * SfAn001fG * SfU * SmU * SfU * SmG * SfC * SmC * SfG * SfC * SfU * SfGn001fC * SfC * SfC	ACAACAGUUUGCCGCUGCCC	SSnX SSnX SSSSS SSSSS nX SS
WV-21761	fC * SfA * SfAn001fC * SfA * SfGn001fU * SfU * SmU * SfG * SmC * SfC * SfC * SmG * SfC * SfU * SfG * SfCn001fC * SfC * SfA	CAACAGUUUGCCGCUGCCCA	SSnX SSnX SSSSS SSSSS nX SS
WV-21762	fA * SfA * SfCn001fA * SfG * SfUn001fU * SfU * SmG * SfC * SmC * SfG * SmC * SfU * SfG * SfC * SfCn001fC * SfA * SfA	AACAGUUUGCCGCUGCCCAA	SSnX SSnX SSSSS SSSSS nX SS
WV-21763	fA * SfC * SfAn001fG * SfU * SfUn001fU * SfG * SmC * SfC * SmG * SfC * SmU * SfG * SfC * SfC * SfCn001fA * SfA * SfU	ACAGUUUGCCGCUGCCCAAU	SSnX SSnX SSSSS SSSSS nX SS
WV-21764	fC * SfA * SfGn001fU * SfU * SfUn001fG * SfC * SmC * SfG * SmC * SfU * SmG * SfC * SfC * SfC * SfAn001fA * SfU * SfG	CAGUUUGCCGCUGCCCAAUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21765	fA * SfG * SfUn001fU * SfU * SfGn001fC * SfC * SmG * SfC * SmU * SfG * SmC * SfC * SfC * SfA * SfAn001fU * SfG * SfC	AGUUUGCCGCUGCCCAAUGC	SSnX SSnX SSSSS SSSSS nX SS
WV-21766	fG * SfU * SfUn001fU * SfG * SfCn001fC * SfG * SmC * SfU * SmG * SfC * SmC * SfC * SfA * SfA * SfUn001fG * SfC * SfC	GUUUGCCGCUGCCCAAUGCC	SSnX SSnX SSSSS SSSSS nX SS
WV-21767	fU * SfU * SfUn001fG * SfC * SfCn001fG * SfC * SmU * SfG * SmC * SfC * SmC * SfA * SfU * SfGn001fC * SfC * SfA	UUUGCCGCUGCCCAAUGCCA	SSnX SSnX SSSSS SSSSS nX SS

WV-21768	fU * SfU * SfGn001fC * SfC * SfGn001fC * SfU * SmG * SfC * SmC * SfC * SmA * SfA * SfU * SfG * SfCn001fC * SfA * SfU	UUGCCGCUGCCCAAUGCCAU	SSnX SSnX SSSSS SSSSS nX SS
WV-21769	fU * SfG * SfCn001fC * SfG * SfCn001fU * SfG * SmC * SfC * SmC * SfA * SmA * SfU * SfG * SfC * SfCn001fA * SfU * SfC	UGCCGCUGCCCAAUGCCAUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21770	fG * SfC * SfCn001fG * SfC * SfUn001fG * SfC * SmC * SfC * SmA * SfA * SmU * SfG * SfC * SfC * SfAn001fU * SfC * SfC	GCCGCUGCCCAAUGCCAUCC	SSnX SSnX SSSSS SSSSS nX SS
WV-21771	fC * SfC * SfGn001fC * SfU * SfGn001fC * SfC * SmC * SfA * SmA * SfU * SmG * SfC * SfC * SfA * SfUn001fC * SfC * SfU	CCGCUGCCCAAUGCCAUCCU	SSnX SSnX SSSSS SSSSS nX SS
WV-21772	fA * SfU * SfUn001fU * SfU * SfGn001fG * SfG * SmC * SfA * SmG * SfC * SmG * SfG * SfU * SfA * SfAn001fU * SfG * SfA	AUUUUGGGCAGCGGUAAUGA	SSnX SSnX SSSSS SSSSS nX SS
WV-21773	fU * SfU * SfUn001fU * SfG * SfGn001fG * SfC * SmA * SfG * SmC * SfG * SmG * SfU * SfA * SfUn001fG * SfA * SfG	UUUUGGGCAGCGGUAAUGAG	SSnX SSnX SSSSS SSSSS nX SS
WV-21774	fU * SfU * SfUn001fG * SfG * SfGn001fC * SfA * SmG * SfC * SmG * SfG * SmU * SfA * SfA * SfU * SfGn001fA * SfG * SfU	UUUGGGCAGCGGUAAUGAGU	SSnX SSnX SSSSS SSSSS nX SS
WV-21775	fU * SfU * SfGn001fG * SfG * SfCn001fA * SfG * SmC * SfG * SmG * SfU * SmA * SfA * SfU * SfG * SfAn001fG * SfU * SfU	UUGGGCAGCGGUAAUGAGUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21776	fU * SfG * SfGn001fG * SfC * SfAn001fG * SfC * SmG * SfG * SmU * SfA * SmA * SfU * SfG * SfA * SfGn001fU * SfU * SfC	UGGGCAGCGGUAAUGAGUUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21777	fG * SfG * SfGn001fC * SfA * SfGn001fC * SfG * SmG * SfU * SmA * SfA * SmU * SfG * SfA * SfG * SfUn001fU * SfC * SfU	GGGCAGCGGUAAUGAGUUCU	SSnX SSnX SSSSS SSSSS nX SS
WV-21778	fG * SfG * SfCn001fA * SfG * SfCn001fG * SfG * SmU * SfA * SmA * SfU * SmG * SfA * SfG * SfU * SfUn001fC * SfU * SfU	GGCAGCGGUAAUGAGUUCUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21779	fG * SfC * SfAn001fG * SfC * SfGn001fG * SfU * SmA * SfA * SmU * SfG * SmA * SfG * SfU * SfU * SfCn001fU * SfU * SfC	GCAGCGGUAAUGAGUUCUUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21780	fC * SfA * SfGn001fC * SfG * SfGn001fU * SfA * SmA * SfU * SmG * SfA * SmG * SfU * SfU * SfC * SfUn001fU * SfC * SfC	CAGCGGUAAUGAGUUCUUCC	SSnX SSnX SSSSS SSSSS nX SS
WV-21781	fA * SfG * SfCn001fG * SfG * SfUn001fA * SfA * SmU * SfG * SmA * SfG * SmU * SfU * SfC * SfU * SfUn001fC * SfC * SfA	AGCGGUAAUGAGUUCUUCCA	SSnX SSnX SSSSS SSSSS nX SS
WV-21782	fG * SfC * SfGn001fG * SfU * SfAn001fA * SfU * SmG * SfA * SmG * SfU * SmU * SfC * SfU * SfU * SfCn001fC * SfA * SfA	GCGGUAAUGAGUUCUUCCAA	SSnX SSnX SSSSS SSSSS nX SS
WV-21783	fC * SfG * SfGn001fU * SfA * SfAn001fU * SfG * SmA * SfG * SmU * SfU * SmC * SfU * SfU * SfC * SfCn001fA * SfA * SfC	CGGUAAUGAGUUCUUCCAAC	SSnX SSnX SSSSS SSSSS nX SS
WV-21784	fG * SfG * SfUn001fA * SfA * SfUn001fG * SfA * SmG * SfU * SmU * SfC * SmU * SfU * SfC * SfC * SfAn001fA * SfC * SfU	GGUAAUGAGUUCUUCCAACU	SSnX SSnX SSSSS SSSSS nX SS
WV-21785	fG * SfU * SfAn001fA * SfU * SfGn001fA * SfG * SmU * SfU * SmC * SfU * SmU * SfC * SfC * SfA * SfAn001fC * SfU * SfG	GUAAUGAGUUCUUCCAACUG	SSnX SSnX SSSSS SSSSS nX SS

WV-21786	fU * SfA * SfAn001fU * SfG * SfAn001fG * SfU * SmU * SfC * SmU * SfU * SmC * SfC * SfA * SfCn001fU * SfG * SfG	UAAUGAGUUCUUCCAACUGG	SSnX SSnX SSSSS SSSSS nX SS
WV-21787	fA * SfA * SfUn001fG * SfA * SfGn001fU * SfU * SmC * SfU * SmU * SfC * SmC * SfA * SfA * SfC * SfUn001fG * SfG * SfG	AAUGAGUUCUUCCAACUGGG	SSnX SSnX SSSSS SSSSS nX SS
WV-21788	fA * SfU * SfGn001fA * SfG * SfUn001fU * SfC * SmU * SfU * SmC * SfC * SmA * SfA * SfC * SfU * SfGn001fG * SfG * SfG	AUGAGUUCUUCCAACUGGGG	SSnX SSnX SSSSS SSSSS nX SS
WV-21789	fU * SfG * SfAn001fG * SfU * SfUn001fC * SfU * SmU * SfC * SmC * SfA * SmA * SfC * SfU * SfG * SfGn001fG * SfG * SfA	UGAGUUCUUCCAACUGGGGA	SSnX SSnX SSSSS SSSSS nX SS
WV-21790	fG * SfA * SfGn001fU * SfU * SfCn001fU * SfU * SmC * SfC * SmA * SfA * SmC * SfU * SfG * SfG * SfGn001fG * SfA * SfC	GAGUUCUUCCAACUGGGGAC	SSnX SSnX SSSSS SSSSS nX SS
WV-21791	fA * SfG * SfUn001fU * SfC * SfUn001fU * SfC * SmC * SfA * SmA * SfC * SmU * SfG * SfG * SfGn001fA * SfC * SfG	AGUUCUUCCAACUGGGGACG	SSnX SSnX SSSSS SSSSS nX SS
WV-21792	fG * SfU * SfUn001fC * SfU * SfUn001fC * SfC * SmA * SfA * SmC * SfU * SmG * SfG * SfG * SfAn001fC * SfG * SfC	GUUCUUCCAACUGGGGACGC	SSnX SSnX SSSSS SSSSS nX SS
WV-21793	fU * SfU * SfCn001fU * SfU * SfCn001fC * SfA * SmA * SfC * SmU * SfG * SmG * SfG * SfA * SfCn001fG * SfC * SfC	UUCUUCCAACUGGGGACGCC	SSnX SSnX SSSSS SSSSS nX SS
WV-21794	fU * SfC * SfUn001fU * SfC * SfCn001fA * SfA * SmC * SfU * SmG * SfG * SmG * SfG * SfA * SfC * SfGn001fC * SfC * SfU	UCUUCCAACUGGGGACGCCU	SSnX SSnX SSSSS SSSSS nX SS
WV-21795	fC * SfU * SfUn001fC * SfC * SfAn001fA * SfC * SmU * SfG * SmG * SfG * SmG * SfA * SfC * SfG * SfCn001fC * SfU * SfC	CUUCCAACUGGGGACGCCUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21796	fU * SfU * SfCn001fC * SfA * SfAn001fC * SfU * SmG * SfG * SmG * SfG * SmA * SfC * SfG * SfC * SfCn001fU * SfC * SfU	UUCCAACUGGGGACGCCUCU	SSnX SSnX SSSSS SSSSS nX SS
WV-21797	fU * SfC * SfCn001fA * SfA * SfCn001fU * SfG * SmG * SfG * SmG * SfA * SmC * SfG * SfC * SfC * SfUn001fC * SfU * SfG	UCCAACUGGGGACGCCUCUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21798	fC * SfC * SfAn001fA * SfC * SfUn001fG * SfG * SmG * SfG * SmA * SfC * SmG * SfC * SfC * SfU * SfCn001fU * SfG * SfU	CCAACUGGGGACGCCUCUGU	SSnX SSnX SSSSS SSSSS nX SS
WV-21799	fC * SfA * SfAn001fC * SfU * SfGn001fG * SfG * SmG * SfA * SmC * SfG * SmC * SfC * SfU * SfC * SfUn001fG * SfU * SfU	CAACUGGGGACGCCUCUGUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21800	fA * SfA * SfCn001fU * SfG * SfGn001fG * SfG * SmA * SfC * SmG * SfC * SmC * SfU * SfC * SfU * SfGn001fU * SfU * SfC	AACUGGGGACGCCUCUGUUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21801	fA * SfC * SfUn001fG * SfG * SfGn001fG * SfA * SmC * SfG * SmC * SfC * SmU * SfC * SfU * SfG * SfUn001fU * SfC * SfC	ACUGGGGACGCCUCUGUUCC	SSnX SSnX SSSSS SSSSS nX SS
WV-21802	fC * SfU * SfGn001fG * SfG * SfGn001fA * SfC * SmG * SfC * SmC * SfU * SmC * SfU * SfG * SfU * SfUn001fC * SfC * SfA	CUGGGGACGCCUCUGUUCCA	SSnX SSnX SSSSS SSSSS nX SS
WV-21803	fU * SfG * SfGn001fG * SfG * SfAn001fC * SfG * SmC * SfC * SmU * SfC * SmU * SfG * SfU * SfCn001fC * SfA * SfA	UGGGGACGCCUCUGUUCCAA	SSnX SSnX SSSSS SSSSS nX SS

WV-21804	fG * SfG * SfGn001fG * SfA * SfCn001fG * SfC * SmC * SfU * SmC * SfU * SmG * SfU * SfC * SfCn001fA * SfA * SfA	GGGGACGCCUCUGUUCCAAA	SSnX SSnX SSSSS SSSSS nX SS
WV-21805	fG * SfG * SfGm001fA * SfC * SfGm001fC * SfC * SmU * SfC * SmU * SfG * SmU * SfU * SfC * SfC * SfAn001fA * SfA * SfU	GGGACGCCUCUGUUCCAAAU	SSnX SSnX SSSSS SSSSS nX SS
WV-21806	fG * SfG * SfAn001fC * SfG * SfCn001fC * SfU * SmC * SfU * SmG * SfU * SmU * SfC * SfC * SfA * SfAn001fA * SfU * SfC	GGACGCCUCUGUUCCAAAUC	SSnX SSnX SSSSS SSSSS nX SS
WV-21807	fG * SfA * SfCn001fG * SfC * SfCn001fU * SfC * SmU * SfG * SmU * SfU * SmC * SfC * SfA * SfA * SfAn001fU * SfC * SfC	GACGCCUCUGUUCCAAAUCC	SSnX SSnX SSSSS SSSSS nX SS
WV-21808	fA * SfC * SfGm001fC * SfC * SfUm001fC * SfU * SmG * SfU * SmU * SfC * SmC * SfA * SfA * SfUn001fC * SfC * SfU	ACGCCUCUGUUCCAAAUCCU	SSnX SSnX SSSSS SSSSS nX SS
WV-21809	fC * SfG * SfCn001fC * SfU * SfCn001fU * SfG * SmU * SfU * SmC * SfC * SmA * SfA * SfU * SfCn001fC * SfU * SfG	CGCCUCUGUUCCAAAUCCUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21810	fG * SfC * SfCn001fU * SfC * SfUm001fG * SfU * SmU * SfC * SmC * SfA * SmA * SfA * SfU * SfC * SfCn001fU * SfG * SfC	GCCUCUGUUCCAAAUCCUGC	SSnX SSnX SSSSS SSSSS nX SS
WV-21811	fC * SfC * SfUn001fC * SfU * SfGm001fU * SfU * SmC * SfC * SmA * SfA * SmA * SfU * SfC * SfC * SfUn001fG * SfC * SfA	CCUCUGUUCCAAAUCCUGCA	SSnX SSnX SSSSS SSSSS nX SS
WV-21812	fC * SfU * SfCn001fU * SfG * SfUn001fU * SfC * SmC * SfA * SmA * SfA * SmU * SfC * SfC * SfU * SfGn001fC * SfA * SfU	CUCUGUUCCAAAUCCUGCAU	SSnX SSnX SSSSS SSSSS nX SS
WV-21813	fU * SfC * SfUn001fG * SfU * SfUn001fC * SfC * SmA * SfA * SmA * SfU * SmC * SfC * SfU * SfG * SfCn001fA * SfU * SfU	UCUGUUCCAAAUCCUGCAUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21814	fC * SfU * SfGn001fU * SfU * SfCn001fC * SfA * SmA * SfA * SmU * SfC * SmC * SfU * SfG * SfC * SfAn001fU * SfU * SfG	CUGUUCCAAAUCCUGCAUUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21815	fU * SfG * SfUn001fU * SfC * SfCn001fA * SfA * SmA * SfU * SmC * SfC * SmU * SfG * SfC * SfA * SfUn001fU * SfG * SfU	UGUUCCAAAUCCUGCAUUGU	SSnX SSnX SSSSS SSSSS nX SS
WV-21816	fG * SfU * SfUn001fC * SfC * SfAn001fA * SfA * SmU * SfC * SmC * SfU * SmG * SfC * SfA * SfU * SfUn001fG * SfU * SfU	GUUCCAAAUCCUGCAUUGUU	SSnX SSnX SSSSS SSSSS nX SS
WV-21817	fU * SfU * SfCn001fC * SfA * SfAn001fA * SfU * SmC * SfC * SmU * SfG * SmC * SfA * SfU * SfU * SfGn001fU * SfU * SfG	UUCCAAAUCCUGCAUUGUUG	SSnX SSnX SSSSS SSSSS nX SS
WV-21818	fU * SfC * SfCn001fA * SfA * SfAn001fU * SfC * SmC * SfU * SmG * SfC * SmA * SfU * SfU * SfG * SfUn001fU * SfG * SfC	UCCAAAUCCUGCAUUGUUGC	SSnX SSnX SSSSS SSSSS nX SS
WV-22753	fU * SfC * SfAn001RfC * SfU * SfCn001RmA * SfG * SfA * SmU * SfA * SmG * SmU * SfU * SfG * SfA * SfAn001RfG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	SSnR SSnR SSSSS SSSSS nR SS
WV-23576	L009n001L009n001L009n001L009fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	nX nX nX OSSSSS SOSS SSOOSSSSS S

WV-23577	L009n001L009n001L009n001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	nX nX nX SSSSS SOSS SSOOSSSSS S
WV-23578	L009n001L009n001L009n001L009fU * SfC * SfAn001fC * SfU * SfCn001mAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfAn001fG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	nX nX nX OSSnX SSnX OSSSSOOSSSnX SS
WV-23579	L009n001L009n001L009n001fU * SfC * SfAn001fC * SfU * SfCn001mAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfAn001fG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	nX nX nX SSnX SSnX OSSSSOOSSSnX SS
WV-23936	L010n001L010n001L010n001L009fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	nX nX nX OSSSS SOSS SSOOSSSSS S
WV-23937	L010n001L010n001L010n001fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	nX nX nX SSSSS SOSS SSOOSSSSS S
WV-23938	L010n001L010n001L010n001L009fU * SfC * SfAn001fC * SfU * SfCn001mAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfAn001fG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	nX nX nX OSSnX SSnX OSSSSOOSSSnX SS
WV-23939	L010n001L010n001L010n001fU * SfC * SfAn001fC * SfU * SfCn001mAfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfAn001fG * SfC * SfC	UCACUCAGAUAGUUGAAGCC	nX nX nX SSnX SSnX OSSSSO OSSSnX SS
WV-XBD108	mU * SGeon009m5Ceon009m5Ceon009mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGACUC	S nX nX nX SSRSS RSSRSS SSSS
WV-XBD109	mU * SGeon009Rm5Ceon009Rm5Ceon009RmA * SG * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGACUC	S nR nR nR SSRSS RSSRSS SSSS
WV-XBD110	mU * SGeon009Sm5Ceon009Sm5Ceon009SmA * SG * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGACUC	S nS nS nS SSRSS RSSRSS SSSS
WV-XKCD108	mU * SGeon010m5Ceon010m5Ceon010mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGACUC	S nX nX nX SSRSS RSSRSS SSSS
WV-XKCD109	mU * SGeon010Rm5Ceon010Rm5Ceon010RmA * SG * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGACUC	S nR nR nR SSRSS RSSRSS SSSS

WV-XKCD 110	mU * SGeon010Sm5Ceon010Sm5Ceon010SmA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGGTTATGACUC	S nS nS nS SSRSS RSSRSS SSSS

WV-3519	Mod032fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGA UGGCAUUUCU	O XXXXX XOXOX OXO XXXXX X
WV-3518	Mod031fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGA UGGCAUUUCU	O XXXXX XOXOX OXO XXXXX X
WV-3517	Mod030fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGA UGGCAUUUCU	O XXXXX XOXOX OXO XXXXX X
WV-3516	fU * fC * fA * fA * fG * fG * mAfA * mGfA * mUfG * mGfC * fA * fU * fU * fU * fC * fU	UCAAGGAAGA UGGCAUUUCU	XXXXX XOXOX OXO XXXXX X
WV-3515	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmAfU * SmGmGfC * SfAfU * SfU * SfU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSSSS SOSOO SOOSOSSSS
WV-3514	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGfAfU * SmGmGfC * SfAfU * SfU * SfU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSSSS SOSOO SOOSOSSSS
WV-3513	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmAfU * SmGmGfC * SmAfU * SfU * SfU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSSSS SOSOO SOOSOSSSS
WV-3512	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGfAfU * SmGmGfC * SmAfU * SfU * SfU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSSSS SOSOO SOOSOSSSS
WV-3511	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmAfU * SmGmGfC * SmA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSSSS SOSOO SOO SSSSS S
WV-3510	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGfAfU * SmGmGfC * SmA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSSSS SOSOO SOO SSSSS S
WV-3509	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfAfU * SfU * SfU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSSSS SOSOS SOOSOSSSS
WV-3508	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGfA * SfU * SmGmGfC * SfAfU * SfU * SfU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSSSS SOSOS SOOSOSSSS
WV-3507	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmAfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSSSS SOSOO SOO SSSSS S
WV-27250	fU * SfC * SfA * SfC * SfU * SfC * SmAn011fG * SfA * SmU * SfA * SmGn011mUn011fU * SfG * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSSSS SnXSSSS nXnX SSSSS S
WV-27249	fU * SfC * SfA * SfC * SfU * SfC * SmAn010fG * SfA * SmU * SfA * SmGm010mUn010fU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSSSS SnXSSSSnXnX SSSSS

			S
WV-24086	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfG	UCAAGGAAGA UGGCAUUUCG	SSSSS SOSOS SOO SSSSS S
WV-24085	fG * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU * SfU * SfC * SfU	GCAAGGAAGAU GGCAUUUCU	SSSSS SOSOS SOO SSSSS S
WV-22919	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmG * SfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSSSS SOSOS SO SSSSS SS
WV-22918	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmG * SmGfC * SfA * SfU * SfU * SfU * SfC * SfU	UCAAGGAAGA UGGCAUUUCU	SSSSS SOSOS SSO SSSSS S
WV-22765	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmG	UCAAGGAAGA UG	SSSSS SOSOS S
WV-22764	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA	UCAAGGAAGA UGGCA	SSSSS SOSOS SOOS
WV-22763	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU	UCAAGGAAGA UGGCAU	SSSSS SOSOS SOOSS
WV-22762	fU * SfC * SfA * SfA * SfG * SfG * SmAfA * SmGmA * SfU * SmGmGfC * SfA * SfU * SfU	UCAAGGAAGA UGGCAUU	SSSSS SOSOS SOOSSS
WV-22752	fU * SfC * SfA * SfC * SfU * SfC * SmA * SfG * SfA * SmU * SfA * SmG * SmU * SfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSSSS SSSSS SSSS
WV-22751	fU * SfC * SfA * SfC * SfU * SfC * SmA * SfG * SfA * SmU * SfA * SmGmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSSSS SSSSS SOO SSSSS S
WV-22750	fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmG * SmUfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSSSS SO SSSSS O SSSSS S
WV-22749	fU * SfC * SfA * SfC * SfU * SfC * SmAfG * SfA * SmU * SfA * SmGmU * SfU * SfG * SfA * SfA * SfG * SfC * SfC	UCACUCAGAUA GUUGAAGCC	SSSSS SOSSSSO SSSSS SS
WV-21502	fA * SfU * SfC * SfA * SfU * SfU * SfU * SmU * SfU * SmC * SfU * SmC * SfA * SfU * SfA * SfC * SfC * SfU * SfU	AUCAUUUUUU CUCAUACCUU	SSSSS SSSSS SSSS SSSS
WV-21501	fU * SfA * SfU * SfC * SfA * SfU * SfU * SmU * SfU * SmU * SfC * SmU * SfC * SfA * SfU * SfA * SfC * SfC * SfU	UAUCAUUUUU UCUCAUACCU	SSSSS SSSSS SSSS SSSS
WV-21500	fU * SfU * SfA * SfU * SfC * SfA * SfU * SmU * SfU * SmU * SfU * SmC * SfU * SfC * SfA * SfU * SfA * SfC * SfC	UUAUCAUUUUU UCUCAUACC	SSSSS SSSSS SSSS SSSS
WV-21499	fU * SfU * SfU * SfA * SfU * SfC * SfA * SfU * SmU * SfU * SmU * SfU * SmU * SfC * SfC * SfA * SfU * SfA * SfC	UUUAUCAUUUU UUCUCAUAC	SSSSS SSSSS SSSS SSSS

WV-21498	fU * SfU * SfU * SfU * SfA * SfU * SfC * SfA * SmU * SfU * SmU * SfU * SmU * SfU * SfC * SfU * SfC * SfA * SfU * SfA	UUUUAUCAUUUU UUCUCAUA	SSSSS SSSSS SSSSS SSSS
WV-21497	fC * SfU * SfU * SfU * SfU * SfA * SfU * SfC * SmA * SfU * SmU * SfU * SmU * SfU * SfU * SfC * SfU * SfC * SfA * SfU	CUUUUAUCAUUU UUUCUCAU	SSSSS SSSSS SSSSS SSSS
WV-21496	fA * SfC * SfU * SfU * SfU * SfU * SfA * SfU * SmC * SfA * SmU * SfU * SmU * SfU * SfU * SfU * SfC * SfU * SfC * SfA	ACUUUUAUCAUU UUUUCUCA	SSSSS SSSSS SSSSS SSSS
WV-21495	fA * SfA * SfC * SfU * SfU * SfU * SfU * SfA * SmU * SfC * SmA * SfU * SmU * SfU * SfU * SfU * SfU * SfC * SfU * SfC	AACUUUUAUCAU UUUUUCUC	SSSSS SSSSS SSSSS SSSS
WV-21494	fC * SfA * SfA * SfC * SfU * SfU * SfU * SfU * SmA * SfU * SmC * SfA * SmU * SfU * SfU * SfU * SfU * SfU * SfC * SfU	CAACUUUUAUCAU UUUUUCU	SSSSS SSSSS SSSSS SSSS
WV-21493	fC * SfC * SfA * SfA * SfC * SfU * SfU * SfU * SmU * SfA * SmU * SfC * SmA * SfU * SfU * SfU * SfU * SfU * SfU * SfC	CCAACUUUUAU CAUUUUUUC	SSSSS SSSSS SSSSS SSSS
WV-21492	fG * SfC * SfC * SfA * SfA * SfC * SfU * SfU * SmU * SfU * SmA * SfU * SmC * SfA * SfU * SfU * SfU * SfU * SfU * SfU	GCCAACUUUUA UCAUUUUUU	SSSSS SSSSS SSSSS SSSS
WV-21491	fU * SfG * SfC * SfC * SfA * SfA * SfC * SfU * SmU * SfU * SmU * SfA * SmU * SfC * SfA * SfU * SfU * SfU * SfU * SfU	UGCCAACUUUU AUCAUUUUU	SSSSS SSSSS SSSSS SSSS
WV-21490	fC * SfU * SfG * SfC * SfC * SfA * SfA * SfC * SmU * SfU * SmU * SfU * SmA * SfU * SfC * SfA * SfU * SfU * SfU * SfU	CUGCCAACUUUU AUCAUUUU	SSSSS SSSSS SSSSS SSSS
WV-21489	fU * SfC * SfU * SfG * SfC * SfC * SfA * SfA * SmC * SfU * SmU * SfU * SmU * SfA * SfU * SfC * SfA * SfU * SfU * SfU	UCUGCCAACUUU UAUCAUUU	SSSSS SSSSS SSSSS SSSS
WV-21488	fU * SfU * SfC * SfU * SfG * SfC * SfC * SfA * SmA * SfC * SmU * SfU * SmU * SfU * SfA * SfU * SfC * SfA * SfU * SfU	UUCUGCCAACUU UUAUCAUU	SSSSS SSSSS SSSSS SSSS
WV-21487	fC * SfU * SfU * SfC * SfU * SfG * SfC * SfC * SmA * SfA * SmC * SfU * SmU * SfU * SfU * SfA * SfU * SfC * SfA * SfU	CUUCUGCCAACU UUUAUCAU	SSSSS SSSSS SSSSS SSSS
WV-21373	fC * SfU * SfCfC * SfG * SfGfU * SfU * SmCfU * SmG * SfA * SmAfG * SfG * SfU * SfGfU * SfU * SfC	CUCCGGUUCUGA AGGUGUUC	SSOSS OSSOS SSOSS SOSS

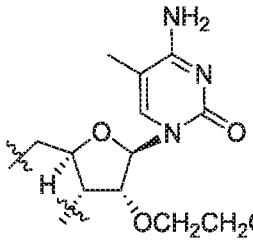
In Table A1 (including Table A1.1., Table A1.2, Table A1.3, etc.):

Spaces in Table A1 are utilized for formatting and readability, e.g., OXXXXX XXXXX XXXXX XXXX illustrates the same stereochemistry as OXXXXXXXXXXXXXXXXXXX; * S and *S both indicate phosphorothioate internucleotidic linkage wherein the linkage phosphorus has *Sp* configuration; etc.

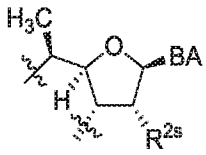
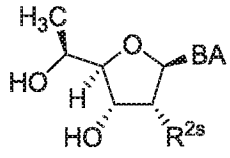
All oligonucleotides listed in Tables A1 are single-stranded. As described in the present application, they may be used as a single strand, or as a strand to form complexes with one or more other strands.

Some sequences, due to their length, are divided into multiple lines.
ID: Identification number for an oligonucleotide.
WV-8806, WV-13405, WV-13406 and WV-13407 are fully PMO (morpholino oligonucleotides; [all PMO] in Table).

Abbreviations in Tables:

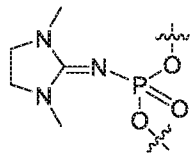
m5Ceo: 5-Methyl 2'-Methoxyethyl C ();

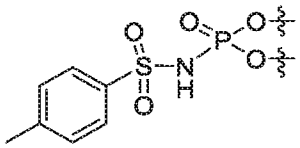
5MS: 5'-(*S*)-CH_3 modification of sugar moieties;

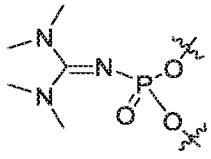
5MSfC: 2'-F-5'-(*S*)-methyl C (in oligonucleotides,  , wherein in BA is nucleobase C and R^{2s} is −F, and the 5' and 3' positions independently connect to −OH, internucleotidic linkages, linkers/linkages−H, linkers/linkages−Mod, etc. Nucleoside form is  wherein in BA is nucleobase C and R^{2s} is −F);

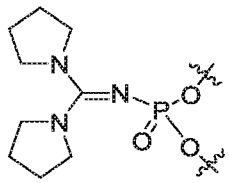
C6: C6 amino linker (L001, −NH−$(CH_2)_6$− wherein −NH− is connected to Mod (e.g., through −C(O)− in Mod) or −H, and −$(CH_2)_6$− is connected to the 5'-end (or 3'-end if indicated) of oligonucleotide chain through, *e.g.*, phosphodiester (−O−P(O)(OH)−O−. May exist as a salt form. May be illustrated in the Tables as O or PO), phosphorothioate (−O−P(O)(SH)−O−. May exist as a salt form. May be illustrated in the Tables as * if the phosphorothioate not chirally controlled; *S, S, or *S*p, if chirally controlled and has an *S*p configuration, and *R, R, or *R*p, if chirally controlled and has an *R*p configuration), or phosphorodithioate (−O−P(S)(SH)−O−. May exist as a salt form. May be illustrated in the Tables as PS2 or : or D) linkage. May also be referred to as C6 linker or C6 amine linker);

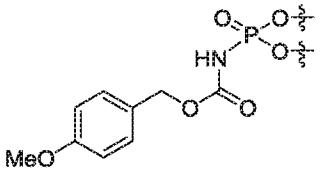
: or D: Phosphodithioate (Phosphorodithioate), represented by D or a colon (:);

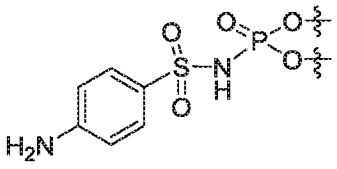
n001: non-negatively charged linkage  (which is stereorandom unless otherwise indicated (e.g., as n001R, or n001S));

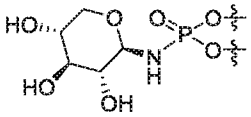
n002: non-negatively charged linkage  (which is stereorandom unless otherwise indicated (e.g., as n002R, or n002S));

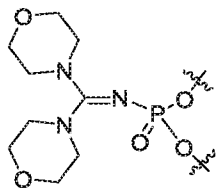
n003: non-negatively charged linkage  (which is stereorandom unless otherwise indicated (e.g., as n003R, or n003S));

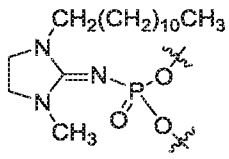
n004: non-negatively charged linkage  (which is stereorandom unless otherwise indicated (e.g., as n004R, or n004S));

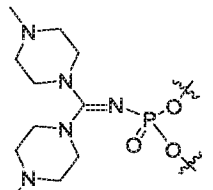
n005: non-negatively charged linkage  (which is stereorandom unless otherwise indicated (e.g., as n005R, or n005S));

n006: non-negatively charged linkage  (which is stereorandom unless otherwise indicated (e.g., as n006R, or n006S));

n007: non-negatively charged linkage  (which is stereorandom at linkage phosphorus unless otherwise indicated (e.g., as n007R, or n007S));

n008: non-negatively charged linkage  (which is stereorandom unless otherwise indicated (e.g., as n008R, or n008S));

n009: non-negatively charged linkage  (which is stereorandom unless otherwise indicated (e.g., as n009R, or n009S));

n010: non-negatively charged linkage  (which is stereorandom unless otherwise indicated (e.g., as n010R, or n010S));

n001R: n001 being chirally controlled and having the Rp configuration;

n002R: n002 being chirally controlled and having the Rp configuration;

n003R: n003 being chirally controlled and having the Rp configuration;

n004R: n004 being chirally controlled and having the Rp configuration;

n005R: n005 being chirally controlled and having the Rp configuration;

n006R: n006 being chirally controlled and having the Rp configuration;

n007R: n007 being chirally controlled and having the Rp configuration;

n008R: n008 being chirally controlled and having the Rp configuration;

n009R: n009 being chirally controlled and having the Rp configuration;

n010R: n010 being chirally controlled and having the Rp configuration;

n001S: n001 being chirally controlled and having the Sp configuration;

n002S: n002 being chirally controlled and having the Sp configuration;

n003S: n003 being chirally controlled and having the Sp configuration;

n004S: n004 being chirally controlled and having the Sp configuration;

n005S: n005 being chirally controlled and having the Sp configuration;

n006S: n006 being chirally controlled and having the Sp configuration;

n007S: n007 being chirally controlled and having the Sp configuration;

n008S: n008 being chirally controlled and having the Sp configuration;

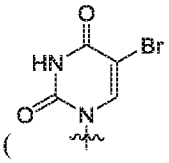
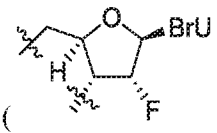
n009S: n009 being chirally controlled and having the Sp configuration;

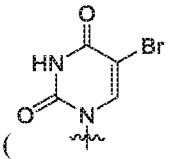
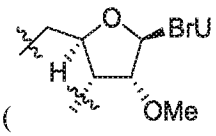
n010S: n010 being chirally controlled and having the Sp configuration;

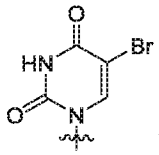
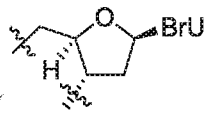
nO, nX: in Linkage / Stereochemistry, nO or nX indicates a stereorandom n001;

nR: in Linkage / Stereochemistry, nR indicates a linkage, *e.g.*, n001, n002, n003, n004, n005, n006, n007, n008, n009, *etc.*, being chirally controlled and having the Rp configuration (*e.g.*, for n001, n001R in Description);

nS: in Linkage / Stereochemistry, nS indicates a linkage, *e.g.*, n001, n002, n003, n004, n005, n006, n007, n008, n009, *etc.*, being chirally controlled and having the Sp configuration (*e.g.*, for n001, n001R in Description);

BrfU: a nucleoside unit wherein the nucleobase is BrU () and wherein the sugar has a 2'-F (f) modification ();

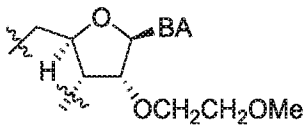
BrmU: a nucleoside unit wherein the nucleobase is BrU () and wherein the sugar has a 2'-OMe (m) modification ();

BrdU: a nucleoside unit wherein the nucleobase is BrU () and wherein the sugar is 2-deoxyribose (as widely found in natural DNA; 2'-deoxy (d)) ();

L004: linker having the structure of $-NH(CH_2)_4CH(CH_2OH)CH_2-$, wherein $-NH-$ is connected to Mod (e.g., through $-C(O)-$ in Mod) or $-H$, and the $-CH_2-$ connecting site is connected to a linkage, *e.g.*, phosphodiester ($-O-P(O)(OH)-O-$. May exist as a salt form. May be illustrated in the Tables as O or PO), phosphorothioate ($-O-P(O)(SH)-O-$. May exist as a salt form. May be illustrated in the Tables as * if the phosphorothioate not chirally controlled; *S, S, or *Sp*, if chirally controlled and has an *Sp* configuration, and *R, R, or *Rp*, if chirally controlled and has an *Rp* configuration), or phosphorodithioate ($-O-P(S)(SH)-O-$. May exist as a salt form. May be illustrated in the Tables as PS2 or : or D) linkage, at the 5'- or 3'-end of an oligonucleotide chain as indicated. For example, an asterisk immediately preceding a L004 (e.g., *L004) indicates that the linkage is a phosphorothioate linkage, and the absence of the indication of any other linkage immediately preceding L004 indicates that the linkage is a phosphodiester linkage. For example, in WV-9858, which terminates in fUL004, the linker L004 is connected (via the $-CH_2-$ site) to the phosphodiester linkage at the 3' position at the 3'-terminal sugar (which is 2'-F and connected to the nucleobase U), and the L004 linker is connected via $-NH-$ to $-H$; similarly, in WV-10886, WV-10887, and WV-10888, the L004 linker is connected (via the $-CH_2-$ site) to the phosphodiester linkage at the 3' position of the 3'-terminal sugar, and the L004 is connected via

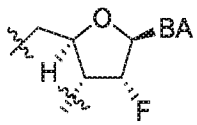
–NH– to Mod012 (WV-10886), Mod085 (WV-10887) or Mod086 (WV-10888);
L005: linker having the structure of –NH(CH_2)$_5$C(O)N(CH_2CH_2OH)CH_2CH_2–, wherein –NH– is connected to Mod (e.g., through –C(O)– in Mod) or –H, and the –CH_2– connecting site is connected to a linkage, *e.g.*, phosphodiester (–O–P(O)(OH)–O–. May exist as a salt form. May be illustrated in the Tables as O or PO), phosphorothioate (–O–P(O)(SH)–O–. May exist as a salt form. May be illustrated in the Tables as * if the phosphorothioate not chirally controlled; *S, S, or *Sp*, if chirally controlled and has an *Sp* configuration, and *R, R, or *Rp*, if chirally controlled and has an *Rp* configuration), or phosphorodithioate (–O–P(S)(SH)–O–. May exist as a salt form. May be illustrated in the Tables as PS2 or : or D) linkage, at the 5'- or 3'-end of an oligonucleotide chain as indicated. For example, an asterisk immediately preceding a L005 (e.g., *L005) indicates that the linkage is a phosphorothioate linkage, and the absence of the indication of any other linkage immediately preceding L005 indicates that the linkage is a phosphodiester linkage. For example, in WV-12571, L005 is connected to –H (no Mod following L005; via the –NH– site) and the phosphodiester linkage at the 3' position of the 3'-terminal sugar (via the –CH_2– site); and in WV-12572, L005 is connected to Mod020 (via the –NH– site) and the phosphodiester linkage at the 3' position of the 3'-terminal sugar (via the –CH_2– site);
L001L005: linker having the structure of –NH(CH_2)$_5$C(O)N(CH_2CH_2–O–P(O)(OH)–O–(CH_2)$_6$NH–)CH_2CH_2–, wherein each of the two –NH– is independently connected to Mod (e.g., through –C(O)–) or –H, and the –CH_2– connecting site is connected to a linkage, *e.g.*, phosphodiester (–O–P(O)(OH)–O–. May exist as a salt form. May be illustrated in the Tables as O or PO), phosphorothioate (–O–P(O)(SH)–O–. May exist as a salt form. May be illustrated in the Tables as * if the phosphorothioate not chirally controlled; *S, S, or *Sp*, if chirally controlled and has an *Sp* configuration, and *R, R, or *Rp*, if chirally controlled and has an *Rp* configuration), or phosphorodithioate (–O–P(S)(SH)–O–. May exist as a salt form. May be illustrated in the Tables as PS2 or : or D) linkage at the 5'- or 3'-end of an oligonucleotide chain as indicated.

eo: 2'-MOE (2'–$OCH_2CH_2OCH_3$) modification on the preceding nucleoside (e.g., Aeo (

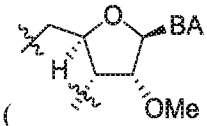


, wherein BA is nucleobase A));

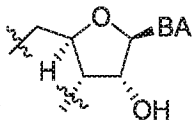
F, f: 2'-F modification on the following nucleoside (e.g., fA (



, wherein BA is nucleobase A));

m: 2'-OMe modification on the following nucleoside (e.g., mA (

, wherein BA is nucleobase A));

r: 2'-OH on the following nucleoside (e.g., rA (

, wherein BA is nucleobase A, as existed in natural RNA));

L012: internucleotidic linkage having the structure of −O−P(O)[O(CH_2)$_2$O(CH_2)$_2$O(CH_2)$_2$OH]−O−. May be illustrated as OO in the Tables;

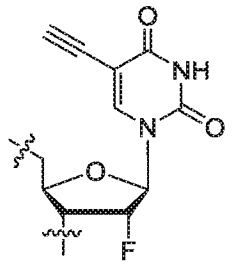
*, PS: Phosphorothioate;

PS2, : D: phosphorodithioate (*e.g.*, WV-3078, wherein a colon (:) indicates a phosphorodithioate);

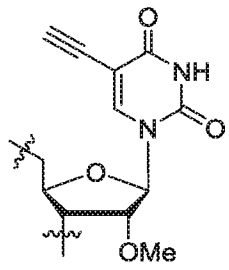
*R, R, Rp: Phosphorothioate in *Rp* conformation;

*S, S, Sp: Phosphorothioate in *Sp* conformation;

X: Phosphorothioate stereorandom;

Acet5fU: 

;

Acet5mU: 

NA: Not Applicable;

O, PO: phosphodiester (phosphate). When no internucleotidic linkage is specified between two nucleoside units, the internucleotidic linkage is a phosphodiester linkage (natural phosphate linkage). When used to indicate linkage between Mod and a linker, e.g., L001, O may indicate −C(O)− (connecting Mod and L001, for example:

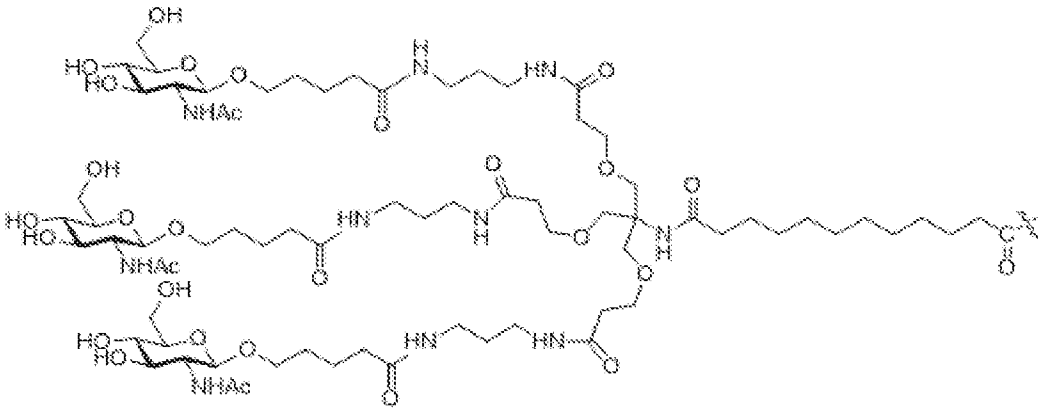
Mod013L001fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU (Description), OOSSSSSSOSOSSOOSSSSSS (Linkage/Stereochemistry). Note the second O in

OOSSSSSSOSOSSOOSSSSSS (Linkage/Stereochemistry) represents phosphodiester linkage connecting L001 and the 5'−O− of the 5'-terminal sugar of the oligonucleotide chain (see illustrations below. Alternatively, the 5'−O− may be considered part of the phosphodiester linkage (or another type of linkage such as a phosphorothioate linkage), in which case the phosphodiester linkage (or another type of linkage such as phosphorothioate linkage) is connected to the 5' position of the 5'-terminal sugar of the oligonucleotide chain). In some instances, "O" for −C(O)− (connecting Mod and L001) is omitted (e.g., for

Mod013L001fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU, "Linkage/Stereochemistry" OSSSSSSOSOSSOOSSSSSS);

Various Mods:

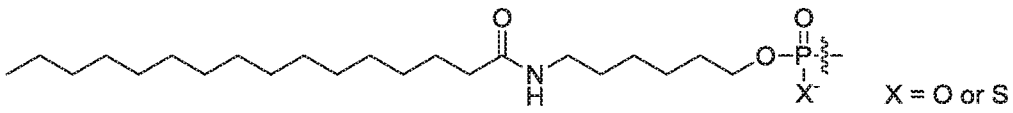
Mod001 (with −C(O)− connecting to, e.g., −NH− of a linker such as L001):



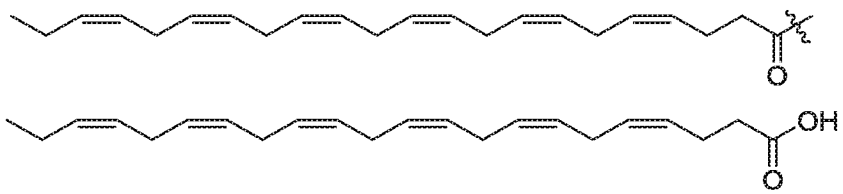
Lauric (in Mod013), Myristic (in Mod014), Palmitic (in Mod005), Stearic (in Mod015), Oleic (in Mod016), Linoleic (in Mod017), alpha-Linoleinc (in Mod018), gamma-Linolenic (in Mod019), DHA (in Mod006), Turbinaric (in Mod020), Dilinoleic (in Mod021), TriGlcNAc (in Mod024), TrialphaMannose (in Mod026), MonoSulfonamide (in Mod 027), TriSulfonamide (in Mod029), Lauric (in Mod030), Myristic (in Mod031), Palmitic (in Mod032), and Stearic (in Mod033): Lauric acid (for Mod013), Myristic acid (for Mod014), Palmitic acid (for Mod005), Stearic acid (for Mod015), Oleic acid (for Mod016), Linoleic acid (for Mod017), alpha-Linolenic acid (for Mod018), gamma-Linolenic acid (for Mod019), docosahexaenoic acid (for Mod006), Turbinaric acid (for Mod020), alcohol for Dilinoleyl (for Mod021), acid for TriGlcNAc (for Mod024), acid for TrialphaMannose (for Mod026), acid for MonoSulfonamide (for Mod 027), acid for TriSulfonamide (for Mod029), Lauryl alcohol (for Mod030), Myristyl alcohol (for Mod031), Palmityl alcohol (for Mod032), and Stearyl alcohol (for Mod033), respectively, conjugated to oligonucleotide chains, e.g., through an amide group, a linker (e.g., C6 amino linker, (L001)), and/or a linkage group (e.g., phosphodiester linkage (PO), phosphorothioate linkage (PS), etc.): e.g., Mod013 (Lauric acid with C6 amino linker and PO or PS), Mod014 (Myristic acid with C6 amino linker and PO or PS), Mod005 (Palmitic acid with C6 amino linker and PO or PS), Mod015

(Stearic acid with C6 amino linker and PO or PS), Mod016 (Oleic acid with C6 amino linker and PO or PS), Mod017 (Linoleic acid with C6 amino linker and PO or PS), Mod018 (alpha-Linolenic acid with C6 amino linker and PO or PS), Mod019 (gamma-Linolenic acid with C6 amino linker and PO or PS), Mod006 (DHA with C6 amino linker and PO or PS), Mod020 (Turbinaric acid with C6 amino linker and PO or PS), Mod021 (alcohol (see below) with PO or PS), Mod024 (acid (see below) with C6 amino linker and PO or PS), Mod026 (acid (see below) with C6 amino linker and PO or PS), Mod027 (acid (see below) with C6 amino linker and PO or PS), Mod029 (acid (see below) with C6 amino linker and PO or PS), Mod030 (Lauryl alcohol with PO or PS), Mod031 (Myristyl alcohol with PO or PS), Mod032 (Palmityl alcohol with PO or PS), and Mod033 (Stearyl alcohol with PO or PS), with PO or PS for each oligonucleotide indicated in Table A1. For example, WV-3557 Steary alcohol conjugated to oligonucleotide chain of WV-3473 via PS:
Mod033*fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU (Description), XSSSSSSOSOSSOOSSSSSS (Stereochemistry); and
WV-4106 Stearic acid conjugated to oligonucleotide chain of WV-3473 via amide group, C6, and PS:
Mod015L001*fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU (Description), XSSSSSSOSOSSOOSSSSSS (Stereochemistry). Certain moieties for conjugation, and example reagents (many of which were previously known and are commercially available or can be readily prepared using known technologies in accordance with the present disclosure, *e.g.*, Lauric acid (for Mod013), Myristic acid (for Mod014), Palmitic acid (for Mod005), Stearic acid (for Mod015), Oleic acid (for Mod016), Linoleic acid (for Mod017), alpha-Linolenic acid (for Mod018), gamma-Linolenic acid (for Mod019), docosahexaenoic acid (for Mod006), Turbinaric acid (for Mod020), alcohol for Dilinoleyl (for Mod021), Lauryl alcohol (for Mod030), Myristyl alcohol (for Mod031), Palmityl alcohol (for Mod032), Stearyl alcohol (for Mod033), *etc.*) are listed below. Certain example moieties (*e.g.*, lipid moieties, targeting moiety, *etc.*) and/or example preparation reagents (*e.g.*, acids, alcohols, *etc.*) for conjugation to oligonucleotide chains include the below with a non-limiting example of a linker:
Mod005 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001) and Palmitic acid:

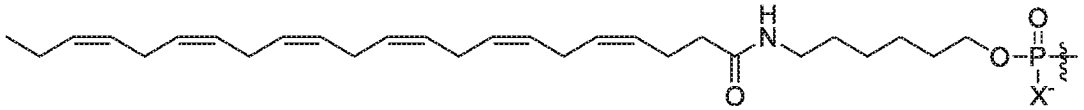
Mod005L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):



Mod006 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001) and DHA:

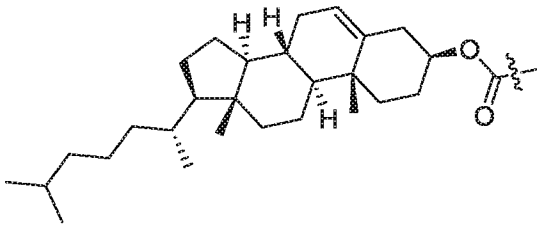


Mod006L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):

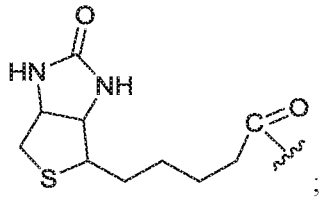


X = O or S

Mod009 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



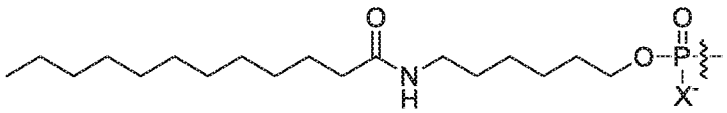
Mod012 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



;

Mod013 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001) and Lauric acid:

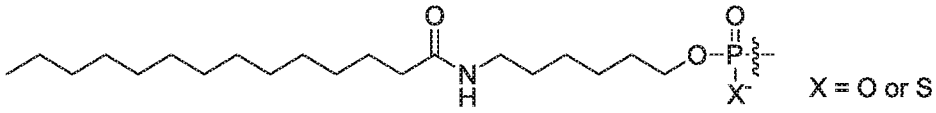
Mod013L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):



X = O or S

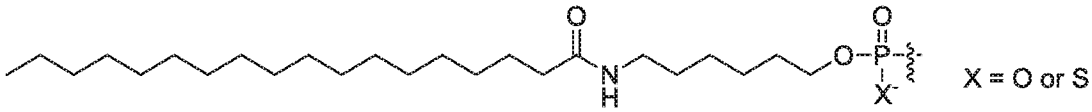
Mod014 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001) and Myristic acid:

Mod014L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):

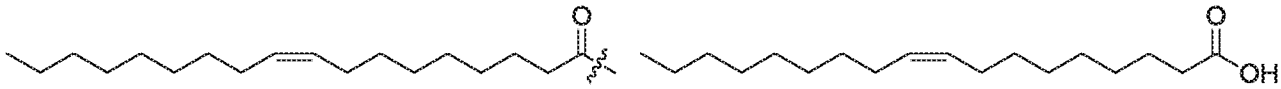


Mod015 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001) and Stearic acid:

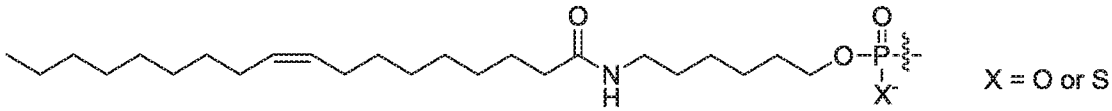
Mod015L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):



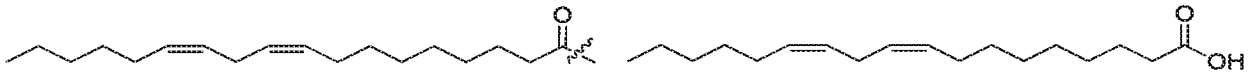
Mod016 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001) and Oleic acid:



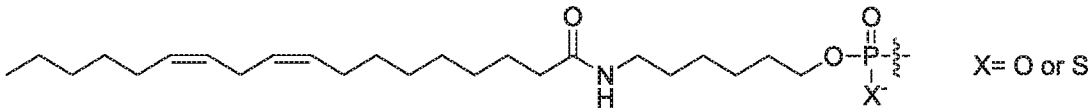
Mod016L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):



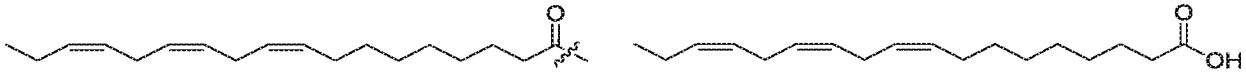
Mod017 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001) and Linoleic acid:



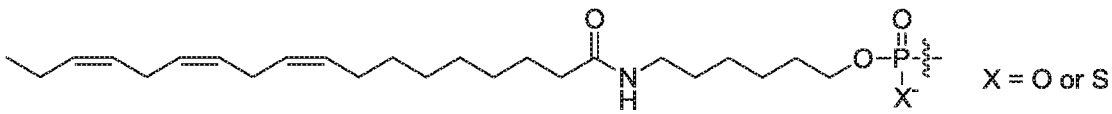
Mod 017L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):



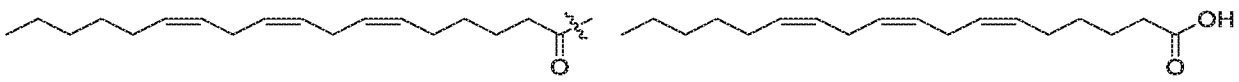
Mod018 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001) and alpha-Linolenic acid:



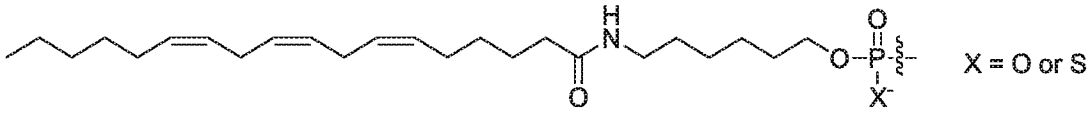
Mod018L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):



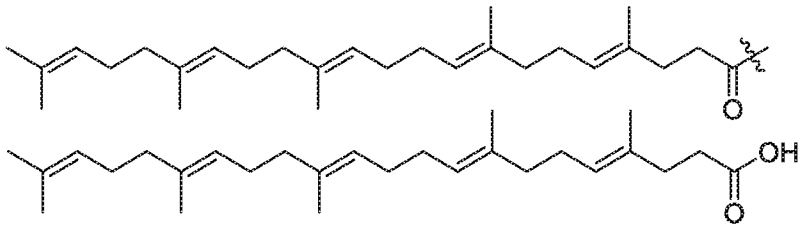
Mod019 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001) and gamma-Linolenic acid:



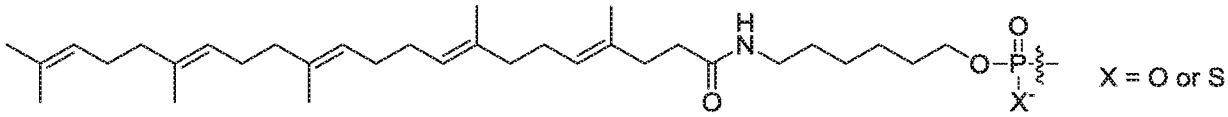
Mod019L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):



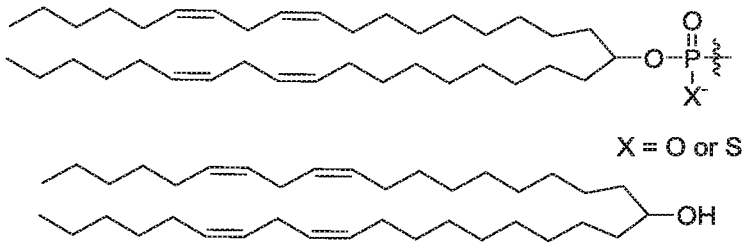
Mod020 (with −C(O)− connecting to, e.g., −NH− of a linker such as L001) and Turbinaric acid:



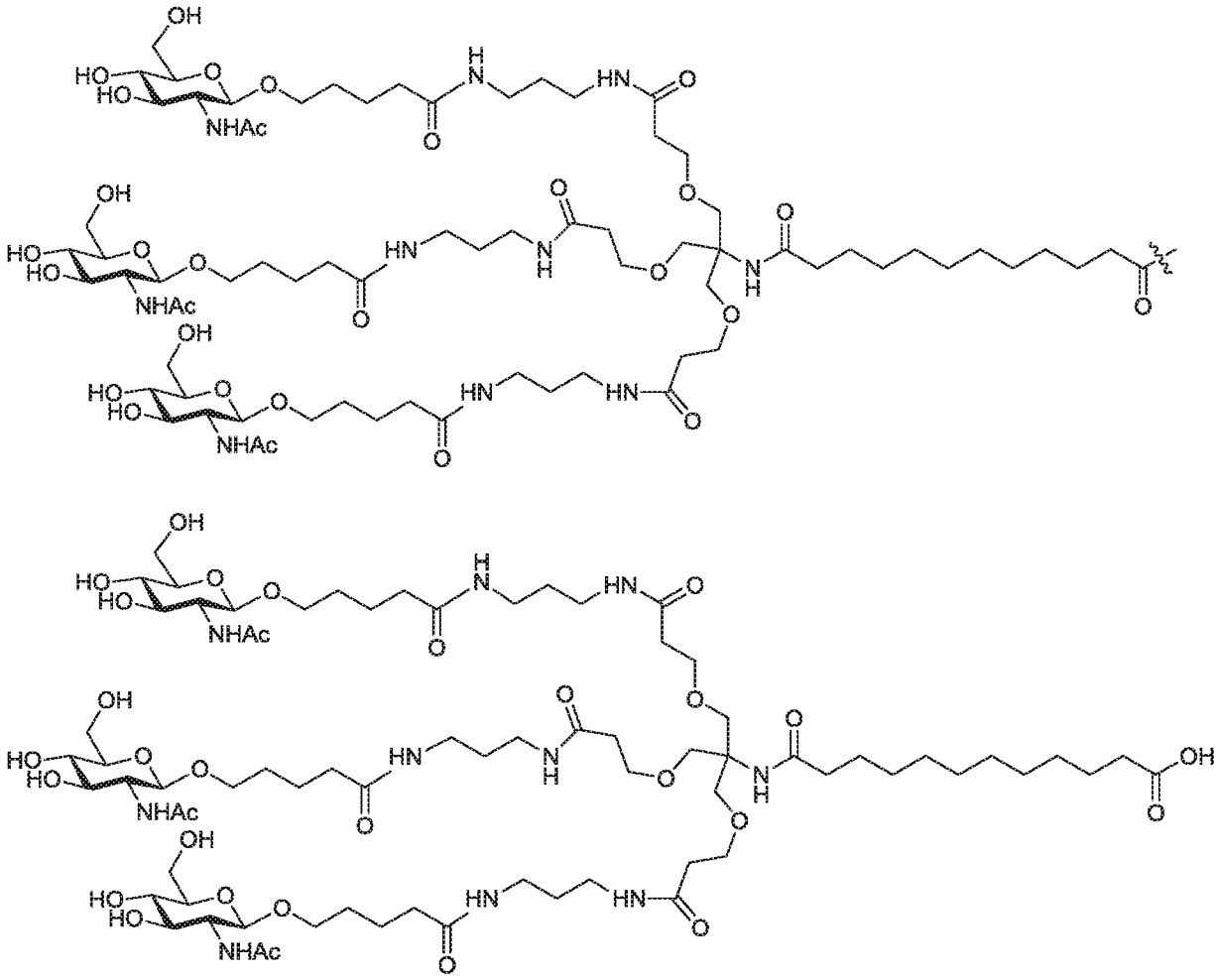
Mod020L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):



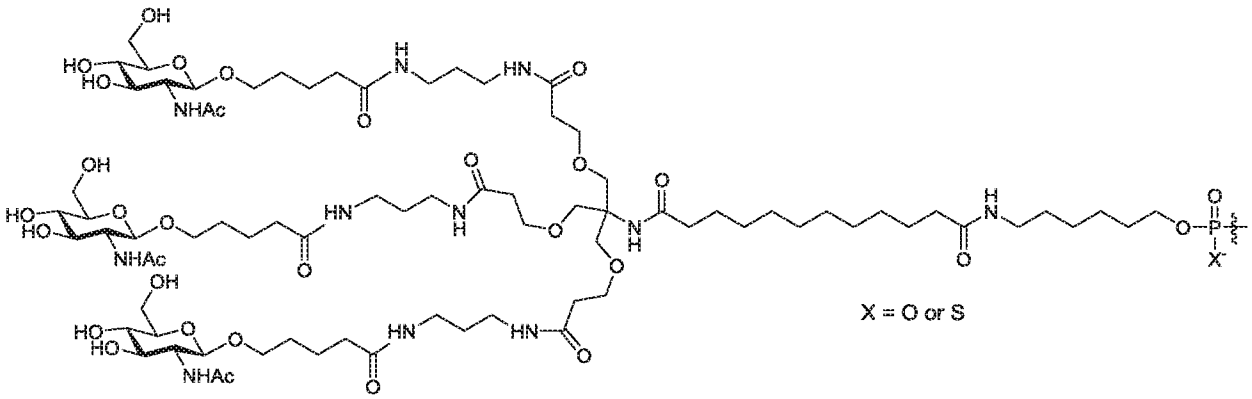
Mod021 (with PO or PS connecting to 5'-O- of an oligonucleotide chain) and alcohol:



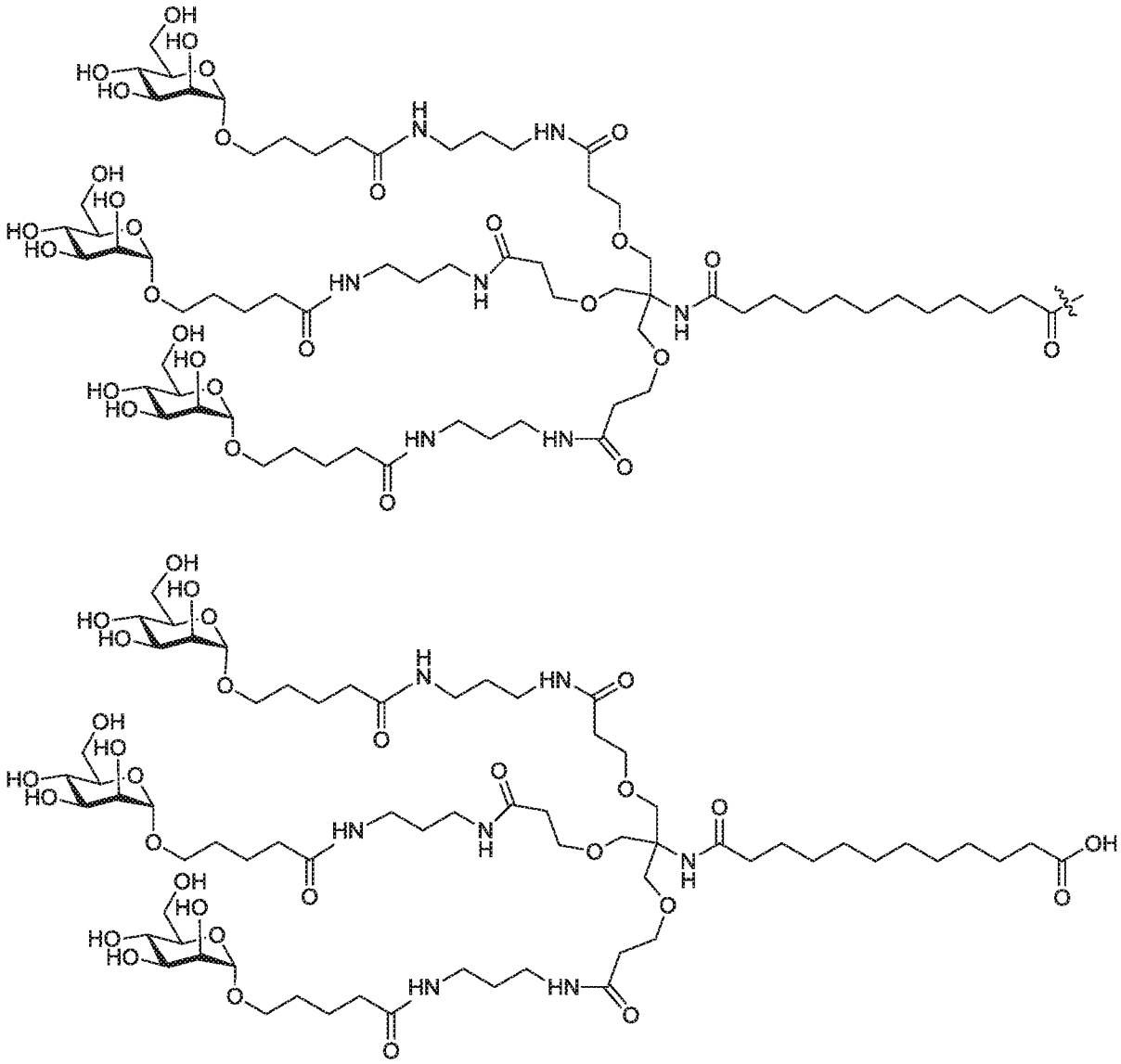
Mod024 (with −C(O)− connecting to, e.g., −NH− of a linker such as L001) and acid:



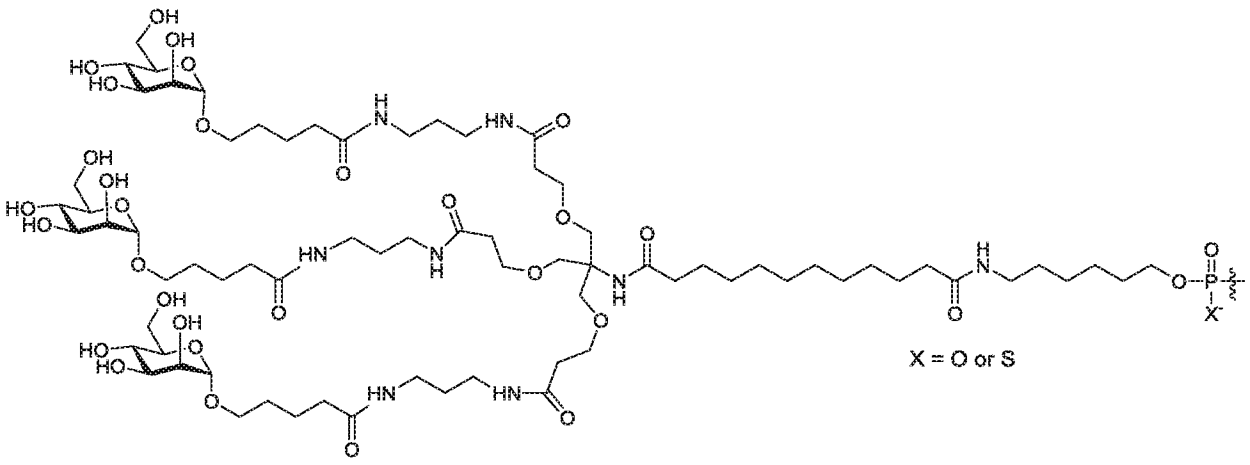
Mod024L001 (with PO or PS connecting to 5`-O- of an oligonucleotide chain):



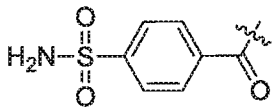
Mod026 (with −C(O)− connecting to, e.g., −NH− of a linker such as L001) and acid:

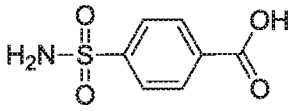


Mod026L001 (with PO or PS connecting to 5`-O- of an oligonucleotide chain):

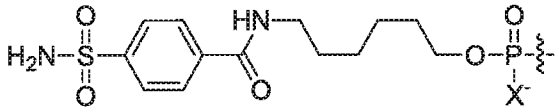


Mod027 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001) and acid:

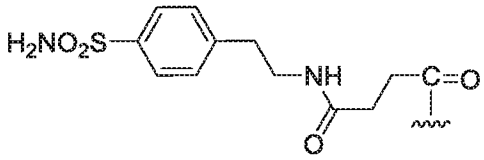




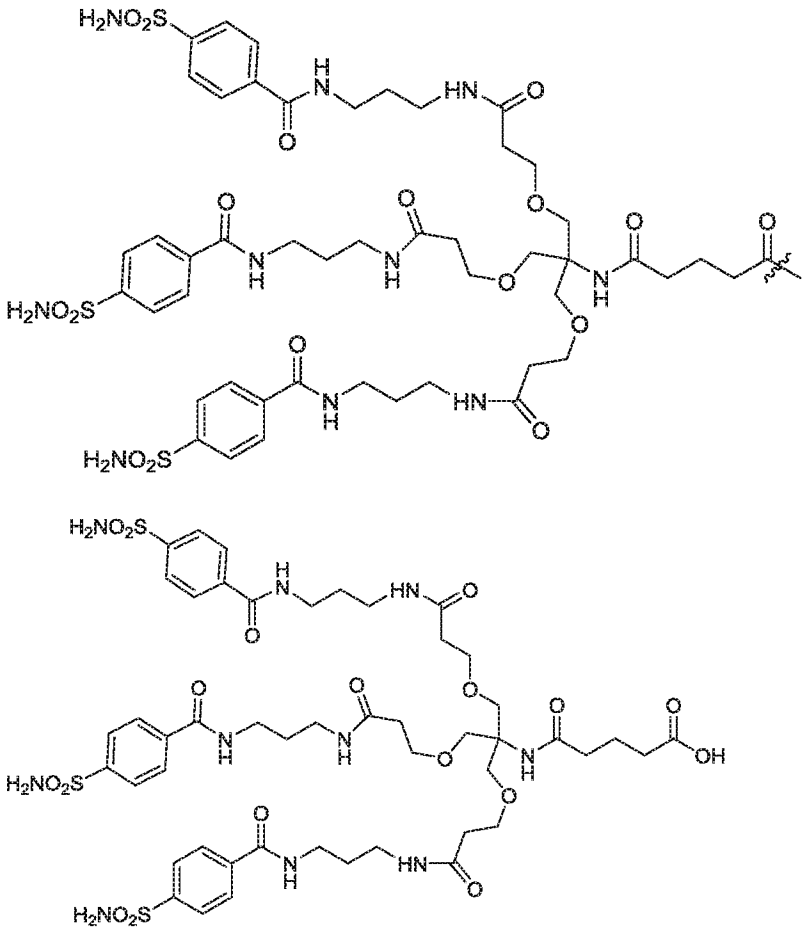
Mod027L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):



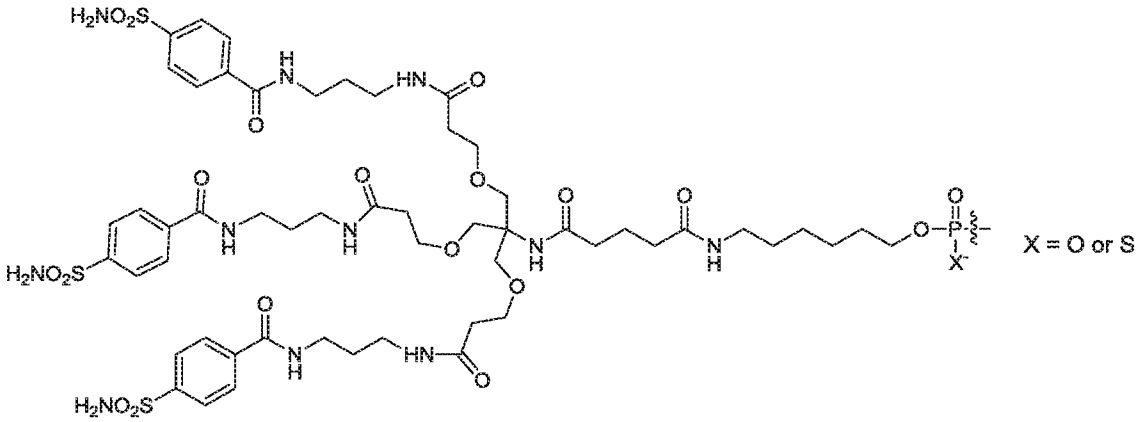
Mod028 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



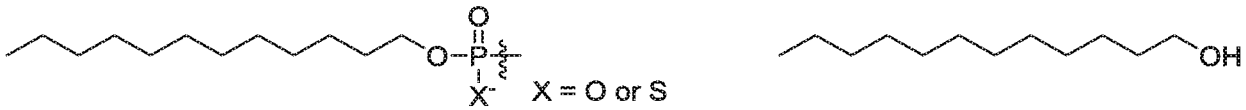
Mod029 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001) and acid:



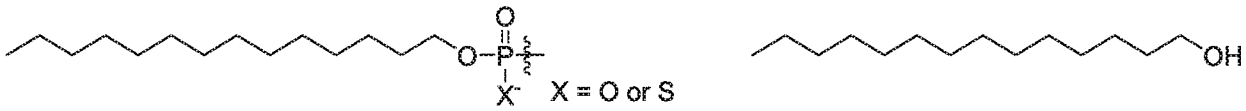
Mod029L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):



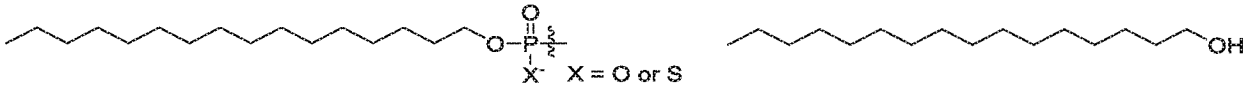
Mod030 (with PO or PS connecting to 5'-O- of an oligonucleotide chain) and Lauryl alcohol:



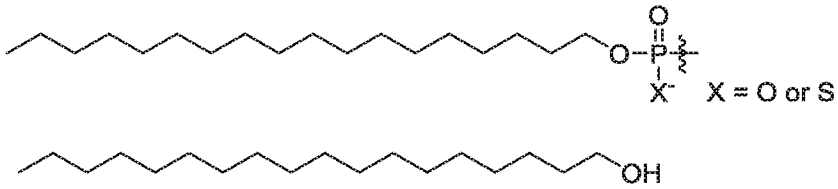
Mod031 (with PO or PS connecting to 5'-O- of an oligonucleotide chain) and Myristyl alcohol:



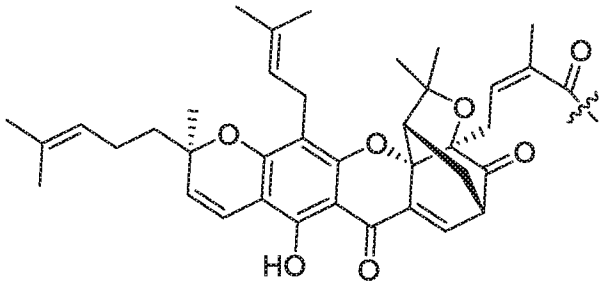
Mod032 (with PO or PS connecting to 5'-O- of an oligonucleotide chain) and Palmityl alcohol:



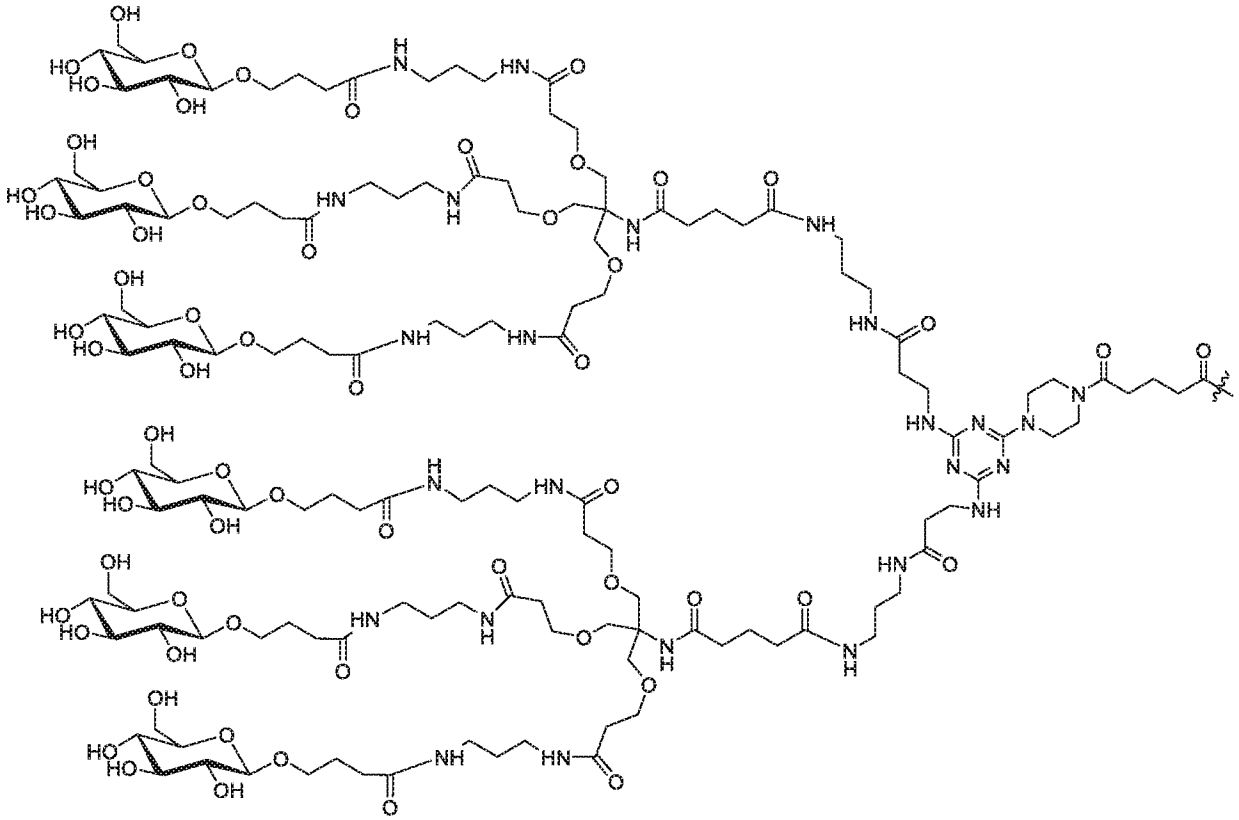
Mod033 (with PO or PS connecting to 5'-O- of an oligonucleotide chain) and Stearyl alcohol:



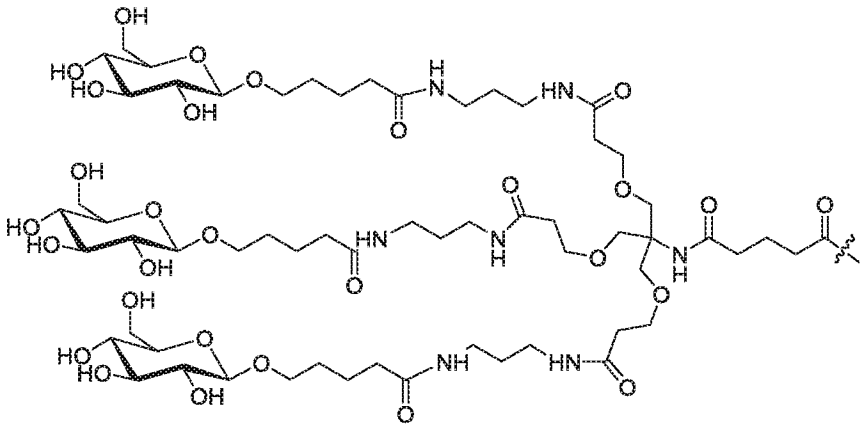
Mod053 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



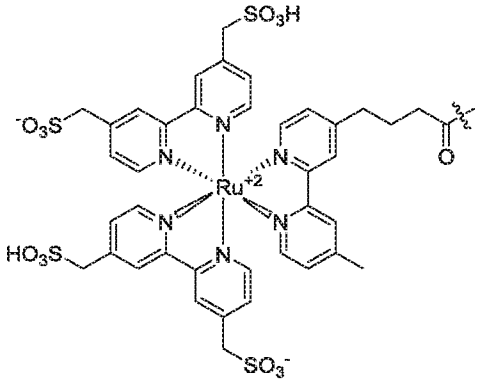
Mod070 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



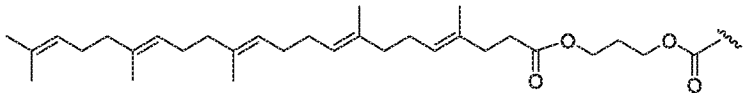
Mod071 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



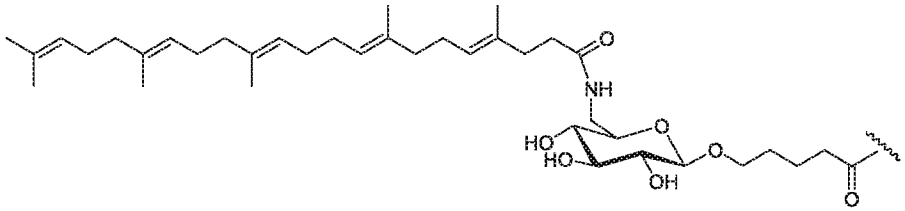
Mod086 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



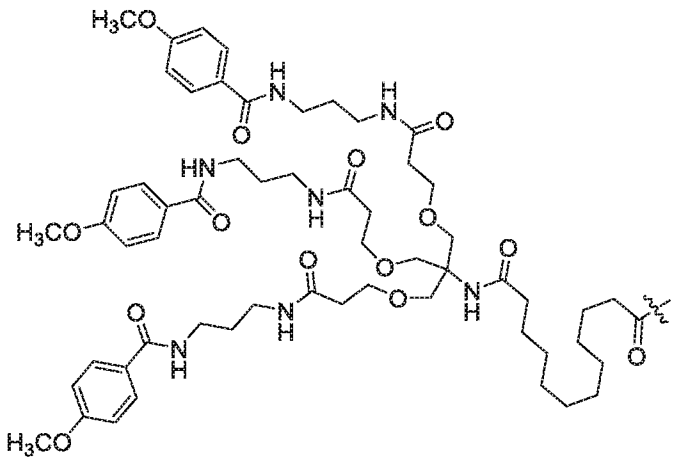
Mod092 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



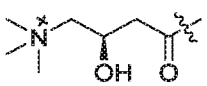
Mod093 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



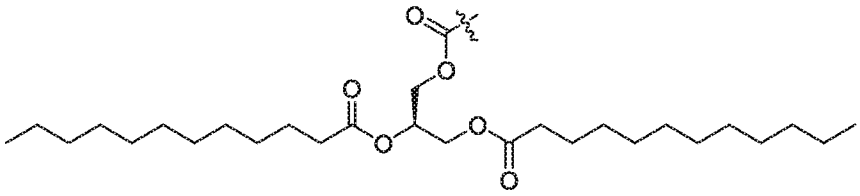
Mod007 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



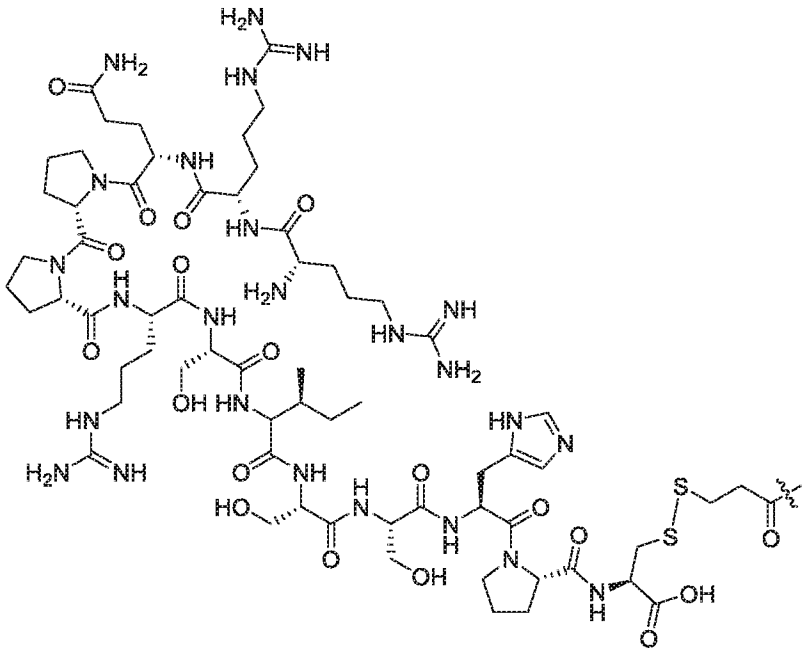
Mod050 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



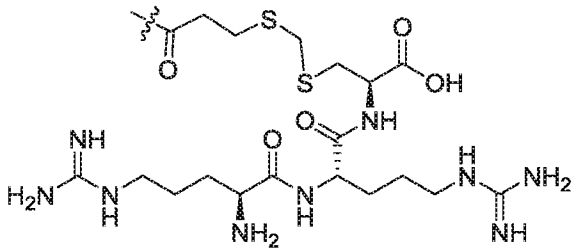
Mod043 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



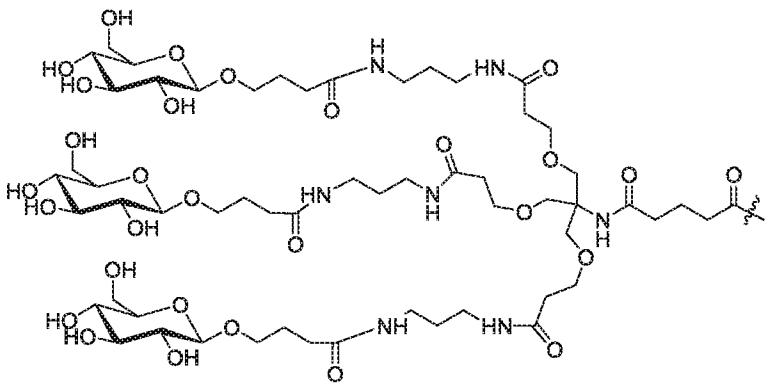
Mod057 (with −C(O)− connecting to, e.g., −NH− of a linker such as L001):



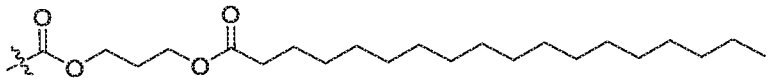
Mod058 (with −C(O)− connecting to, e.g., −NH− of a linker such as L001):



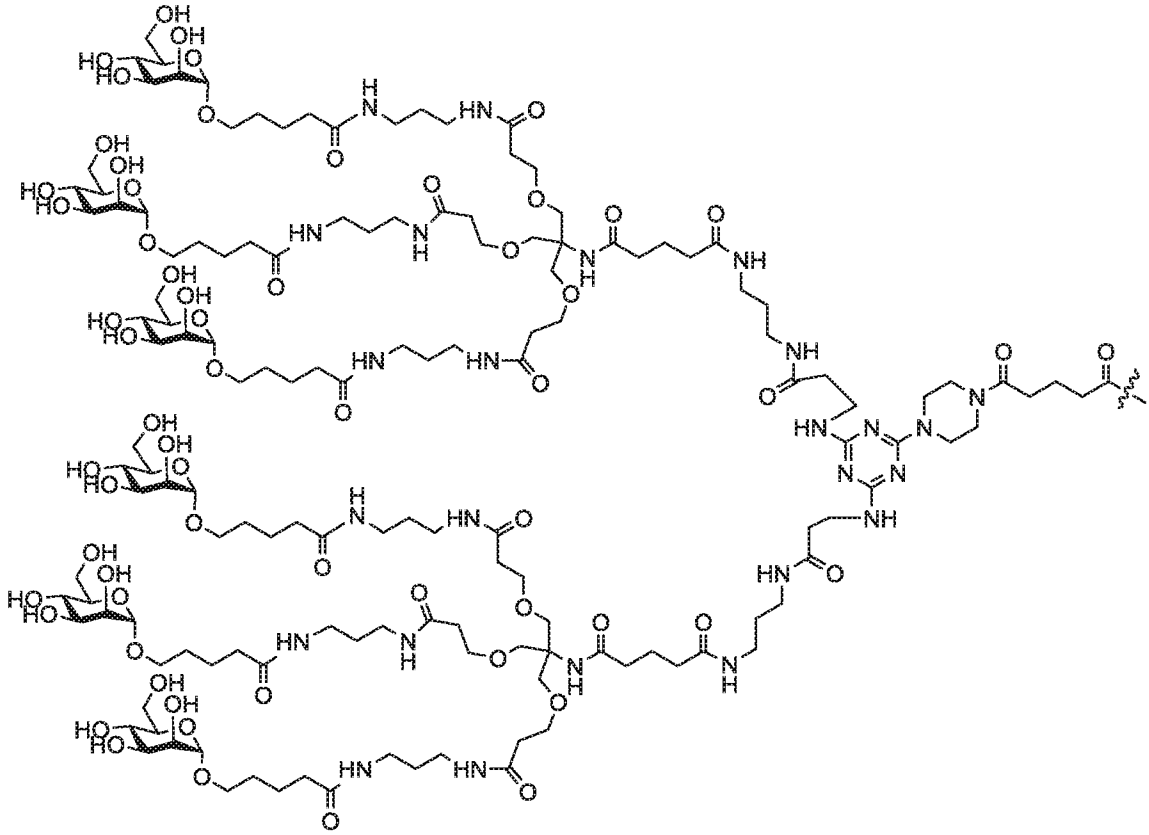
Mod059 (with −C(O)− connecting to, e.g., −NH− of a linker such as L001):



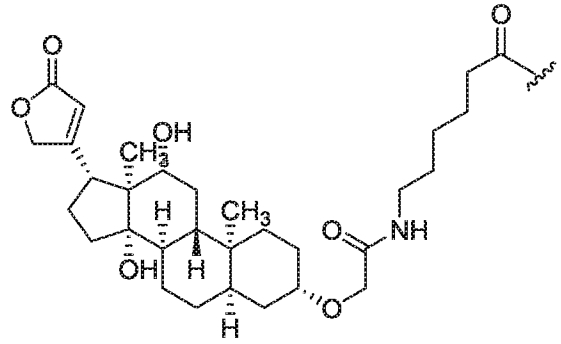
Mod066 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



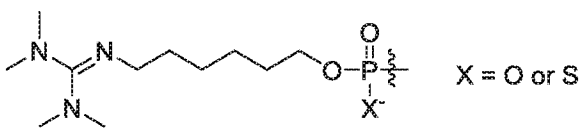
Mod074 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



Mod085 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):

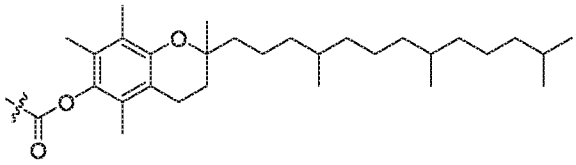


Mod091L001 (with PO or PS connecting to 5`-O- of an oligonucleotide chain):

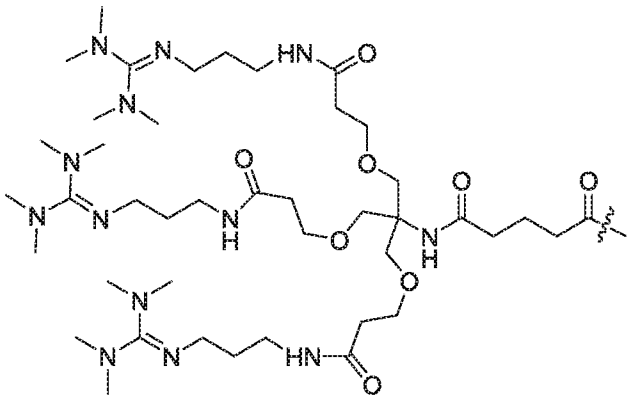


(e.g., in WV-11114, X = O (PO) and connecting to 5'-O- of the oligonucleotide chain)

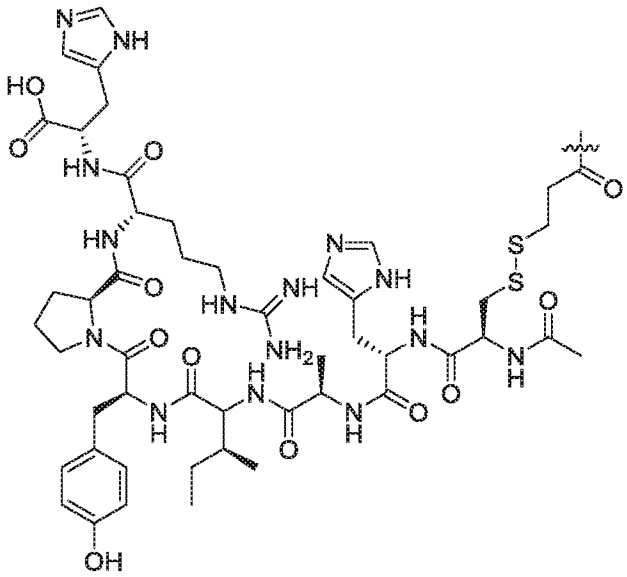
Mod097 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



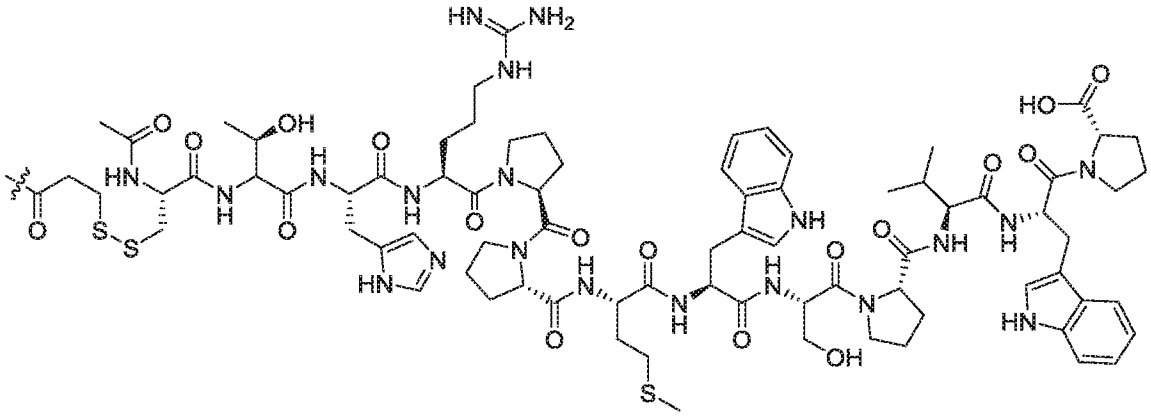
Mod098 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



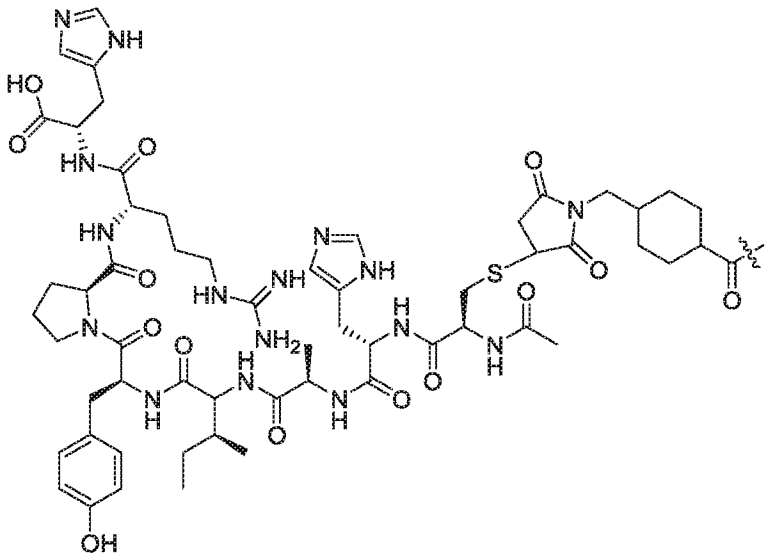
Mod099 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



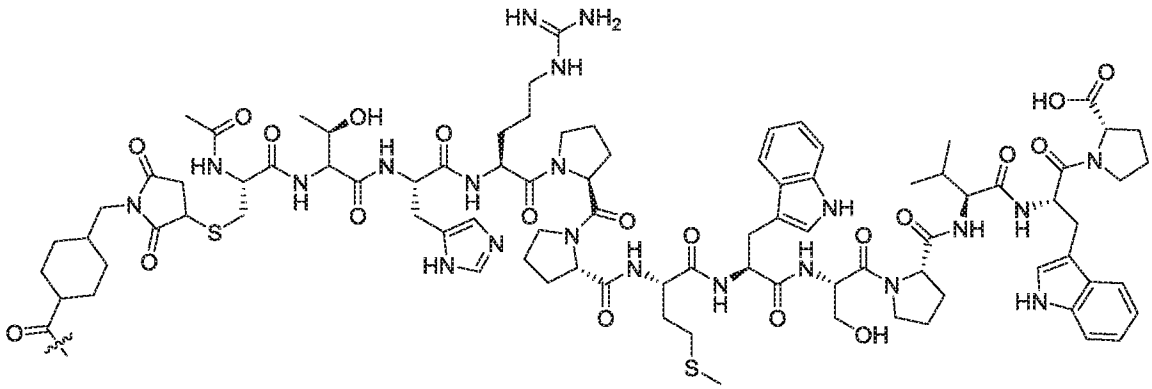
Mod100 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



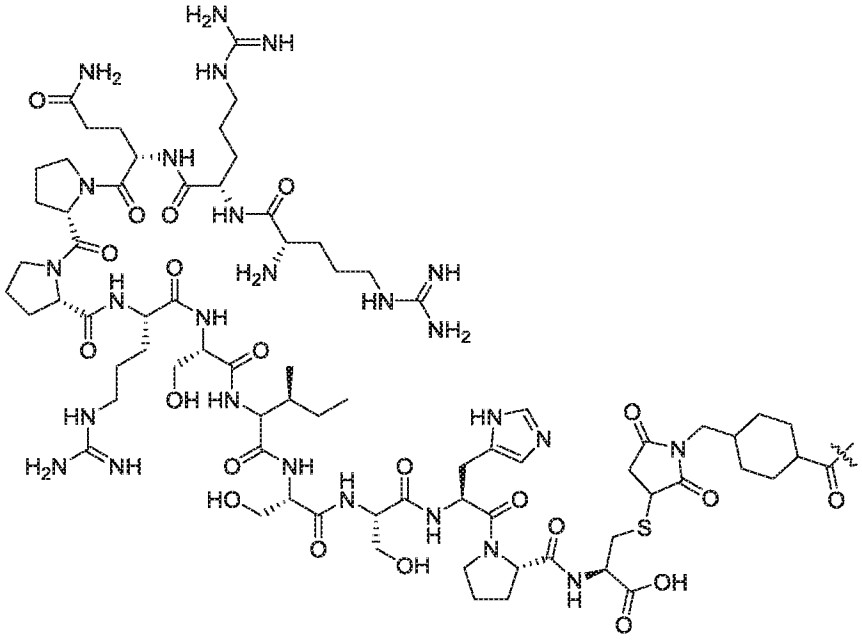
Mod102 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



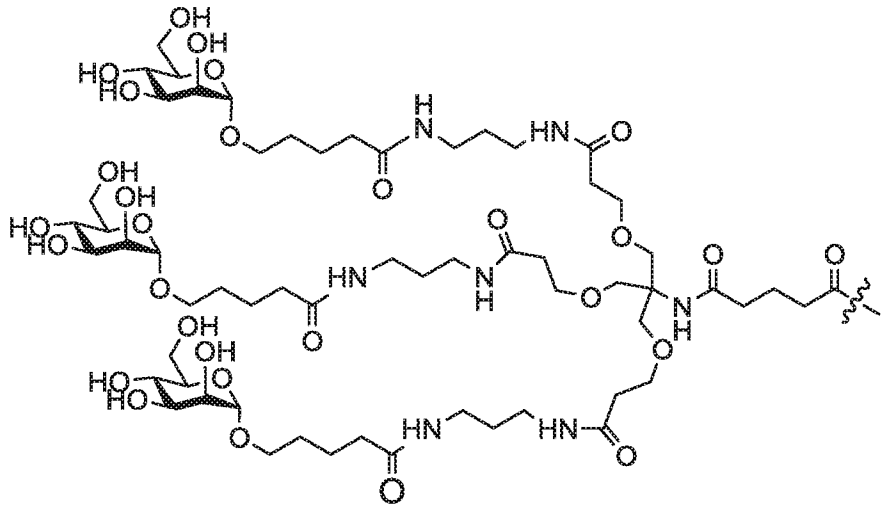
Mod103 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



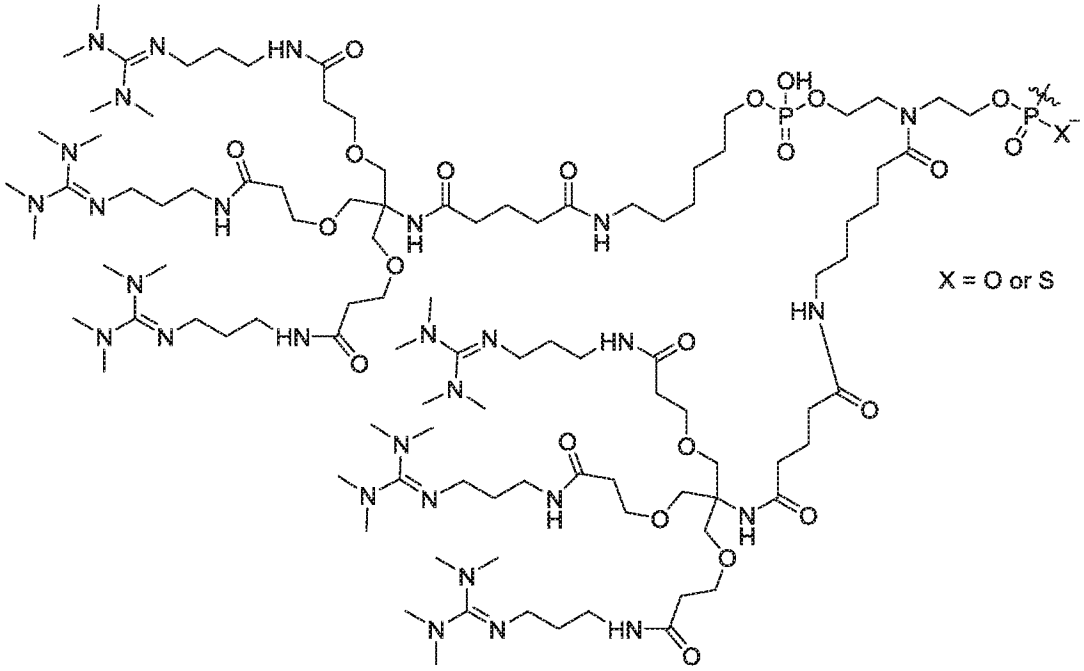
Mod104 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



Mod105 (with −C(O)− connecting to, e.g., −NH− of a linker such as L001):

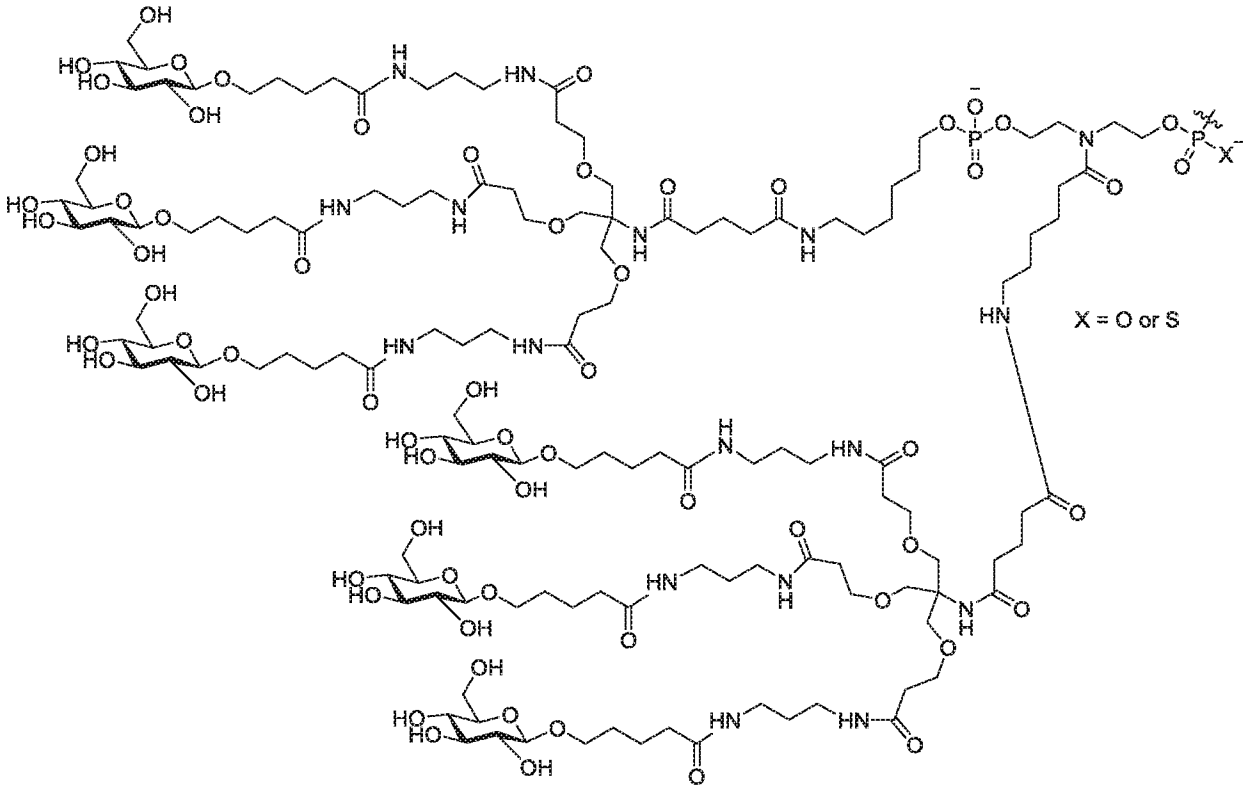


Mod106 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):



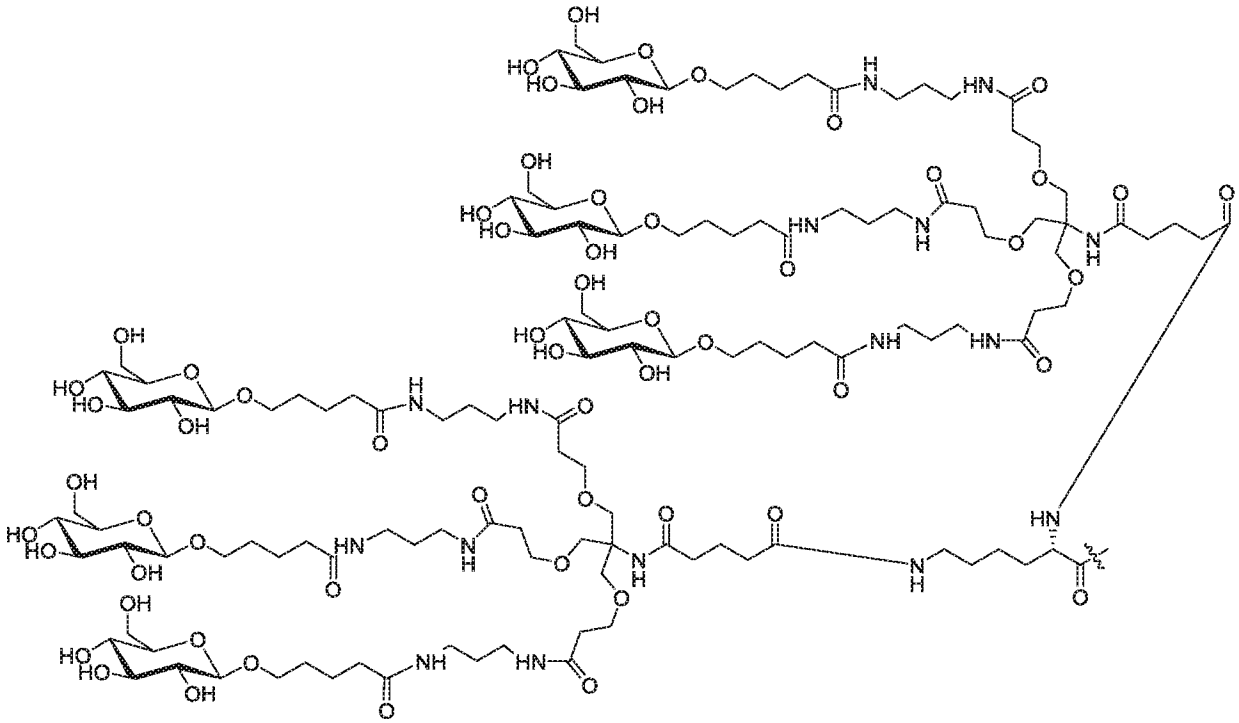
(e.g., in WV-15844, X = O (PO) and connecting to 5'-O- of the oligonucleotide chain)

Mod107 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):

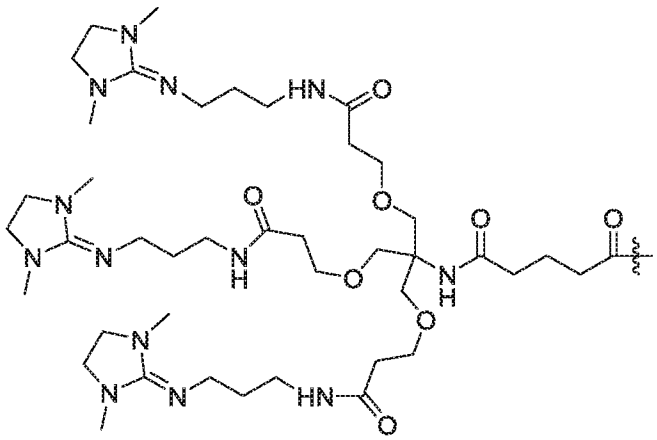


(e.g., in WV-15845 and WV-16011, X = O (PO) and connecting to 5'-O- of the oligonucleotide chain)

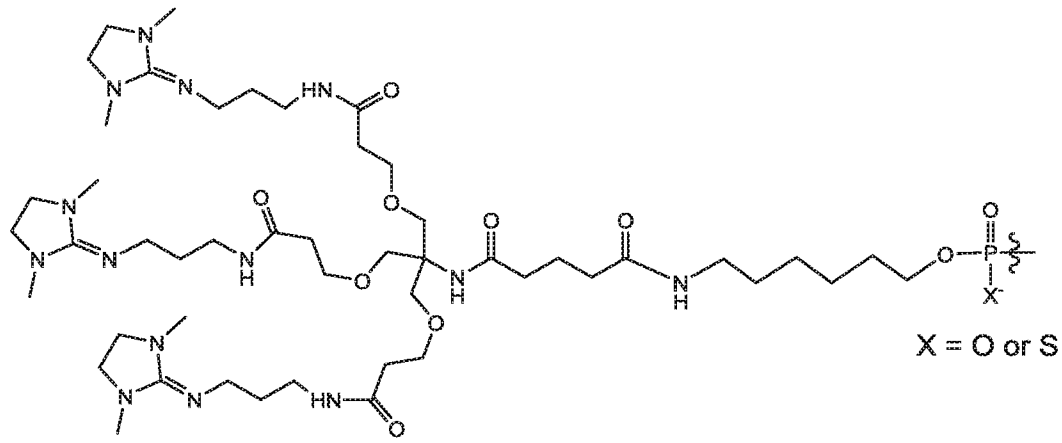
Mod108 (with –C(O)– connecting to, e.g., –NH– of a linker such as L001):



Mod109:

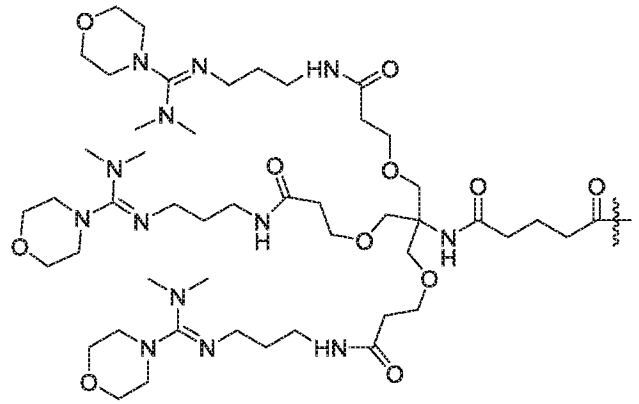


Mod109L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):

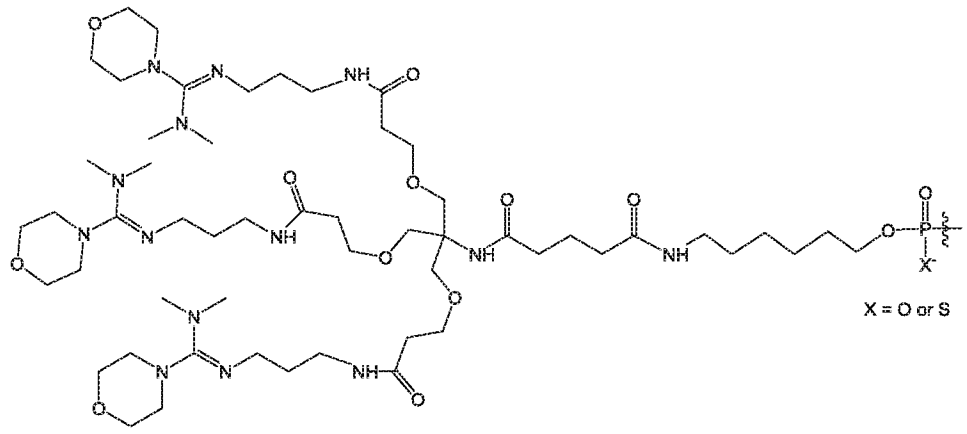


(e.g., in WV-19792, X = O)

Mod110:

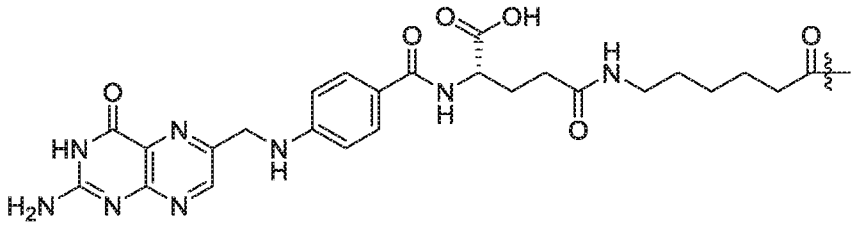


Mod110L001 (with PO or PS connecting to 5`-O- of an oligonucleotide chain):

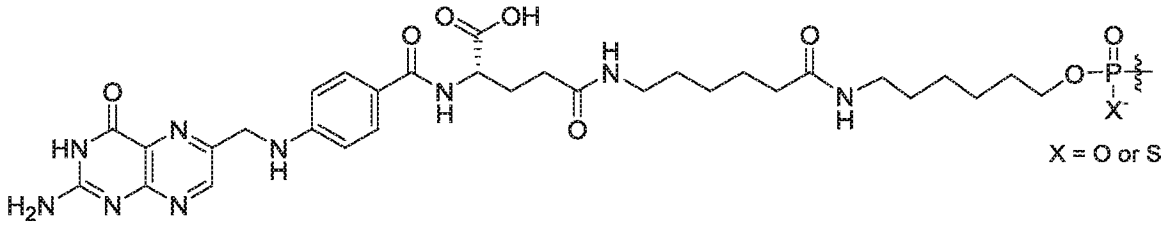


(e.g., in WV-19793, X = O)

Mod111:

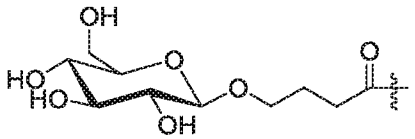


Mod111L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):

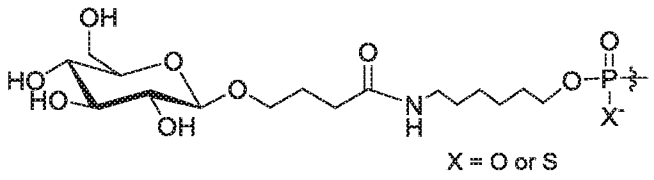


(e.g., in WV-19794, X = O)

Mod 112:

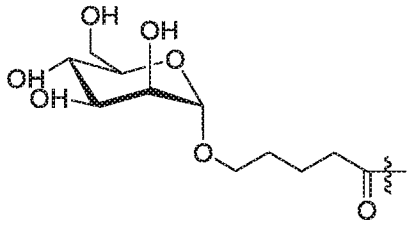


Mod112L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):

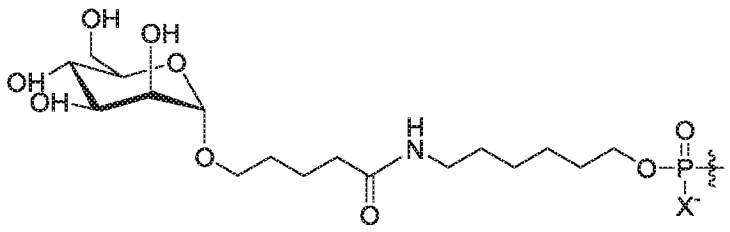


(e.g., in WV-19795, X = O)

Mod113:

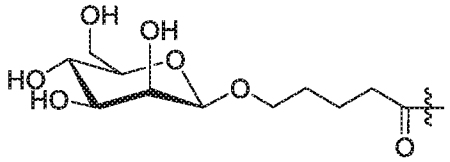


Mod113L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):

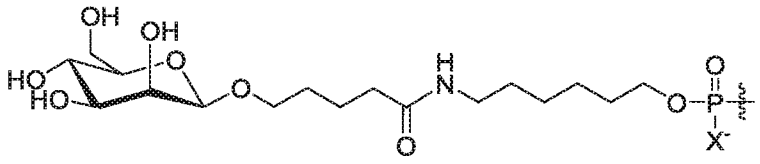


(e.g., in WV-19796, X = O)

Mod114:

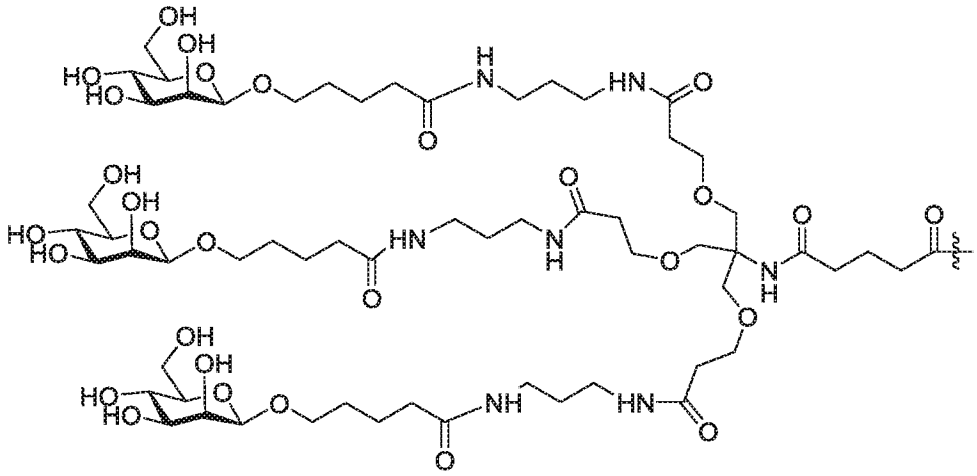


Mod114L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):

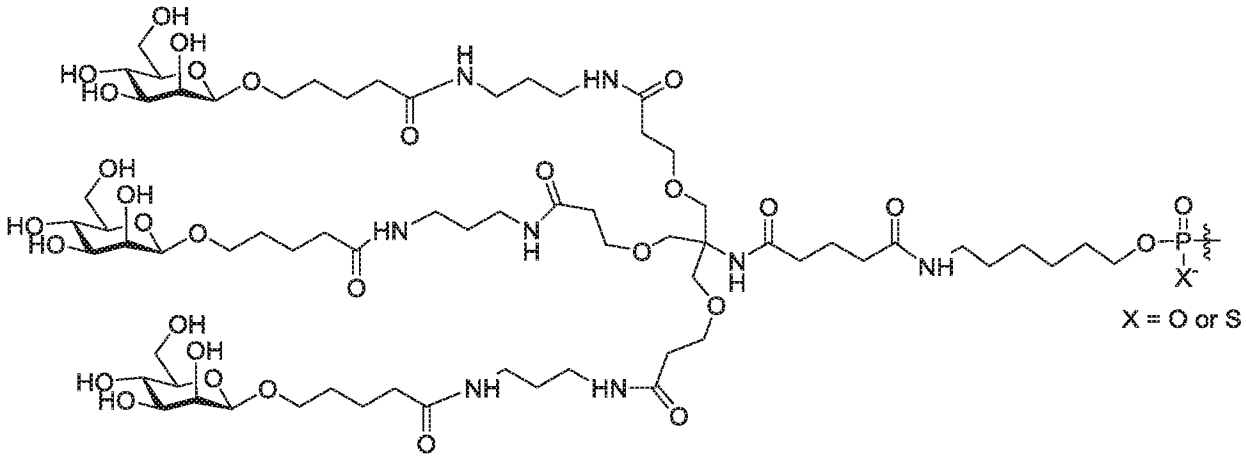


X = O or S (e.g., in WV-19797, X = O)

Mod115:



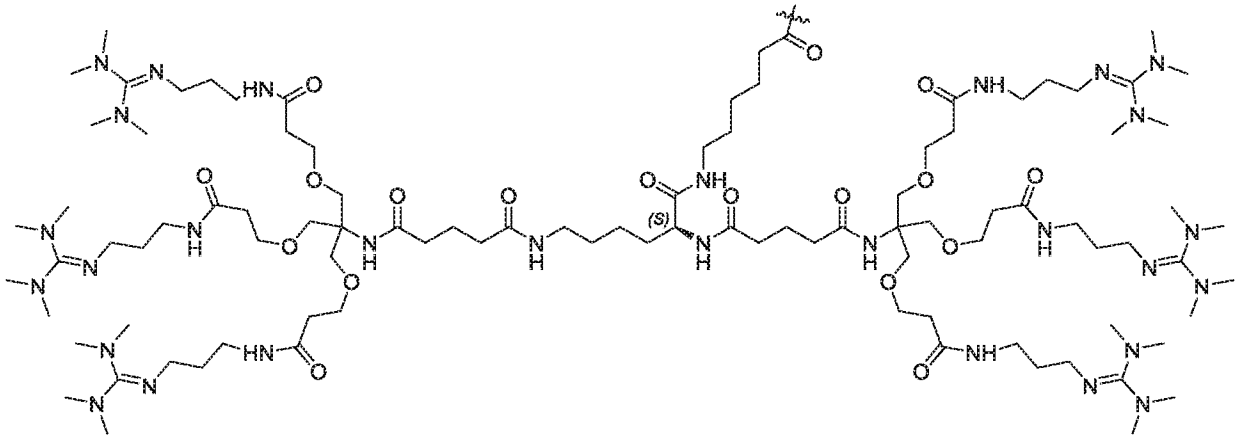
Mod115L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):



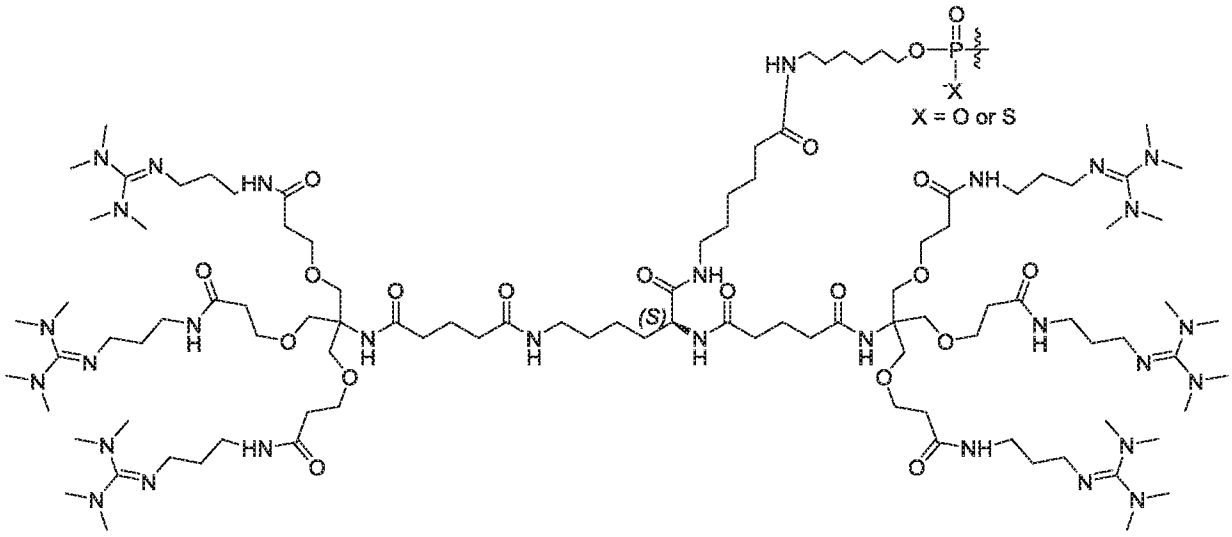
X = O or S

(e.g., in WV-19798, X = O)

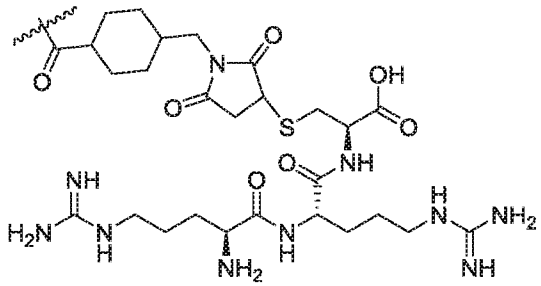
Mod118:



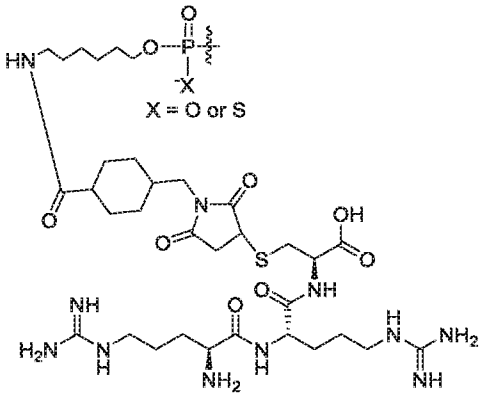
Mod118L001 (with PO or PS connecting to 5`-O- of an oligonucleotide chain):



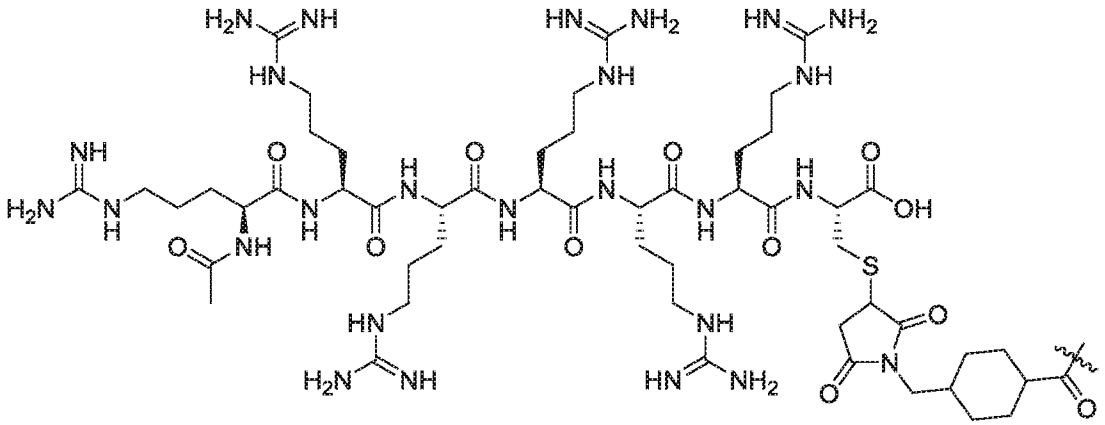
Mod119:



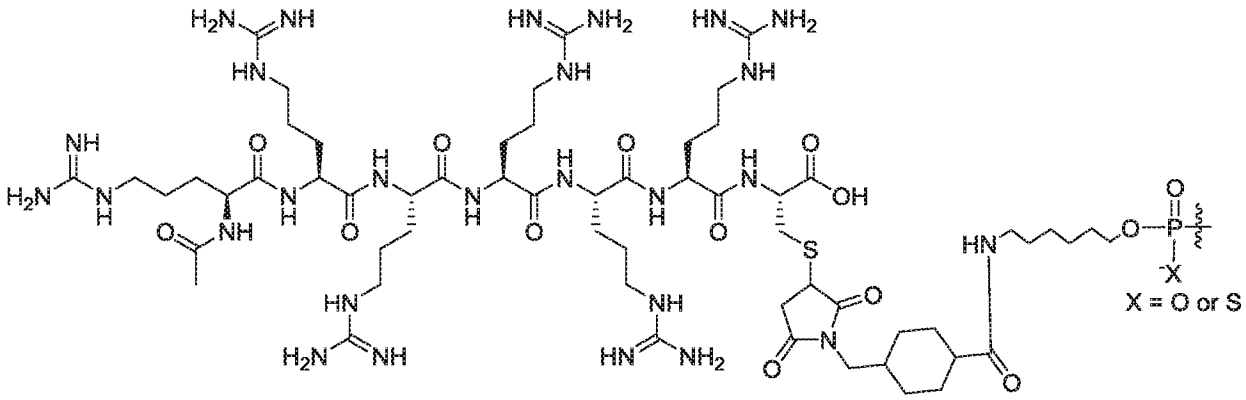
Mod119L001 (with PO or PS connecting to 5`-O- of an oligonucleotide chain):



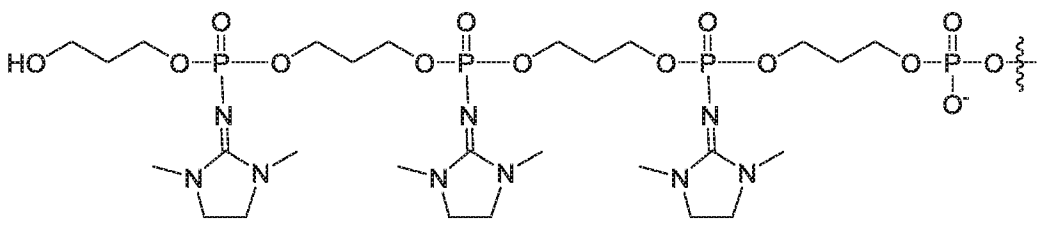
Mod120:



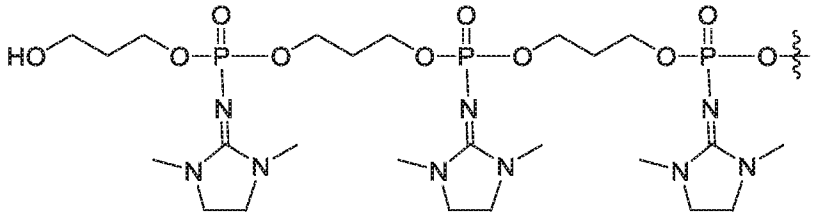
Mod120L001 (with PO or PS connecting to 5'-O- of an oligonucleotide chain):



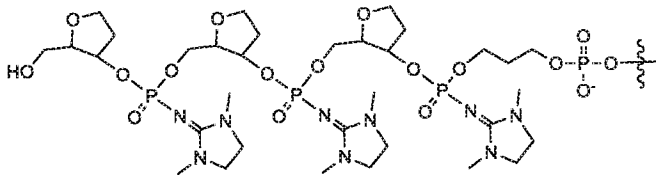
L009n001L009n001L009n001L009: connected to the 5'-position of the 5' terminal sugar of an oligonucleotide chain (e.g., for WV-23576 and WV-23578, sugar of fU) through a phosphodiester:



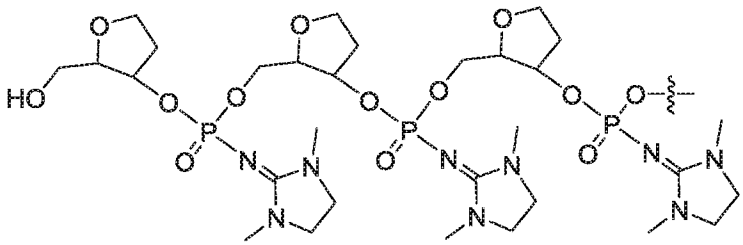
L009n001L009n001L009n001: connected to the 5'-position of the 5' terminal sugar of an oligonucleotide chain (e.g., for WV-23577 and WV-23579, sugar of fU) through n001:



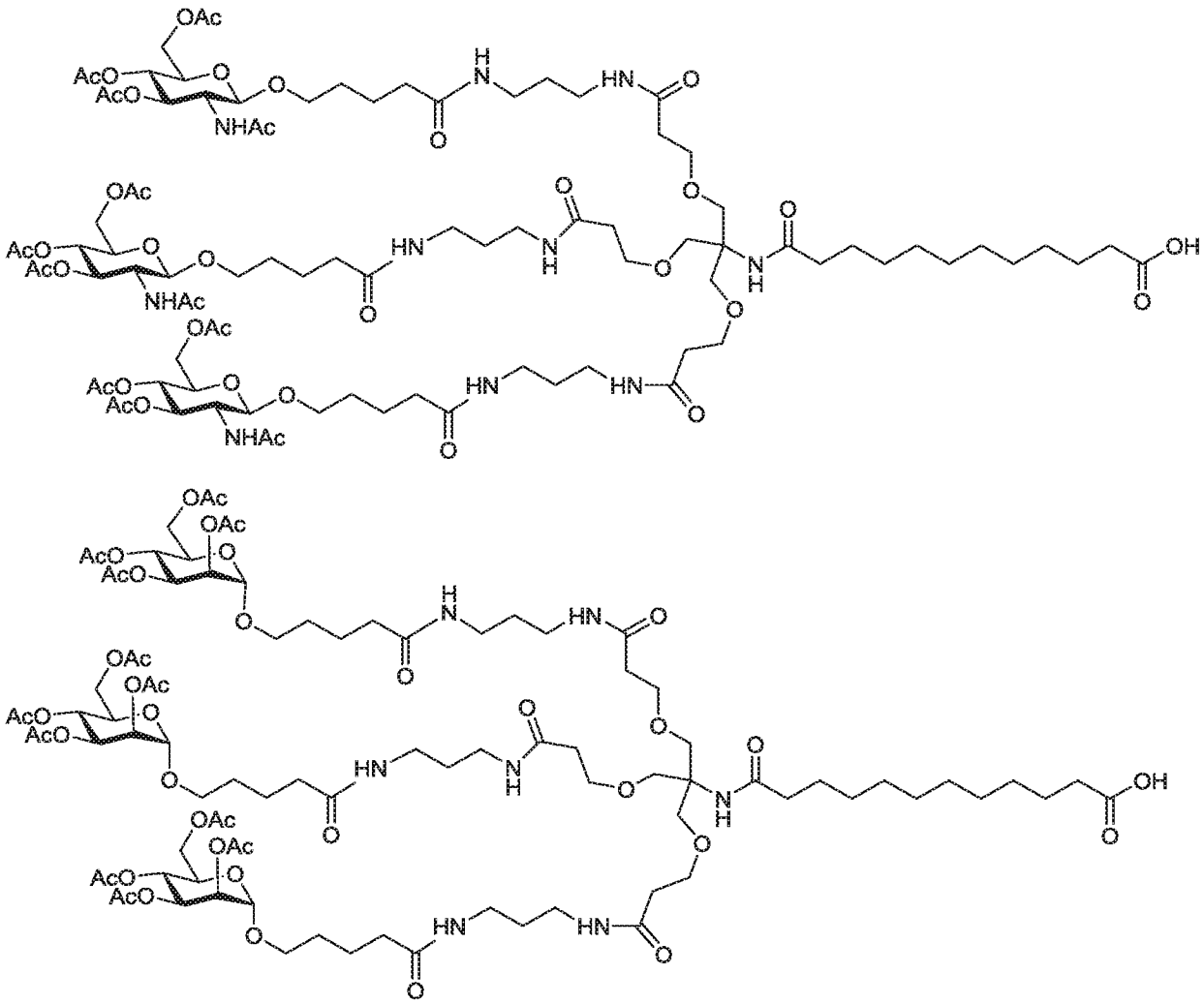
L010n001L010n001L010n001L009: connected to the 5'-position of the 5' terminal sugar of an oligonucleotide chain (e.g., for WV-23936 and WV-23938, sugar of fU) through a phosphodiester:



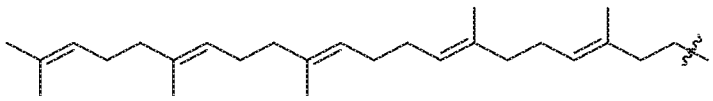
L010n001L010n001L010n001: connected to the 5'-position of the 5' terminal sugar of an oligonucleotide chain (e.g., for WV-23937 and WV-23939, sugar of fU) through n001:



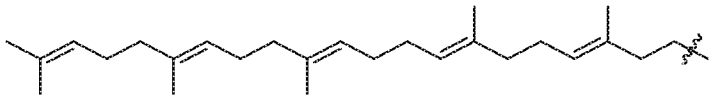
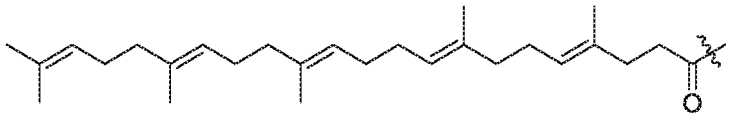
[00737] In some embodiments, some functional groups are optionally protected, e.g., for Mod024 and/or Mod 026, the hydroxyl groups are optionally protected as AcO−, before and/or during conjugation to oligonucleotide chains, and the functional groups, e.g., hydroxyl groups, can be deprotected, for example, during oligonucleotide cleavage and/or deprotection:



[00738] Applicant notes that presented in Table A1 are example ways of presenting structures of provided oligonucleotides, for example, WV-3546 (Mod020L001fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU) can be presented as a lipid moiety (Mod020,



) connected via −C(O)− (OOSSSSSSOSOSSOOSSSSSS, which "O" may be omitted as in Table A1) to the −NH− of −NH−$(CH_2)_6$−, wherein the −$(CH_2)_6$− is connected to the 5`-end of the oligonucleotide chain via a

phosphodiester linkage (OOSSSSSSOSOSSOOSSSSSS). One having ordinary skill in the art understands that a provided oligonucleotide can be presented as combinations of lipid, linker and oligonucleotide chain units in many different ways, wherein in each way the combination of the units provides the same oligonucleotide. For example, WV-3546, can be considered to have a structure of A^c–[–L^{LD}–(R^{LD})$_a$]$_b$, wherein a is 1, b is 1, and have a lipid moiety R^{LD} of ) connected to its oligonucleotide chain (A^c) unit through a linker L^{LD} having the structure of –C(O)–NH–$(CH_2)_6$–OP(=O)(OH)–O–, wherein –C(O)– is connected to R^{LD}, and –O– is connected to A^c (as 5'–O– of the oligonucleotide chain); one of the many alternative ways is that R^{LD} is  , and L^{LD} is –NH–$(CH_2)_6$–OP(=O)(OH)–O–, wherein –NH– is connected to R^{LD}, and –O– is connected to A^c (as 5'–O– of the oligonucleotide chain).

[00739] In some embodiments, each phosphorothioate internucleotidic linkage of an oligonucleotide is independently a chirally controlled internucleotidic linkage. In some embodiments, a provided oligonucleotide composition is a chirally controlled oligonucleotide composition of an oligonucleotide type listed in Table A1, wherein each phosphorothioate internucleotidic linkage of the oligonucleotide is independently a chirally controlled internucleotidic linkage.

[00740] In some embodiments, the present disclosure provides compositions comprising or consisting of a plurality of provided oligonucleotides (*e.g.*, chirally controlled oligonucleotide compositions). In some embodiments, all oligonucleotides of the plurality are of the same type, i.e., all have the same base sequence, pattern of backbone linkages, pattern of backbone chiral centers, and pattern of backbone phosphorus modifications. In some embodiments, all oligonucleotides of the same type are structural identical. In some embodiments, provided compositions comprise oligonucleotides of a plurality of oligonucleotides types, typically in controlled amounts. In some embodiments, a provided chirally controlled oligonucleotide composition comprises a combination of two or more provided oligonucleotide types.

[00741] In some embodiments, an oligonucleotide composition of the present disclosure is a chirally controlled oligonucleotide composition, wherein the sequence of the oligonucleotides of its plurality comprises or consists of a base sequence listed in **Table A1**.

[00742] In some experiments, provided oligonucleotides can provide surprisingly high activities, *e.g.*, when compared to those of Drisapersen and/or Eteplirsen. For example, chirally controlled oligonucleotide compositions of WV-887, WV-892, WV-896, WV-1714, WV-2444, WV-2445, WV-

2526, WV-2527, WV-2528, and WV-2530, and many others, each showed a superior capability, in some embodiments many fold higher, to mediate skipping of an exon in dystrophin, compared to Drisapersen and/or Eteplirsen. Certain data are provided in the present disclosure as examples.

[00743] In some embodiments, the present disclosure pertains to a composition comprising a chirally controlled oligonucleotide selected from any DMD oligonucleotide listed herein, or any DMD oligonucleotide having a base sequence comprising at least 15 consecutive bases of any DMD oligonucleotide listed herein.

[00744] In some embodiments, a provided oligonucleotide is no more than 25 bases long. In some embodiments, a provided oligonucleotide is no more than 25 to 60 bases long. In some embodiments, a U can be replaced with T, or vice versa.

[00745] In some embodiments, when assaying example oligonucleotides in mice, oligonucleotides (*e.g.*, WV-3473, WV-3545, WV-3546, WV-942, *etc.*) are intravenous injected via tail vein in male C57BL/10ScSndmdmdx mice (4-5 weeks old), at tested amounts, *e.g.*, 10 mg/kg, 30 mg/kg, *etc.* In some embodiments, tissues are harvested at tested times, *e.g.*, on Day, *e.g.*, 2, 7 and/or 14, *etc.*, after injection, in some embodiments, fresh-frozen in liquid nitrogen and stored in -80 °C until analysis.

[00746] Various assays can be used to assess oligonucleotide levels in accordance with the present disclosure. In some embodiments, hybrid-ELISA is used to quantify oligonucleotide levels in tissues using test article serial dilution as standard curve: for example, in an example procedure, maleic anhydride activated 96-well plate (Pierce 15110) was coated with 50 µl of capture probe at 500 nM in 2.5% NaHCO3 (Gibco, 25080-094) for 2 hours at 37 °C. The plate was then washed 3 times with PBST (PBS + 0.1% Tween-20), and blocked with 5% fat free milk-PBST at 37 °C for 1 hour. Test article oligonucleotide was serial diluted into matrix. This standard together with original samples were diluted with lysis buffer (4 M Guanidine; 0.33% N-Lauryl Sarcosine; 25 mM Sodium Citrate; 10 mM DTT) so that oligonucleotide amount in all samples is less than 100 ng/mL. 20 µl of diluted samples were mixed with 180 µl of 333 nM detection probe diluted in PBST, then denatured in PCR machine (65 °C, 10 min, 95 °C, 15 min, 4 C ∞). 50 µl of denatured samples were distributed in blocked ELISA plate in triplicates, and incubated overnight at 4 °C. After 3 washes of PBST, 1:2000 streptavidin-AP in PBST was added, 50 µl per well and incubated at room temperature for 1 hour. After extensive wash with PBST, 100 µl of AttoPhos (Promega S1000) was added, incubated at room temperature in dark for 10 min and read on plate reader (Molecular Device, M5) fluorescence channel: Ex435 nm, Em555 nm. Oligonucleotides in samples were calculated according to standard curve by 4-parameter regression.

[00747] In some embodiments, provided oligonucleotides are stable in both plasma and tissue homogenates.

Additional Embodiments and Examples of Oligonucleotides and Compositions, including Dystrophin (DMD) Oligonucleotides and Compositions

[00748] Among other things, the present disclosure provides oligonucleotides, compositions, and methods for, modulating splicing, reducing target levels, treating various conditions, disorders, diseases, etc. For example, in some embodiments, the present disclosure provides dystrophin (DMD) oligonucleotides and/or DMD oligonucleotide compositions that are useful for various purposes. In some embodiments, a DMD oligonucleotide and/or composition is capable of mediating skipping of exon 23 in the mouse DMD gene. In some embodiments, a DMD oligonucleotide and/or composition is capable of mediating skipping of exon 44 in the human or mouse DMD gene. In some embodiments, a DMD oligonucleotide and/or composition is capable of mediating skipping of exon 46 in the human or mouse DMD gene. In some embodiments, a DMD oligonucleotide and/or composition is capable of mediating skipping of exon 47 in the human or mouse DMD gene. In some embodiments, a DMD oligonucleotide and/or composition is capable of mediating skipping of exon 51 in the human or mouse DMD gene. In some embodiments, a DMD oligonucleotide and/or composition is capable of mediating skipping of exon 52 in the human or mouse DMD gene. In some embodiments, a DMD oligonucleotide and/or composition is capable of mediating skipping of exon 53 in the human or mouse DMD gene. In some embodiments, a DMD oligonucleotide and/or composition is capable of mediating skipping of exon 54 in the human or mouse DMD gene. In some embodiments, a DMD oligonucleotide and/or composition is capable of mediating skipping of exon 55 in the human or mouse DMD gene.

[00749] In some embodiments, a DMD oligonucleotide and/or composition is capable of mediating skipping of multiple exons in the human or mouse DMD gene.

[00750] In some embodiments, a provided oligonucleotide, e.g., a DMD oligonucleotide, comprises a modification. In some embodiments, a DMD oligonucleotide comprises a sugar modification. In some embodiments, a DMD oligonucleotide comprises a sugar modification at the 2' position. In some embodiments, a DMD oligonucleotide comprises a sugar modification at the 2' position selected from 2'-F, 2'-OMe and 2'-MOE.

[00751] In some embodiments, a DMD oligonucleotide comprises a 2'-F, 2'-OMe and/or 2'-MOE. In some embodiments, a DMD oligonucleotide comprises a 2'-F. In some embodiments, in a DMD oligonucleotide, each sugar comprises a 2'-F.

[00752] In some embodiments, a DMD oligonucleotide comprises a 2'-OMe. In some embodiments, in a DMD oligonucleotide, each sugar comprises a 2'-OMe. In some embodiments, a DMD oligonucleotide comprises a 2'-MOE. In some embodiments, in a DMD oligonucleotide, each sugar comprises a 2'-MOE.

[00753] In some embodiments, a provided oligonucleotide, e.g., a DMD oligonucleotide comprises a 2'-OMe and a 2'-F. In some embodiments, a provided oligonucleotide, e.g., a DMD oligonucleotide, comprises a pattern of 2' sugar modifications, wherein the pattern comprises a sequence selected from: fm, mf, ffm, fffm, ffffm, fffffm, ffffffm, fffffffm, ffffffffm, fffffffffm, mf, mff, mfff, mffff, mfffff, mffffff, mfffffff, mffffffff, fmf, fmmf, fmmmf, fmmmmf, fmmmmmf, fmmmmmmf, fmmmmmmmf, fmmmmmmmmf, fmmmmmmmmmf, fmmmmmmmmmmf, ffffffmmmmmmmmffffff, fffffmmmmmmmmmmmffffff, ffffmmmmmmmmmmmmmffff, fffmmmmmmmmmmmmmmmfff, ffmmmmmmmmmmmmmmmmmmmff, fmmmmmmmmmmmmmmmmmmmmf, fffffffffffmmmmmmmmmm, fffffmmmmmmmmmffffff, ffffmmmmmmmmmmmmffff, fffmmmmmmmmmmmmmmfff, ffmmmmmmmmmmmmmmmmfff, fmmmmmmmmmmmmmmmmmmff, mmmmmmmmmmmmmmmmmmmmf, fffffffffmmmmmmmmmm, ffffmmmmmmmmmffffff, fffmmmmmmmmmmmmmffff, ffmmmmmmmmmmmmmmmffff, fmmmmmmmmmmmmmmmmmfff, mmmmmmmmmmmmmmmmmmmff, mmmmmmmmmmmmmmmmmmmmf, fffffffffmmmmmmmmmm, fffmmmmmmmmmffffff, ffmmmmmmmmmmmffffff, fmmmmmmmmmmmmmffffff, mmmmmmmmmmmmmmmmffff, mmmmmmmmmmmmmmmmfff, mmmmmmmmmmmmmmmmmff, mmmmmmmmmmmmmmmmmmf, fffffffffmmmmmmmmmm, ffmmmmmmmmmffffff, fmmmmmmmmmmmmmffffff, mmmmmmmmmmmmmmmffffff, mmmmmmmmmmmmmmmmffff, mmmmmmmmmmmmmmmmfff, mmmmmmmmmmmmmmmmmff, mmmmmmmmmmmmmmmmmmf, fffffffffmmmmmmmmmm, fffffmmmmmmmmmffffff, fffffmmmmmmmmmmmffffff, ffffmmmmmmmmmmmmmffff, fffmmmmmmmmmmmmmmmfff, ffmmmmmmmmmmmmmmmmmmf, fmmmmmmmmmmmmmmmmmmmm, fffffffffmmmmmmmmmm, ff

fmmmmmmmmmmmm, fffffffffmmm, fffffmmmmmm, fffffmmmmmmm, ffffmmmmmmmm, fffmmmmmmmmm, ffmmmmmmmmmm, fmmmmmmmmmmm, fffffffffm, mmmmmmmmmmmmfffffffff, fffffmmmmmmmmmmmmmm, mmmmmmmmmmmmmmmmffffff, ffmmmmmmmmmfmmfmfffff, mmfffffffffmffmfmmmmm, mfmfmfmfmfmfmfmfmfmf, mmmmmmmfffffffffmmmmmm, fffffmmmmmmmmmffffff, mfmmffmmfmmfffmmmmmfm, fmffmmffmffmmmmfffffmf, fmff, mffm, fmffm, mfmmf, fmmf, fmffmm, mfmmff, mmff, fmmff, mmffm, fmffmmf, mfmmffm, mfmm, mfmmf, mfmmff, fmffmmf, mfmmffm, mmffm, ffmmf, fmfff, mfffm, fmfffm, fmffmm, mfmmfff, mmfff, fmmfff, mmfffm, fmfffmmf, mfmmfffm, mfmm, mfmmf, mfmmfff, fmffmmf, mfmmfffm, mmfffm, fffmmf, mfmmmf, fmmmf, fmffmmm, mfmmmff, mmmff, fmmmff, mmmffm, fmffmmmf, mfmmmffm, mfmmm, mfmmmf, mfmmmff, fmffmmmf, mfmmmffm, mmmffm, ffmmmf, or any portion thereof comprising at least five consecutive modifications, wherein f is 2'-F and m is 2'-OMe.

[00754] In some embodiments, a provided oligonucleotide, e.g., a DMD oligonucleotide, comprises a pattern which comprises any of: O, OO, OOO, OOOO, OOOOO, OOOOOO, OOOOOOO, OOOOOOOO, OOOOOOOOO, OOOOOOOOOO, OOOOOOOOOOO, S, SS, SSS, SSSS, SSSSS, SSSSSS, SSSSSSS, SSSSSSSS, SSSSSSSSS, SSSSSSSSSS, SSSSSSSSSSS, X, XX, XXX, XXXX, XXXXX, XXXXXX, XXXXXXX, XXXXXXXX, XXXXXXXXX, XXXXXXXXXX, XXXXXXXXXXX, R, RR, RRR, RRRR, RRRRR, RRRRRR, RRRRRRR, RRRRRRRR, RRRRRRRRR, RRRRRRRRRR, RRRRRRRRRRR, OSOOO, OSOO, OSO, SOOO, OXOOO, OXOO, OXO, XOO, ROOOR, RORORR, RORORR, ROORR, RROOR, ROOR, OOR, RRROR, RRRO, RROR, ROR, SOOOR, ROOOS, ROOO, ROO, RO, OOOS, SOOOS, SOOO, SOOSS, SOSOS, SOSO, OSOS, SOS, SSOOS, SSOO, SSO, SOO, SSSOS, SSSO, SOS, XOOOX, XOOO, XOO, XO, OOOX, OOX, OX, SOOOS, SOOO, SOO, SO, OOOS, OOS, XXXXXXXXXXXXX, XXXXXXXXXXXX, XXXXXXXXXXX, XXXXXXXXXX, XXXXXXXXX, XXXXXXXX, XXXXXXX, XXXXXX, XXXXX, XXXX, SSSSRSSRSS, SSSSRSSRS, SSSSRSSR, SSSSRSS, SSSSRS, SSSS, SSS, SSSRSSRSS, SSRSSRSS, SRSSRSS, RSSRSS, SSRSS, SSRS, SSSRSSRSSS, SSRSSRSSS, SSSRSSRSS, SSRSSRSSSS, SRSSRSSSS, SSRSSRSSS, SSRSSSSSSS, SRSSSSSSS, SSRSSSSSS, SSSSSSRSSS, SSSSSRSSS, SSSSSSRSS, SSO, SOS, OSO, OSSO, SSOS, SSOSS, SSOSSO, SSOSSOS, SSOSSOSS, XO, XXO, XOX, XXOX, XXOXX, XXXOXX, XXXOX, XXOXX, XXXOXXX, XXOXXO, XXOXX, XXOXXOX, or XXOXXOXX, or any portion thereof comprising at least 5 consecutive internucleotidic linkages, wherein X is a stereorandom phosphorothioate linkage, S is a phosphorothioate linkage of the Sp configuration, and R is a phosphorothioate linkage of the Rp configuration.

[00755] Various oligonucleotides, including DMD oligonucleotides, having these modifications and patterns thereof, or portions thereof, are described in the present disclosure, including those listed in Table A1.

[00756] In some embodiments, a DMD oligonucleotide comprises a non-negatively charged internucleotidic linkage. Non-limiting examples of such an oligonucleotide include, inter alia: WV-11237, WV-11238, WV-11239, WV-11340, WV-11341, WV-11342, WV-11343, WV-11344, WV-11345, WV-11346, WV-11347, WV-12123, WV-12124, WV-12125, WV-12126, WV-12127, WV-12128, WV-12129, WV-12130, WV-12131, WV-12132, WV-12133, WV-12134, WV-12135, WV-12136, WV-12553, WV-12554, WV-12555, WV-12556, WV-12557, WV-12558, WV-12559, WV-12872, WV-12873, WV-12876, WV-12877, WV-12878, WV-12879, WV-12880, WV-12881, WV-12882, WV-12883, WV-12884, WV-12885, WV-12887, WV-12888, WV-13408, WV-13409, WV-13594, WV-13595, WV-13596, WV-13597, WV-13812, WV-13813, WV-13814, WV-13815, WV-13816, WV-13817, WV-13820, WV-13821, WV-13822, WV-13823, WV-13824, WV-13825, WV-13857, WV-13858, WV-13859, WV-13860, WV-13861, WV-13862, WV-13863, WV-13864, WV-13865, WV-14342, WV-14343, WV-14344, WV-14345, WV-14522, WV-14523, WV-14525, WV-14526, WV-14528, WV-14529, WV-14530, WV-14532, WV-14533, WV-14565, WV-14566, WV-14773, WV-14774, WV-14776, WV-14777, WV-14778, WV-14779, WV-14790, WV-14791, WV-15052, WV-15053, WV-15143, WV-15322, WV-15323, WV-15324, WV-15325, WV-15326, WV-15327, WV-15328, WV-15329, WV-15330, WV-15331, WV-15332, WV-15333, WV-15334, WV-15335, WV-15336, WV-15337, WV-15338, WV-15366, WV-15369, WV-15589, WV-15647, WV-15844, WV-15845, WV-15846, WV-15850, WV-15851, WV-15852, WV-15853, WV-15854, WV-15855, WV-15856, WV-15857, WV-15858, WV-15859, WV-15860, WV-15861, WV-15862, WV-15912, WV-15913, WV-15928, WV-15929, WV-15930, WV-15931, WV-15932, WV-15933, WV-15934, WV-15935, WV-15937, WV-15939, WV-15940, WV-15941, WV-15942, WV-15943, WV-15944, WV-15945, WV-15946, WV-15947, WV-15948, WV-15949, WV-15962, WV-15963, WV-15964, WV-15965, WV-15966, WV-15967, WV-15968, WV-15969, WV-15970, WV-15971, WV-15972, WV-15973, WV-16004, WV-16005, WV-16010, WV-16011, WV-16366, WV-16368, WV-16369, WV-16371, WV-16372, WV-16499, WV-16505, WV-16506, WV-16507, WV-17765, WV-17774, WV-17775, WV-17801, WV-17802, WV-17803, WV-17831, WV-17832, WV-17833, WV-17834, WV-17838, WV-17839, WV-17840, WV-17841, WV-17842, WV-17843, WV-17854, WV-17855, WV-17856, WV-17857, WV-17858, WV-17859, WV-17860, WV-17861, WV-17862, WV-17863, WV-17864, WV-17865, WV-17866, WV-17881, WV-17882, WV-17883, WV-18853, WV-18854, WV-18855, WV-18856, WV-18857, WV-18858, WV-18859, WV-18860, WV-18861, WV-18862, WV-18863, WV-18864, WV-18865, WV-18866, WV-18867, WV-18868, WV-18869, WV-

18870, WV-18871, WV-18872, WV-18873, WV-18874, WV-18875, WV-18876, WV-18877, WV-18878, WV-18879, WV-18880, WV-18881, WV-18882, WV-18883, WV-18884, WV-18885, WV-18886, WV-18887, WV-18888, WV-18889, WV-18890, WV-18891, WV-18892, WV-18893, WV-18894, WV-18895, WV-18896, WV-18897, WV-18898, WV-18899, WV-18900, WV-18901, WV-18902, WV-18903, WV-18904, WV-18905, WV-18906, WV-18907, WV-18908, WV-18909, WV-18910, WV-18911, WV-18912, WV-18913, WV-18914, WV-18915, WV-18916, WV-18917, WV-18918, WV-18919, WV-18920, WV-18921, WV-18922, WV-18923, WV-18924, WV-18925, WV-18926, WV-18927, WV-18928, WV-18929, WV-18930, WV-18931, WV-18932, WV-18933, WV-18934, WV-18935, WV-18936, WV-18937, WV-18938, WV-18939, WV-18940, WV-18941, WV-18942, WV-18944, WV-18945, WV-19790, WV-19791, WV-19792, WV-19793, WV-19794, WV-19795, WV-19796, WV-19797, WV-19798, WV-19803, WV-19804, WV-19805, WV-19806, WV-19886, WV-19887, WV-19888, WV-19889, WV-19890, WV-19891, WV-19892, WV-19893, WV-19894, WV-19895, WV-19896, WV-19897, WV-19898, WV-19899, WV-19900, WV-19901, WV-19902, WV-19903, WV-19904, WV-19905, WV-19906, WV-19907, WV-19908, WV-19909, WV-19910, WV-19911, WV-19912, WV-19913, WV-19914, WV-19915, WV-19916, WV-19917, WV-19918, WV-19919, WV-19920, WV-19921, WV-19922, WV-19923, WV-19924, WV-19925, WV-19926, WV-19927, WV-19928, WV-19929, WV-19930, WV-19931, WV-19932, WV-19933, WV-19934, WV-19935, WV-19936, WV-19937, WV-19938, WV-19939, WV-19940, WV-19941, WV-19942, WV-19943, WV-19944, WV-19945, WV-19946, WV-19947, WV-19948, WV-19949, WV-19950, WV-19951, WV-19952, WV-19953, WV-19954, WV-19955, WV-19956, WV-19957, WV-19958, WV-19959, WV-19960, WV-19961, WV-19962, WV-19963, WV-19964, WV-19965, WV-19966, WV-19967, WV-19968, WV-19969, WV-19970, WV-19971, WV-19972, WV-19973, WV-19974, WV-19975, WV-19976, WV-19977, WV-19978, WV-19979, WV-19980, WV-19981, WV-19982, WV-19983, WV-19984, WV-19985, WV-19986, WV-19987, WV-19988, WV-19989, WV-19990, WV-19991, WV-19992, WV-19993, WV-19994, WV-19995, WV-19996, WV-19997, WV-19998, WV-19999, WV-20000, WV-20001, WV-20002, WV-20003, WV-20004, WV-20005, WV-20006, WV-20007, WV-20008, WV-20009, WV-20010, WV-20011, WV-20012, WV-20013, WV-20014, WV-20015, WV-20016, WV-20017, WV-20018, WV-20019, WV-20020, WV-20021, WV-20022, WV-20023, WV-20024, WV-20025, WV-20026, WV-20027, WV-20028, WV-20029, WV-20030, WV-20031, WV-20032, WV-20033, WV-20034, WV-20035, WV-20036, WV-20037, WV-20038, WV-20039, WV-20040, WV-20041, WV-20042, WV-20043, WV-20044, WV-20045, WV-20046, WV-20047, WV-20048, WV-20049, WV-20050, WV-20051, WV-20052, WV-20053, WV-20054, WV-20055, WV-20056, WV-20057, WV-20058, WV-20059, WV-20060, WV-20061, WV-20062, WV-20063, WV-20064, WV-20065, WV-20066, WV-20067, WV-20068, WV-20069, WV-

20070, WV-20071, WV-20072, WV-20073, WV-20074, WV-20075, WV-20076, WV-20077, WV-20078, WV-20079, WV-20080, WV-20081, WV-20082, WV-20083, WV-20084, WV-20085, WV-20086, WV-20087, WV-20088, WV-20089, WV-20090, WV-20091, WV-20092, WV-20093, WV-20094, WV-20095, WV-20096, WV-20097, WV-20098, WV-20099, WV-20100, WV-20101, WV-20102, WV-20103, WV-20104, WV-20105, WV-20106, WV-20107, WV-20108, WV-20109, WV-20110, WV-20111, WV-20112, WV-20113, WV-20114, WV-20115, WV-20116, WV-20117, WV-20118, WV-20119, WV-20120, WV-20121, WV-20122, WV-20123, WV-20124, WV-20125, WV-20126, WV-20127, WV-20128, WV-20129, WV-20130, WV-20131, WV-20132, WV-20133, WV-20134, WV-20135, WV-20136, WV-20137, WV-20138, WV-20139, WV-20140, WV-20141, WV-20142, WV-20143, WV-20144, WV-20145, WV-20146, WV-20147, WV-20148, WV-20149, WV-20150, WV-20151, WV-20152, WV-20153, WV-20154, WV-20155, WV-20156, WV-20157, WV-20158, WV-20159, WV-20160, WV-21210, WV-21211, WV-21212, WV-21217, WV-21218, WV-21219, WV-21226, WV-21245, WV-21252, WV-21253, WV-21257, WV-21258, WV-21374, WV-21375, WV-21376, WV-21377, WV-21378, WV-21379, WV-21380, WV-21381, WV-21382, WV-21383, WV-21384, WV-21385, WV-21386, WV-21387, WV-21388, WV-21389, WV-21390, WV-21578, WV-21579, WV-21580, WV-21581, WV-21582, WV-21583, WV-21584, WV-21585, WV-21586, WV-21587, WV-21588, WV-21589, WV-21590, WV-21591, WV-21592, WV-21593, WV-21594, WV-21595, WV-21596, WV-21597, WV-21598, WV-21599, WV-21600, WV-21601, WV-21602, WV-21603, WV-21604, WV-21605, WV-21606, WV-21607, WV-21608, WV-21609, WV-21610, WV-21611, WV-21612, WV-21613, WV-21614, WV-21615, WV-21616, WV-21617, WV-21618, WV-21619, WV-21620, WV-21621, WV-21622, WV-21623, WV-21624, WV-21625, WV-21626, WV-21627, WV-21628, WV-21629, WV-21630, WV-21631, WV-21632, WV-21633, WV-21634, WV-21635, WV-21636, WV-21637, WV-21638, WV-21639, WV-21640, WV-21641, WV-21642, WV-21643, WV-21644, WV-21645, WV-21646, WV-21647, WV-21648, WV-21649, WV-21650, WV-21651, WV-21652, WV-21653, WV-21654, WV-21655, WV-21656, WV-21657, WV-21658, WV-21659, WV-21660, WV-21661, WV-21662, WV-21663, WV-21664, WV-21665, WV-21666, WV-21667, WV-21668, WV-21669, WV-21670, WV-21671, WV-21672, WV-21673, WV-21723, WV-21724, WV-21725, WV-21726, WV-21727, WV-21728, WV-21729, WV-21730, WV-21731, WV-21732, WV-21733, WV-21734, WV-21735, WV-21736, WV-21737, WV-21738, WV-21739, WV-21740, WV-21741, WV-21742, WV-21743, WV-21744, WV-21745, WV-21746, WV-21747, WV-21748, WV-21749, WV-21750, WV-21751, WV-21752, WV-21753, WV-21754, WV-21755, WV-21756, WV-21757, WV-21758, WV-21759, WV-21760, WV-21761, WV-21762, WV-21763, WV-21764, WV-21765, WV-21766, WV-21767, WV-21768, WV-21769, WV-21770, WV-21771, WV-21772, WV-21773, WV-21774, WV-21775, WV-21776, WV-21777, WV-21778, WV-

21779, WV-21780, WV-21781, WV-21782, WV-21783, WV-21784, WV-21785, WV-21786, WV-21787, WV-21788, WV-21789, WV-21790, WV-21791, WV-21792, WV-21793, WV-21794, WV-21795, WV-21796, WV-21797, WV-21798, WV-21799, WV-21800, WV-21801, WV-21802, WV-21803, WV-21804, WV-21805, WV-21806, WV-21807, WV-21808, WV-21809, WV-21810, WV-21811, WV-21812, WV-21813, WV-21814, WV-21815, WV-21816, WV-21817, WV-21818, WV-22753, WV-23576, WV-23577, WV-23578, WV-23579, WV-23936, WV-23937, WV-23938, and WV-23939.

Example Dystrophin Oligonucleotides and Compositions for Exon Skipping of Exon 23

[00757] In some embodiments, the present disclosure provides oligonucleotides, oligonucleotide compositions, and methods of use thereof for mediating skipping of exon 23 in mouse DMD. Non-limiting examples include oligonucleotides and compositions of WV-10256, WV-10257, WV-10258, WV-10259, WV-10260, WV-1093, WV-1094, WV-1095, WV-1096, WV-1097, WV-1098, WV-1099, WV-1100, WV-1101, WV-1102, WV-1103, WV-1104, WV-1105, WV-1106, WV-1121, WV-1122, WV-1123, WV-11231, WV-11232, WV-11233, WV-11234, WV-11235, WV-11236, WV-1124, WV-1125, WV-1126, WV-1127, WV-1128, WV-1129, WV-1130, WV-11343, WV-11344, WV-11345, WV-11346, WV-11347, WV-1141, WV-1142, WV-1143, WV-1144, WV-1145, WV-1146, WV-1147, WV-1148, WV-1149, WV-1150, WV-1678, WV-1679, WV-1680, WV-1681, WV-1682, WV-1683, WV-1684, WV-1685, WV-2733, WV-2734, WV-4610, WV-4611, WV-4614, WV-4615, WV-4616, WV-4617, WV-4618, WV-4619, WV-4620, WV-4621, WV-4622, WV-4623, WV-4624, WV-4625, WV-4626, WV-4627, WV-4628, WV-4629, WV-4630, WV-4631, WV-4632, WV-4633, WV-4634, WV-4635, WV-4636, WV-4637, WV-4638, WV-4639, WV-4640, WV-4641, WV-4642, WV-4643, WV-4644, WV-4645, WV-4646, WV-4647, WV-4648, WV-4649, WV-4650, WV-4651, WV-4652, WV-4653, WV-4654, WV-4655, WV-4656, WV-4657, WV-4658, WV-4659, WV-4660, WV-4661, WV-4662, WV-4663, WV-4664, WV-4665, WV-4666, WV-4667, WV-4668, WV-4669, WV-4670, WV-4671, WV-4672, WV-4673, WV-4674, WV-4675, WV-4676, WV-4677, WV-4678, WV-4679, WV-4680, WV-4681, WV-4682, WV-4683, WV-4684, WV-4685, WV-4686, WV-4687, WV-4688, WV-4689, WV-4690, WV-4691, WV-4692, WV-4693, WV-4694, WV-4695, WV-4696, WV-4697, WV-6010, WV-7677, WV-7678, WV-7679, WV-7680, WV-7681, WV-7682, WV-7683, WV-7684, WV-7685, WV-7686, WV-7687, WV-7688, WV-7689, WV-7690, WV-7691, WV-7692, WV-7693, WV-7694, WV-7695, WV-7696, WV-7697, WV-7698, WV-7699, WV-7700, WV-7701, WV-7702, WV-7703, WV-7704, WV-7705, WV-7706, WV-7707, WV-7708, WV-7709, WV-7710, WV-7711, WV-7712, WV-7713, WV-7714, WV-7715, WV-7716, WV-7717, WV-7718, WV-7719, WV-7720, WV-7721, WV-7722, WV-7723, WV-7724, WV-7725, WV-7726, WV-7727, WV-7728, WV-7729, WV-7730, WV-

7731, WV-7732, WV-7733, WV-7734, WV-7735, WV-7736, WV-7737, WV-7738, WV-7739, WV-7740, WV-7741, WV-7742, WV-7743, WV-7744, WV-7745, WV-7746, WV-7747, WV-7748, WV-7749, WV-7750, WV-7751, WV-7752, WV-7753, WV-7754, WV-7755, WV-7756, WV-7757, WV-7758, WV-7759, WV-7760, WV-7761, WV-7762, WV-7763, WV-7764, WV-7765, WV-7766, WV-7767, WV-7768, WV-7769, WV-7770, WV-7771, WV-9163, WV-9164, WV-9165, WV-9166, WV-9167, WV-9168, WV-9169, WV-9170, WV-9171, WV-9172, WV-9173, WV-9174, WV-9175, WV-9176, WV-9177, WV-9178, WV-9179, WV-9180, WV-9181, WV-9182, WV-9183, WV-9184, WV-9185, WV-9186, WV-9187, WV-9188, WV-9189, WV-9190, WV-9191, WV-9192, WV-9193, WV-9194, WV-9195, WV-9196, WV-9197, WV-9198, WV-9199, WV-9200, WV-9201, WV-9202, WV-9203, WV-9204, WV-9205, WV-9206, WV-9207, WV-9208, WV-9209, WV-9210, WV-9408, WV-9409, WV-9410, WV-9411, WV-9412, WV-9413, WV-9414, WV-9415, WV-9416, WV-9417, WV-9418, WV-9419, WV-9420, WV-943, WV-9875, WV-9876, WV-9877, WV-9878, and WV-9879, and other oligonucleotides having a base sequence which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

[00758] In some embodiments, a DMD oligonucleotide is capable of mediating skipping of exon 23. Non-limiting examples of such DMD oligonucleotides include: WV-12566, WV-12567, WV-12568, WV-12884, WV-12885, WV-12886, WV-12887, WV-12888, WV-12571, and WV-12572, and other DMD oligonucleotides having a base sequence which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

[00759] Exon skipping of DMD exon 23 and other exons may be assayed in patient-derived cell lines and in cells from the mdx mouse model (which carries a nonsense point mutation in the in-frame exon 23 (Sicinski et al. 1989 Science 244: 1578–1580). By skipping exon 23 the nonsense mutation is bypassed while the reading frame is maintained). Additional strains of mdx mice, including the mdx^{2cv}, mdx^{4cv} and mdx^{5cv} alleles were reported by Wha Bin Im et al. 1996 Hum. Mol. Gen. 5: 1149–1153.

[00760] Data showing the capability of various DMD oligonucleotides to mediate skipping of exon 23 is shown herein, inter alia, in Table 1A.1, Table 1A.2, Table 1A.3, and Table 25C.1 to Table 25C.5.

[00761] Example Dystrophin Oligonucleotides and Compositions Targeting Exon 44 and Adjoining Intronic Region 3' to Exon 44

[00762] In some embodiments, a DMD oligonucleotide targets DMD exon 44 or the adjoining intronic region 3' to DMD exon 44.

[00763] In some embodiments, a DMD oligonucleotide targets DMD exon 44 or the adjoining intronic region 3' to DMD exon 44, and the oligonucleotide is capable of mediating multiple exon

skipping (e.g., of exons 45 to 55, or 45 to 57).

[00764] Reportedly, a phenomenon known as back-splicing can occur, in which, for example, a portion of the 3' end of exon 55 interacts with a portion of the 5' end of exon 45, forming a circular RNA (circRNA), which can thus skip multiple exons, e.g., all exons from exon 45 to 55, inclusive. The phenomenon can also reportedly occur between exon 57 and exon 45, skipping multiple exons, e.g., all exons from exon 45 to 57, inclusive. Back-splicing is described in the literature, e.g., in Suzuki et al. 2016 Int. J. Mol. Sci. 17.

[00765] Without wishing to be bound by any particular theory, the present disclosure suggests that it may be possible for a DMD oligonucleotide targeting DMD exon 44 or the adjoining intronic region 3' to exon 44 may be able to mediate splicing of exons 45 to 55, or of exons 45 to 57, which exons are excised as a single piece of circular RNA (circRNA) designated 45-55 (or 55-45) or 45-57 (or 57-45), respectively.

[00766] Several oligonucleotides were designed to target exon 44 or intron 44, or which straddle exon 44 and intron 44. In some embodiments, oligonucleotides designed to target exon 44 or intron 44, or which straddle exon 44 and intron 44 are tested to determine if they can increase the amount of backslicing and/or multiple-exon skipping.

[00767] In some embodiments, the present disclosure provides oligonucleotides, oligonucleotide compositions, and methods of use thereof for mediating exon skipping in human DMD, wherein the base sequence of the oligonucleotide is a sequence of exon 44 or intron 44, or a portion of both exon 44 and intron 44. Non-limiting examples include oligonucleotides and compositions of WV-13963, WV-13964, WV-13965, WV-13966, WV-13967, WV-13968, WV-13969, WV-13970, WV-13971, WV-13972, WV-13973, WV-13974, WV-13975, WV-13976, WV-13977, WV-13978, WV-13979, WV-13980, WV-13981, WV-13982, WV-13983, WV-13984, WV-13985, WV-13986, WV-13987, WV-13988, WV-13989, WV-13990, WV-13991, WV-13992, WV-13993, WV-13994, WV-13995, WV-13996, WV-13997, WV-13998, WV-13999, WV-14000, WV-14001, WV-14002, WV-14003, WV-14004, WV-14005, WV-14006, WV-14007, WV-14008, WV-14009, WV-14010, WV-14011, WV-14012, WV-14013, WV-14014, WV-14015, WV-14016, WV-14017, WV-14018, WV-14019, WV-14020, WV-14021, WV-14022, WV-14023, WV-14024, WV-14025, WV-14026, WV-14027, WV-14028, WV-14029, WV-14030, WV-14031, WV-14032, WV-14033, WV-14034, WV-14035, WV-14036, WV-14037, WV-14038, WV-14039, WV-14040, WV-14041, WV-14042, WV-14043, WV-14044, WV-14045, WV-14046, WV-14047, WV-14048, WV-14049, WV-14050, WV-14051, WV-14052, WV-14053, WV-14054, WV-14055, WV-14056, WV-14057, and WV-14058, and other oligonucleotides having a base sequence which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

[00768] Data showing the capability of various DMD oligonucleotides targeting exon 44 or the adjacent intron 3' to exon 44 are shown in Table 22A.2 and Table 22A.3.

[00769] Table 1A.1. Example data of certain oligonucleotides

[00770] Oligonucleotides to DMD exon 23 were tested in vitro for their ability to induce skipping of exon 23.

[00771] H2K cells were dosed with oligonucleotide in differentiation media for 4days. RNA was extracted with Trizol, pre-amp then treated with TaqMan with multiplexed reading of skipped and total DMD transcript; absolute quantification was via standard curve g-Blocks. In these and various other studies, numbers indicate amount of skipping (i.e., skipping efficiency; or the percentage of skipping as a percentage of total mRNA transcript).

[00772] Oligonucleotides were tested at 10, 3.33, 1.11, 0.37, or 0.12 uM.

Oligo-nucleotide	10	3.33	1.11	0.37	0.12
WV-7684	4.2	2.1	1	0.2	0.1
	4.1	2.1	0.9	0.2	0.1
	5.2	3.2	1.5	0	0
	5.1	3.3	1.1	0	0
WV-12886	27.7	17.5	10	5	2.4
	28	17.6	9.8	5	2.3
	29.8	22.8	13.1		3.7
	32.7	21.5	11.9		3.5
WV-11231	3.8	2.1	1.4	0.4	0.3
	3.8	2.1	1.3	0.5	0.3
	5.3	2.7	1.4	0.7	0.2
	5.1	2.4	1.6	0.8	0.2
WV-10258	24.5	19.9	9.5	4.8	2.8
	25.3	20.1	9.1	4.8	2.7
	24.4	19.4	13.2	6.2	3.4
	24.2	19.7	13.6	6.3	3.5
WV-11345	29.2	24.9	15.9	12.1	5
	30.2	24.9	15.5	11.9	5.1
	30.8	25.8	17.8		
	32.3	25.3	17.6		
WV-12885	26.8	23.3	16.5	8	2.8
	27.5	23	17.2	8.2	3.8
	32.3	25.8	16.3		6.1
	30.7	27.1	16.3		6.3

WV-15589	22.2	14.8	11.2	4.6	2.2
	21.7	15	12.3	4.4	2.3
	24.1	11.3	11.4		
	23.5	8.6	10.8		

[00773] Table 1A.2. Activity of certain oligonucleotides

[00774] In this study, in vivo skipping activity was measured in MDX mouse model after single IV dose.

[00775] MDX mice received single IV dose of 150mg/kg. Necropsied flash frozen tissues (Quadriceps, Diaphragm, etc.) were pulverized and RNA extracted with Trizol. Skipping efficiency was determined by multiplex TaqMan assay for 'total' and 'exon-23 skipped' DMD transcripts, normalized to gBlock standard curves.

[00776] Numbers indicate amount of skipping DMD exon 23 (as a percentage of total mRNA, where 100 would represent 100% skipped).

Quadriceps							
PBS		WV-11345		WV-17774		WV-18945	
0.01	0.01	28.61	30.25	3.93	3.92	2.1	1.53
0.01	0.12	26.34	24.53	10.82	10.73	1.16	0.91
0.15	0.06	40.29	36.57	14.79	13.47	2.04	0.92
		30	30.05	10.13	6.19	5.05	3.97
		23.24	25.18	13.92	14.36	2.4	1.77
Gastrocnemius							
PBS		WV-11345		WV-17774		WV-18945	
0.02	0.02	22.27	13.18	36.41	33.55	2.46	1.95
0.02	0.01	14.74	8.03	18.02	19.55	0.6	0.27
0.09	0.11	11.12	3.68	16.17	15.44	0.36	0.41
		22.82	28.29	11.22	10.94	0.72	0.75
		18.09	15.66	28.85	27.9	0.61	3.14
Diaphram							
PBS		WV-11345		WV-17774		WV-18945	
0.04	0.03	27.05	24	7.11	4.07	0.72	0.82
0.01	1.13	16.22	16.2	18.1	18.6	0.81	0.68
0.04	0.09	15.16	13.23	9.66	10.02	0.33	0.32
		33.66	36.52	4.55	4.86	0.63	0.21
		20.03	20.55	8.38	9.46	0.56	0.91
Tibialis							

PBS		WV-11345		WV-17774		WV-18945	
0.01	0.01	34.34	35.04	16.2	15.77	0	0
0	0	28.7	23.07	42.94	42.97		
0.04	0.02	7.87	9.87	12.1	14.51		
		17.01	14.68	15.16	13.91		
		45.6	41.54				

[00777] Table 1A.3. Activity of certain oligonucleotides

[00778] Oligonucleotides were tested in vitro for ability to skip DMD exon 23.

[00779] Oligonucleotides were tested at 10, 3.3., 1.1, 0.3, and 0.1 uM.

[00780] Numbers indicate amount of skipping DMD exon 23 (as a percentage of total mRNA, where 100 would represent 100% skipped).

	10uM	3.3uM	1.1uM	0.3uM	0.1uM
WV-10258	32.1	17.7	11.1	3.9	1.9
	33.2	19.4	13	4.6	2.1
	29	18.5	11.5	11.1	6.4
	29	18.6	12.4	11.3	6
WV-11233	6.8	7.6	0.7	1.6	0.1
	6.9	7.8	0.5	1.3	0
	11.1	1.3	1.6	0.6	0.7
	11	1.3	1.6	0.4	0.7
WV-11345					
	42	29.3	16.6	8.1	5
	40	27.4	17.4	8.2	4.7
WV-18944					
	7.7	4	1.4	1	0.7
	8	4	1.7	1	0.8
WV-17774	44.5	38.2	26.7	11.9	6.6
	45.2	37.5	26.3	12.5	6.6
	44	37.2	26.7	14.7	4.8
	44.7	35.6	27.2	13.2	4.5
WV-18945	14.1	11.6	5	1.9	1.5
	14.3	11.2	4.8	2	1.5
	21.4	11.4	4.7	2.4	2.6
	21.3	11.1	4.7	2.3	3
Mock	0.2		0.6	0	

	0.3		0.8	0	
	2.5	0	0.3	2.5	1.2
	2	0	0.4	2.5	1.1

Example Dystrophin Oligonucleotides and Compositions for Exon Skipping of Exon 45

[00781] In some embodiments, the present disclosure provides oligonucleotides, oligonucleotide compositions, and methods of use thereof for mediating skipping of exon 45 in DMD (e.g., of mouse, human, etc.).

[00782] In some embodiments, a provided DMD oligonucleotide and/or composition is capable of mediating skipping of exon 45. Non-limiting examples of such DMD oligonucleotides and compositions include those of: WV-11047, WV-11048, WV-11049, WV-11050, WV-11051, WV-11052, WV-11053, WV-11054, WV-11055, WV-11056, WV-11057, WV-11058, WV-11059, WV-11060, WV-11061, WV-11062, WV-11063, WV-11064, WV-11065, WV-11066, WV-11067, WV-11068, WV-11069, WV-11070, WV-11071, WV-11072, WV-11073, WV-11074, WV-11075, WV-11076, WV-11077, WV-11078, WV-11079, WV-11080, WV-11081, WV-11082, WV-11083, WV-11084, WV-11085, WV-11086, WV-11087, WV-11088, WV-11089, WV-11090, WV-11091, WV-11092, WV-11093, WV-11094, WV-11095, WV-11096, WV-11097, WV-11098, WV-11099, WV-11100, WV-11101, WV-11102, WV-11103, WV-11104, WV-11105, WV-9594, WV-9595, WV-9596, WV-9597, WV-9598, WV-9599, WV-9600, WV-9601, WV-9602, WV-9603, WV-9604, WV-9605, WV-9606, WV-9607, WV-9608, WV-9609, WV-9610, WV-9611, WV-9612, WV-9613, WV-9614, WV-9615, WV-9616, WV-9617, WV-9618, WV-9619, WV-9620, WV-9621, WV-9622, WV-9623, WV-9624, WV-9625, WV-9626, WV-9627, WV-9628, WV-9629, WV-9630, WV-9631, WV-9632, WV-9633, WV-9634, WV-9635, WV-9636, WV-9637, WV-9638, WV-9639, WV-9640, WV-9641, WV-9642, WV-9643, WV-9644, WV-9645, WV-9646, WV-9647, WV-9648, WV-9649, WV-9650, WV-9651, WV-9652, WV-9653, WV-9654, WV-9655, WV-9656, WV-9657, WV-9658, WV-9659, WV-9762, WV-9763, WV-9764, WV-9765, WV-9766, WV-9767, WV-9768, WV-9769, WV-9770, WV-9771, WV-9772, WV-9773, WV-9774, WV-9775, WV-9776, WV-9777, WV-9778, WV-9779, WV-9780, WV-9781, WV-9782, WV-9783, WV-9784, WV-9785, WV-9786, WV-9787, WV-9788, WV-9789, WV-9790, WV-9791, WV-9792, WV-9793, WV-9794, WV-9795, WV-9796, WV-9797, WV-9798, WV-9799, WV-9800, WV-9801, WV-9802, WV-9803, WV-9804, WV-9805, WV-9806, WV-9807, WV-9808, WV-9809, WV-9810, WV-9811, WV-9812, WV-9813, WV-9814, WV-9815, WV-9816, WV-9817, WV-9818, WV-9819, WV-9820, WV-9821, WV-9822, WV-9823, WV-9824, WV-9825, and WV-9826, and other DMD oligonucleotides having a base sequence which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

[00783] As shown in various tables from Table 1 to Table 22 (and parts thereof), various DMD oligonucleotides comprising various patterns of modifications were testing for skipping of various exons. The Tables show test results of certain DMD oligonucleotides. To assay exon skipping of DMD, certain DMD oligonucleotides were tested in vitro in Δ52 human patient-derived myoblast cells (also designated DEL52) and/or Δ45-52 human patient-derived myoblast cells (human cells wherein the exon 52 or exons 45-52 were already deleted, also designated DEL45-52). Unless noted otherwise, in various experiments, oligonucleotides were delivered gymnotically. In the tables, generally, 100.00 would represent 100% skipping and 0.0 would represent 0% skipping. Various DMD oligonucleotides are described in detail in Table A1.

[00784] Table 1A.4, below, shows example data of some DMD oligonucleotides in skipping exon 45. Procedure: Δ48-50 (Del48-50 or D48-50) myoblasts were treated with 10 uM oligonucleotides for 4 days in differentiation media.

Table 1A.4. Example data of certain oligonucleotides.

Numbers represent level of skipping, wherein 100 would represent 100% skipping and 0 would represent 0% skipping. For various data described herein, "Mock" is a negative control, in which water was used instead of an oligonucleotide.

WV-11047	0.024	0.009	0.012	0.016
WV-11051	0.022	0.024	0.046	0.014
WV-11052	0.024	0.032	0.014	0.026
WV-11053	0.027	0.009	0.017	0.023
WV-11054	0.029	0.038	0.035	0.028
WV-11055	0.030	0.025	0.016	0.033
WV-11056	0.029	0.043	0.018	0.031
WV-11057	0.000	0.015	0.000	0.032
WV-11058	0.044	0.029	0.049	0.024
WV-11059	0.025	0.041	0.049	0.024
WV-11062	0.218	0.175	0.151	0.231
WV-11063	0.472	0.730	0.456	0.594
WV-11064	0.297	0.307	0.334	0.345
WV-11065	0.651	0.630	0.675	0.544
WV-11066	0.124	0.087	0.137	0.153
WV-11067	0.183	0.210	0.238	0.224
WV-11068	0.212	0.266	0.244	0.406
WV-11069	0.389	0.715	0.407	0.744
WV-11070	1.677	1.473	1.483	1.677
WV-11071	0.385	0.362	0.413	0.310

WV-11072	0.146	0.250	0.142	0.268
WV-11073	0.709	0.876	0.721	0.835
WV-11074	2.015	2.207	1.992	2.527
WV-11075	0.254	0.238	0.157	0.220
WV-11076	0.000	2.715	0.000	2.315
WV-11077	1.568	1.414	1.388	1.308
WV-11078	3.915	3.122	4.175	3.076
WV-11079	7.178	8.083	8.257	6.955
WV-11080	1.467	1.202	1.726	1.155
WV-11081	9.279	4.780	10.244	4.512
WV-11082	3.377	2.646	3.242	2.256
WV-11083	3.964	2.631	4.001	2.419
WV-11084	11.336	7.481	13.752	8.270
WV-11085	1.818	0.679	1.787	2.003
WV-11086	16.017	15.215	17.207	15.191
WV-11087	1.104	0.766	1.728	1.030
WV-11088	14.320	12.940	14.287	10.746
WV-11089	16.126	13.507	15.515	15.389
WV-11090	1.148	0.596	1.405	0.647
WV-11091	0.105	0.069	0.311	0.049
WV-11092	0.094	0.066	0.111	0.066
WV-11093	0.123	0.060	0.087	0.037
WV-11094	0.054	0.062	0.060	0.038
WV-11095	0.317	0.064	0.241	0.109
WV-11096	0.062	0.061	0.096	0.059
WV-11098	0.026	0.033	0.032	0.024
WV-11100	0.015	0.012	0.014	0.011
WV-11101	0.000	0.021	0.000	0.011
WV-11102	0.019	0.030	0.025	0.017
WV-11103	0.017	0.023	0.014	0.029
WV-11104	0.053	0.050	0.067	0.035
WV-11105	0.017	0.033	0.034	0.051
Mock	0.050	0.018	0.010	0.037
Mock	0.019	0.023	0.009	0.023

Table 1B.1. and 1B.2. Example data of certain oligonucleotides.

The Tables below show example data of some DMD oligonucleotides in skipping exon 45. Procedure: Δ48-50 (Del48-50 or DEL48-50 or D48-50) myoblasts were treated with 10 or 3 uM oligonucleotides for 4 days in differentiation media.

Oligonucleotides were dosed at 10 μM and 3 μM for 4 days in DEL48-50 Myoblasts. Certain

oligonucleotides comprise a non-negatively charged internucleotidic linkage, as detailed in Table A1.

Table 1B.1. Example data of certain oligonucleotides.

	10um				3um			
WV-13810	7.0	6.5	7.1	6.5	2.7	2.8	2.5	2.3
WV-13811	8.4	8.0	9.1	9.5	3.3	3.2	2.4	2.8
WV-13812	22.8	21.1	22.9	23.7	9.2	9.2	10.0	9.7
WV-13813	19.4	19.9	20.1	20.2	7.6	8.1	7.5	7.4
WV-13814	13.6	13.6	13.5	13.3	5.1	4.3	4.9	4.9
WV-13815	26.9	25.6	23.9	24.3	9.0	8.9	8.2	8.6
WV-13816	37.0	35.0	31.8	33.8	14.0	14.5	14.6	12.0
WV-13817	52.7	55.4	54.3	54.2	24.9	26.1	21.9	21.7
WV-14531	2.9	2.7	2.8	2.9	0.7	0.9	1.0	1.2
WV-14532	4.3	4.3	3.8	4.1	1.4	1.3	1.1	1.0
WV-14533	7.9	7.6	7.3	7.9	1.9	2.1	2.4	2.1
WV-11086	18.3	20.1	18.4	18.4	7.9	7.7	7.6	8.1

Table 1B.2. Example data of certain oligonucleotides.

	10uM				3uM			
WV-13818	3.2	2.8	3.2	2.9	0.9	0.8	1.1	1.2
WV-13819	3.8	3.8	3.0	2.9	1.0	0.9	0.9	1.0
WV-13820	6.6	6.7	6.4	6.3	3.2	3.0	2.9	3.0
WV-13821	7.4	6.5	7.4	6.9	2.2	1.9	2.5	1.9
WV-13822	9.5	9.5	8.1	8.6	3.4	3.5	3.4	3.9
WV-13823	10.4	10.9	11.2	10.5	4.2	5.0	4.1	4.4
WV-13824	17.1	16.3	16.1	15.6	8.1	7.6	7.1	7.0
WV-13825	20.1	19.3	22.5	20.6	9.9	9.8	9.0	9.6
WV-14527	2.2	1.9	1.4	2.0	0.7	0.7	0.9	0.7
WV-14528	2.3	2.2	2.5	2.4	1.0	0.9	1.0	1.0
WV-14529	5.2	1.8	2.0	2.0	0.7	0.7	0.8	0.8
WV-11089	2.6	2.7	2.9	2.5	0.9	0.9	1.4	1.3

Additional data related to multiple exon skipping mediated by DMD oligonucleotides which target DMD exon 45 are shown in Table 22A.1.

Example Dystrophin Oligonucleotides and Compositions Which Target Exon 46

[00785] In some embodiments, the present disclosure provides oligonucleotides, oligonucleotide compositions, and methods of use thereof for targeting exon 46 and/or mediating skipping of exon 46 in human DMD. Non-limiting examples include oligonucleotides and compositions of WV-13701, WV-

13702, WV-13703, WV-13704, WV-13705, WV-13706, WV-13707, WV-13708, WV-13709, WV-13710, WV-13711, WV-13712, WV-13713, WV-13714, WV-13715, WV-13716, WV-13780, and WV-13781, and other oligonucleotides having a base sequence which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

[00786] In some embodiments, DMD oligonucleotides are first tested for single exon skipping to select suitable oligonucleotides, then tested combinatorially (in combination with another DMD oligonucleotide) for multi-exon skipping.

[00787] In some embodiments, DMD oligonucleotides targeting DMD exon 46, 47, 52, 54 or 55 are first tested for single exon skipping to select suitable oligonucleotides, then tested combinatorially (in combination with another DMD oligonucleotide) for multi-exon skipping.

Table 2A. Example data of certain oligonucleotides. Numbers indicate percentage of exon 46 skipping.

WV-13701	0.3	0.3	0.5	0.4
WV-13702	0.3	0.4	0.5	0.3
WV-13703	0.9	0.9	1.1	0.8
WV-13704			9.7	5.4
WV-13705	4.9	5.1	5.9	3.4
WV-13706			4.6	4.8
WV-13707	8.5	7.4	5.2	5.1
WV-13708	9.4	10.8	6.0	5.6
WV-13709	8.8	12.1	8.1	4.9
WV-13710	0.1	0.1	0.1	0.1
WV-13711	0.1	0.1	0.0	0.1
WV-13712	3.4	4.7	2.4	2.4
WV-13713	0.5		0.7	0.5
WV-13714	0.6		0.5	0.4
WV-13715	0.9		0.6	0.7
WV-13716	1.5	3.9	1.1	2.8
WV-13780	10.1	5.2		6.1
WV-13781	7.7	6.4		5.0
Mock	0.0	0.0	0.0	0.0
Mock	0.0			0.0

Example Dystrophin Oligonucleotides and Compositions Which Target Exon 47

[00788] In some embodiments, the present disclosure provides oligonucleotides, oligonucleotide compositions, and methods of use thereof for targeting exon 47 and/or mediating skipping of exon 47 in human DMD. Non-limiting examples include oligonucleotides and compositions of exon 47 oligos include: WV-13717, WV-13718, WV-13719, WV-13720, WV-13721, WV-13722, WV-13723, WV-

13724, WV-13725, WV-13726, WV-13727, WV-13728, WV-13729, WV-13730, WV-13731, WV-13732, WV-13788, and WV-13789, and other oligonucleotides having a base sequence which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

Table 3A. Example data of certain oligonucleotides. Numbers represent percentage of exon 47 skipping.

WV-13717	0.0	0.0
WV-13718	0.0	0.0
WV-13719	0.0	0.0
WV-13720	0.0	0.0
WV-13721	0.0	0.0
WV-13722	0.0	0.0
WV-13723	0.5	0.5
WV-13724	1.4	1.8
WV-13725	0.6	0.4
WV-13726	0.0	0.0
WV-13727	1.1	1.1
WV-13728	1.1	1.1
WV-13729	0.2	0.2
WV-13730	0.5	0.6
WV-13731	1.6	1.8
WV-13732	0.1	0.6

Example Dystrophin Oligonucleotides and Compositions for Exon Skipping of Exon 51

[00789] In some embodiments, the present disclosure provides oligonucleotides, oligonucleotide compositions, and methods of use thereof for mediating skipping of exon 51 in DMD (e.g., of mouse, human, etc.).

[00790] In some embodiments, a provided DMD oligonucleotide and/or composition is capable of mediating skipping of exon 51. Non-limiting examples of such DMD oligonucleotides and compositions include those of: ONT-395, WV-10255, WV-10261, WV-10262, WV-10634, WV-10635, WV-10636, WV-10637, WV-10868, WV-10869, WV-10870, WV-10871, WV-10872, WV-10873, WV-10874, WV-10875, WV-10876, WV-10877, WV-10878, WV-10879, WV-10880, WV-10881, WV-10882, WV-10883, WV-10884, WV-10885, WV-10886, WV-10887, WV-10888, WV-1107, WV-1108, WV-1109, WV-1110, WV-1111, WV-1112, WV-1113, WV-1114, WV-1115, WV-1116, WV-1117, WV-1118, WV-1119, WV-1120, WV-11237, WV-11238, WV-11239, WV-1131, WV-1132, WV-1133, WV-1134, WV-1135, WV-1136, WV-1137, WV-1138, WV-1139, WV-1140, WV-1151, WV-1152, WV-1153, WV-1154, WV-1155, WV-1156, WV-1157, WV-1158, WV-1159, WV-1160, WV-1709, WV-1710, WV-1711, WV-1712, WV-1713, WV-1714, WV-1715, WV-1716, WV-2095, WV-2096, WV-2097, WV-

2098, WV-2099, WV-2100, WV-2101, WV-2102, WV-2103, WV-2104, WV-2105, WV-2106, WV-2107, WV-2108, WV-2109, WV-2165, WV-2179, WV-2180, WV-2181, WV-2182, WV-2183, WV-2184, WV-2185, WV-2186, WV-2187, WV-2188, WV-2189, WV-2190, WV-2191, WV-2192, WV-2193, WV-2194, WV-2195, WV-2196, WV-2197, WV-2198, WV-2199, WV-2200, WV-2201, WV-2202, WV-2203, WV-2204, WV-2205, WV-2206, WV-2207, WV-2208, WV-2209, WV-2210, WV-2211, WV-2212, WV-2213, WV-2214, WV-2215, WV-2216, WV-2217, WV-2218, WV-2219, WV-2220, WV-2221, WV-2222, WV-2223, WV-2224, WV-2225, WV-2226, WV-2227, WV-2228, WV-2229, WV-2230, WV-2231, WV-2232, WV-2233, WV-2234, WV-2235, WV-2236, WV-2237, WV-2238, WV-2239, WV-2240, WV-2241, WV-2242, WV-2243, WV-2244, WV-2245, WV-2246, WV-2247, WV-2248, WV-2249, WV-2250, WV-2251, WV-2252, WV-2253, WV-2254, WV-2255, WV-2256, WV-2257, WV-2258, WV-2259, WV-2260, WV-2261, WV-2262, WV-2263, WV-2264, WV-2265, WV-2266, WV-2267, WV-2268, WV-2273, WV-2274, WV-2275, WV-2276, WV-2277, WV-2278, WV-2279, WV-2280, WV-2281, WV-2282, WV-2283, WV-2284, WV-2285, WV-2286, WV-2287, WV-2288, WV-2289, WV-2290, WV-2291, WV-2292, WV-2293, WV-2294, WV-2295, WV-2296, WV-2297, WV-2298, WV-2299, WV-2300, WV-2301, WV-2302, WV-2303, WV-2304, WV-2305, WV-2306, WV-2307, WV-2308, WV-2309, WV-2310, WV-2311, WV-2312, WV-2313, WV-2314, WV-2315, WV-2316, WV-2317, WV-2318, WV-2319, WV-2320, WV-2321, WV-2322, WV-2323, WV-2324, WV-2325, WV-2326, WV-2327, WV-2328, WV-2329, WV-2330, WV-2331, WV-2332, WV-2333, WV-2334, WV-2335, WV-2336, WV-2337, WV-2338, WV-2339, WV-2340, WV-2341, WV-2342, WV-2343, WV-2344, WV-2345, WV-2346, WV-2347, WV-2348, WV-2349, WV-2350, WV-2351, WV-2352, WV-2353, WV-2354, WV-2361, WV-2362, WV-2363, WV-2364, WV-2365, WV-2366, WV-2367, WV-2368, WV-2369, WV-2370, WV-2381, WV-2382, WV-2383, WV-2384, WV-2385, WV-2432, WV-2433, WV-2434, WV-2435, WV-2436, WV-2437, WV-2438, WV-2439, WV-2440, WV-2441, WV-2442, WV-2443, WV-2444, WV-2445, WV-2446, WV-2447, WV-2448, WV-2449, WV-2526, WV-2527, WV-2528, WV-2529, WV-2530, WV-2531, WV-2532, WV-2533, WV-2534, WV-2535, WV-2536, WV-2537, WV-2538, WV-2578, WV-2579, WV-2580, WV-2581, WV-2582, WV-2583, WV-2584, WV-2585, WV-2586, WV-2587, WV-2588, WV-2625, WV-2627, WV-2628, WV-2660, WV-2661, WV-2662, WV-2663, WV-2664, WV-2665, WV-2666, WV-2667, WV-2668, WV-2669, WV-2670, WV-2737, WV-2738, WV-2739, WV-2740, WV-2741, WV-2742, WV-2743, WV-2744, WV-2745, WV-2746, WV-2747, WV-2748, WV-2749, WV-2750, WV-2752, WV-2783, WV-2784, WV-2785, WV-2786, WV-2787, WV-2788, WV-2789, WV-2790, WV-2791, WV-2792, WV-2793, WV-2794, WV-2795, WV-2796, WV-2797, WV-2798, WV-2799, WV-2800, WV-2801, WV-2802, WV-2803, WV-2804, WV-2805, WV-2806, WV-2807, WV-2808, WV-2812, WV-2813, WV-2814, WV-3017, WV-3018, WV-3019, WV-3020, WV-3022, WV-3023, WV-

3024, WV-3025, WV-3026, WV-3027, WV-3028, WV-3029, WV-3030, WV-3031, WV-3032, WV-3033, WV-3034, WV-3035, WV-3036, WV-3037, WV-3038, WV-3039, WV-3040, WV-3041, WV-3042, WV-3043, WV-3044, WV-3045, WV-3046, WV-3047, WV-3048, WV-3049, WV-3050, WV-3051, WV-3052, WV-3053, WV-3054, WV-3055, WV-3056, WV-3057, WV-3058, WV-3059, WV-3060, WV-3061, WV-3070, WV-3071, WV-3072, WV-3073, WV-3074, WV-3075, WV-3076, WV-3077, WV-3078, WV-3079, WV-3080, WV-3081, WV-3082, WV-3083, WV-3084, WV-3085, WV-3086, WV-3087, WV-3088, WV-3089, WV-3113, WV-3114, WV-3115, WV-3116, WV-3117, WV-3118, WV-3120, WV-3121, WV-3152, WV-3153, WV-3357, WV-3358, WV-3359, WV-3360, WV-3361, WV-3362, WV-3363, WV-3364, WV-3365, WV-3366, WV-3463, WV-3464, WV-3465, WV-3466, WV-3467, WV-3468, WV-3469, WV-3470, WV-3471, WV-3472, WV-3473, WV-3506, WV-3507, WV-3508, WV-3509, WV-3510, WV-3511, WV-3512, WV-3513, WV-3514, WV-3515, WV-3516, WV-3517, WV-3518, WV-3519, WV-3520, WV-3543, WV-3544, WV-3545, WV-3546, WV-3547, WV-3548, WV-3549, WV-3550, WV-3551, WV-3552, WV-3553, WV-3554, WV-3555, WV-3556, WV-3557, WV-3558, WV-3559, WV-3560, WV-3753, WV-3754, WV-3820, WV-3821, WV-3855, WV-3856, WV-3971, WV-4106, WV-4107, WV-4191, WV-4231, WV-4232, WV-4233, WV-4890, WV-6137, WV-6409, WV-6410, WV-6560, WV-6826, WV-6827, WV-6828, WV-7109, WV-7110, WV-7333, WV-7334, WV-7335, WV-7336, WV-7337, WV-7338, WV-7339, WV-7340, WV-7341, WV-7342, WV-7343, WV-7344, WV-7345, WV-7346, WV-7347, WV-7348, WV-7349, WV-7350, WV-7351, WV-7352, WV-7353, WV-7354, WV-7355, WV-7356, WV-7357, WV-7358, WV-7359, WV-7360, WV-7361, WV-7362, WV-7363, WV-7364, WV-7365, WV-7366, WV-7367, WV-7368, WV-7369, WV-7370, WV-7371, WV-7372, WV-7373, WV-7374, WV-7375, WV-7376, WV-7377, WV-7378, WV-7379, WV-7380, WV-7381, WV-7382, WV-7383, WV-7384, WV-7385, WV-7386, WV-7387, WV-7388, WV-7389, WV-7390, WV-7391, WV-7392, WV-7393, WV-7394, WV-7395, WV-7396, WV-7397, WV-7398, WV-7399, WV-7400, WV-7401, WV-7402, WV-7410, WV-7411, WV-7412, WV-7413, WV-7414, WV-7415, WV-7457, WV-7458, WV-7459, WV-7460, WV-7461, WV-7506, WV-7596, WV-8130, WV-8131, WV-8230, WV-8231, WV-8232, WV-8449, WV-8478, WV-8479, WV-8480, WV-8481, WV-8482, WV-8483, WV-8484, WV-8485, WV-8486, WV-8487, WV-8488, WV-8489, WV-8490, WV-8491, WV-8492, WV-8493, WV-8494, WV-8495, WV-8496, WV-8497, WV-8498, WV-8499, WV-8500, WV-8501, WV-8502, WV-8503, WV-8504, WV-8505, WV-8506, WV-8806, WV-884, WV-885, WV-886, WV-887, WV-888, WV-889, WV-890, WV-891, WV-892, WV-893, WV-894, WV-895, WV-896, WV-897, WV-9222, WV-9223, WV-9224, WV-9225, WV-9226, WV-9227, WV-942, WV-9540, WV-9541, WV-9737, WV-9738, WV-9739, WV-9740, WV-9741, WV-9742, WV-9827, WV-9828, WV-9829, WV-9830, WV-9831, WV-9832, WV-9833, WV-9834, WV-9835, WV-9836, WV-9837, WV-9838, WV-9839, WV-9840, WV-9841, WV-9842, WV-

9843, WV-9844, WV-9845, WV-9846, WV-9847, WV-9848, WV-9849, WV-9850, WV-9851, WV-9852, WV-9858, and WV-8937, and other DMD oligonucleotides having a base sequence which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

[00791] Additional non-limiting examples of such DMD oligonucleotides and compositions include those of: WV-2444, WV-2528, WV-2531, WV-2578, WV-2579, WV-2580, WV-2581, WV-2669, WV-2745, WV-3032, WV-3152, WV-3153, WV-3360, WV-3363, WV-3364, WV-3465, WV-3466, WV-3470, WV-3472, WV-3473, WV-3507, WV-3545, WV-3546, WV-3552, WV-4106, WV-4231, WV-4232, WV-4233, WV-887, WV-896, WV-942, and other DMD oligonucleotides having a base sequence which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

[00792] Additional non-limiting examples of such DMD oligonucleotides and compositions include those of: WV-12494, WV-12130, WV-12131, WV-12132, WV-12133, WV-12134, WV-12135, WV-12136, WV-12496, WV-12495, WV-12123, WV-12124, WV-12125, WV-12126, WV-12127, WV-12128, WV-12129, WV-12553, WV-12554, WV-12555, WV-12556, WV-12557, WV-12558, WV-12559, WV-12872, WV-12873, WV-12876, WV-12877, WV-12878, WV-12879, WV-12880, WV-12881, WV-12882, and WV-12883, and other DMD oligonucleotides having a base sequence which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

[00793] In some embodiments, the sequence of the region of interest for exon 51 skipping differs between the mouse and human.

[00794] Various assays can be utilized to assess oligonucleotides for exon skipping in accordance with the present disclosure. In some embodiments, in order to test the efficacy of a particular combination of chemistry and stereochemistry of an oligonucleotide intended for exon 51 skipping in human, a corresponding oligonucleotide can be prepared which has the mouse sequence, and then tested in mouse. The present disclosure recognizes that in the human and mouse homologs of exon 51, a few differences exist (underlined below):

M GTGGTTACTAAGGAAACTGTCATCTCCAAACTAGAAATGCCATCTTCTTTGCTGTTGGAG

H GTGGTTACTAAGGAAACTGCCATCTCCAAACTAGAAATGCCATCTTCCTTGATGTTGGAG

where M is Mouse, nt 7571-7630; and H is Human, nt 7665-7724.

[00795] Because of these differences, slightly different DMD oligonucleotides for skipping exon 51 can be prepared for testing in mouse and human. As a non-limiting example, the following DMD oligonucleotide sequences can be used for testing in human and mouse:

HUMAN DMD oligonucleotide sequence: UCAAGGAAGAUGGCAUUUCU

MOUSE DMD oligonucleotide sequence: GCAAAGAAGAUGGCAUUUCU

Mismatches between human and mouse are underlined.

[00796] A DMD oligonucleotide intended for treating a human subject can be constructed with a

particular combination of base sequence (e.g., UCAAGGAAGAUGGCAUUUCU), and a particular pattern of chemistry, internucleotidic linkages, stereochemistry, and additional chemical moieties (if any). Such a DMD oligonucleotide can be tested in vitro in human cells or in vivo in human subjects, but may have limited suitability for testing in mouse, for example, because base sequences of the two have mismatches.

[00797] A corresponding DMD oligonucleotide can be constructed with the corresponding mouse base sequence (GCAAAGAAGAUGGCAUUUCU) and the same pattern of chemistry, internucleotidic linkages, stereochemistry, and additional chemical moieties (if any). Such an oligonucleotide can be tested in vivo in mouse. Several DMD oligonucleotides comprising the mouse base sequence were constructed and tested.

[00798] In some embodiments, a human DMD exon skipping oligonucleotide can be tested in a mouse which has been modified to comprise a DMD gene comprising the human sequence.

[00799] Various DMD oligonucleotides comprising various patterns of modifications are described herein. The Tables below show test results of certain DMD oligonucleotides. To assay exon skipping of DMD, DMD oligonucleotides were tested in vitro in Δ52 human patient-derived myoblast cells and/or Δ45-52 human patient-derived myoblast cells (human cells wherein the exon 52 or exons 45-52 were already deleted). Unless noted otherwise, in various experiments, oligonucleotides were delivered gymnotically.

Table 4A. Example data of certain oligonucleotides.

DMD oligonucleotides were tested in vitro at 10uM and 3uM, in triplicates. Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown. Full descriptions of the oligonucleotides tested in this Table (and other Tables) are provided in Table A1.

	10uM			3uM		
WV-942	1.0	2.2	1.5	0.2	0.5	0.2
WV-1709	8.5	12.9	7.7	3.3	5.8	3.7
WV-1710	4.1	6.1	4.7	1.1	2.5	1.3
WV-1711	4.4	5.8	3.7	1.1	2.4	1.4
WV-1712	2.6	4.4	3.1	0.9	2.0	1.7
WV-1713	2.1	3.5	2.3	0.6	1.6	0.3
WV-1714	7.8	10.5	10.2	2.3	4.1	2.3
WV-1715	2.2	3.8	3.3	0.8	1.8	1.1
WV-1716	2.1	3.5	2.4	0.9	1.8	0.9

[00800] In Table 4B, below, additional data of DMD oligonucleotides for skipping exon 51 were presented.

Table 4B. Example data of certain oligonucleotides.

DMD oligonucleotides were tested at 10uM and 3uM, in triplicates. Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

	10uM			3uM		
WV-942	1.0	2.2	1.5	0.2	0.5	0.2
WV-1714	7.8	10.5	10.2	2.3	4.1	2.3
WV-2444	22.2	26.7	28.6	9.1	12.6	11.9
WV-2445	17.1	20.7	18.7	7.0	9.7	9.1
WV-2528	32.4	34.6	39.3	16.9	19.9	22.3
WV-2529	3.2	5.8	6.1	2.2	4.5	3.0
WV-2530	18.6	21.1	25.4	7.6	11.5	11.4

[00801] In Table 4C, below, additional data of DMD oligonucleotides for skipping exon 51 were presented.

Table 4C. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

	WV-942		WV-887		WV-1714		WV-2438	
10uM	1.1	0.7	5.1	3.9	3.6	3.7	9.3	9.3
3uM	0.5	0.3	1.0	2.2	1.6	1.5	3.9	3.1
1uM	0.2	0.2	0.6	0.7	0.6	0.3	1.4	1.1

	WV-2439		WV-2444		WV-2445		Mock	
10uM	3.2	2.1	12.9	14.3	9.7	8.9	0.4	0.1
3uM	0.8	0.7	4.7	4.1	3.3	3.5	0.1	0.1
1uM	0.4	0.3	1.4	1.0	1.1	1.0	0.1	

[00802] In Table 4D, below, additional data of DMD oligonucleotides for skipping exon 51 were presented.

Table 4D. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

	10uM			
WV-942	0.6	0.6	0.6	0.6
WV-2660	0.2	0.3	0.1	0.1
WV-2661	0.4	0.4		
WV-2662	0.2	0.2	0.1	0.1
WV-2663	0.5	0.5	0.4	0.5

WV-2670	5.1	5.2	6.2	7.3

[00803] In Table 5, below, additional data of DMD oligonucleotides for skipping exon 51 were presented.

Table 5. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

	10uM	3uM	1uM
Mock	0.0	0.1	0.0
WV-2531	21.7	8.7	3.2
WV-3152	26.1	15.3	5.7
WV-2745	24.0	10.7	4.8
WV-3463	6.6	3.0	0.8
WV-3464	16.1	6.2	2.4
WV-3465	16.4	6.0	1.8
WV-3466	13.0	5.7	2.0
WV-3467	12.6	5.8	2.6
WV-3469	14.2	6.0	1.5
WV-3470	24.9	11.9	6.4
WV-3471	4.9	1.6	1.0
WV-3472	20.1	12.4	7.2
WV-3473	24.9	11.4	7.6
WV-942	3.3	2.1	0.7

Table 6. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown. Numbers are approximate.

Oligonucleotides were delivered gymnotically to Δ48-50 patient-derived myoblasts (4 days post-differentiation). The oligonucleotide designated as "PMO" in this table and other tables related to skipping of DMD exon 51 is WV-8806 CTCCAACATCAAGGAAGATGGCATTTCTAG, which is fully PMO (Morpholino).

	5 uM	**1 uM**
WV-942	.2	
PMO	.1	
WV-6137	1	.9
WV-7333	.3	.2
WV-7334	.7	.4
WV-7335	1.7	.4
WV-7336	2.2	.6

WV-7337	1.7	.4
WV-7343	1.4	.5
WV-7344	2.8	.7
WV-7345	2.9	1
WV-7346	1.9	.7
WV-7347	1.2	.5
WV-7348	2.5	1
WV-7349	3	.6
WV-7350	3.1	1
WV-7351	1.7	.6
WV-7352	2.7	.8
WV-7353	2.8	.2
WV-7354	2.2	.3
WV-7355	2.7	1.6
WV-7356	3.3	1.2
WV-7357	2.7	1.1
WV-7358	2.2	.6
WV-7359	.7	.3
WV-7360	.6	.5
WV-7361	2.8	.8
WV-7362	4.1	.8
WV-7363	2	.7

[00804] In Table 7, below, additional data of DMD oligonucleotides for skipping exon 51 were presented.

Table 7. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown. Numbers are approximate.

Mock	.1	
WV-942	.2	
PMO	.1	
WV-7364	2	.5
WV-7365	1.8	.5
WV-7366	1.1	5.7
WV-7367	.2	.3
WV-7368	.4	.4
WV-7369	.4	.2
WV-7370	.2	.3
WV-7371	.3	.2
WV-7372	.3	
WV-7373	.5	1.3
WV-7374	.3	.4
WV-7375	.2	.8
WV-7376	.2	.5
WV-7377	.3	.5
WV-7378	.4	

WV-7379	7.8	1
WV-7380	2.8	.3
WV-7381	4.1	.2
WV-7382	1.3	.1
WV-7383	1.7	.3
WV-7384	2.8	.4
WV-7385		1.8
WV-7386	4	1.6
WV-7387	3	1.8
WV-7388	1.2	.7
WV-7389	.5	.4
WV-7390	1	.5

[00805] In some embodiments, the present disclosure pertains to metabolites of any oligonucleotide, e.g., DMD oligonucleotide, disclosed herein, or any combination thereof. In some embodiments, a metabolite of an oligonucleotide, e.g., a DMD oligonucleotide is the result of an oligonucleotide, e.g., a DMD oligonucleotide being acted upon by a nuclease (e.g., an exonuclease or endonuclease or other enzymes, including those may chemically process one or more modifications of an oligonucleotide). In some embodiments, a "metabolite" of an oligonucleotide, e.g., a DMD oligonucleotide is not the physical product of such an oligonucleotide being metabolized or physically treated with a nuclease, but rather a compound which corresponds chemically to a product of an oligonucleotide being metabolized or treated with an enzyme, e.g., a nuclease. In some embodiments, metabolite of an oligonucleotide, e.g., a DMD oligonucleotide, is chemically synthesized, without any metabolic process, and optionally administered to a subject.

[00806] In some embodiments, a metabolite is a truncation of an oligonucleotide on the 5' end and/or 3' end by one or two nucleotides or nucleosides. In some embodiments, the present disclosure provides an oligonucleotide, e.g., DMD oligonucleotide which corresponds to an oligonucleotide, e.g., DMD oligonucleotide listed herein, but is truncated at the 5' end by one or two nucleotides. In some embodiments, the present disclosure provides an oligonucleotide, e.g., a DMD oligonucleotide which corresponds to an oligonucleotide, e.g., a DMD oligonucleotide listed herein, but is truncated at the 3' end by one or two nucleotides. In some embodiments, the present disclosure provides an oligonucleotide, e.g., a DMD oligonucleotide which corresponds to an oligonucleotide, e.g., a DMD oligonucleotide listed herein, but is truncated at the 3' end and 5' end by one or two nucleotides. Among other things, such oligonucleotides may perform various of biological functions, e.g., such DMD oligonucleotides can mediate skipping of exon 23, 45, 51, 53, or any other DMD exon.

[00807] In some embodiments, the present disclosure pertains to a DMD oligonucleotide which has the base sequence of a DMD oligonucleotide listed herein, except that the base sequence is shorter on

the 5' end by one or two bases. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which has the base sequence of a DMD oligonucleotide listed herein, except that the base sequence is shorter on the 3' end by one or two bases. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which has the base sequence of a DMD oligonucleotide disclosed herein, except that the base sequence is shorter on the 3' end and the 5' end by one or two bases. Such DMD oligonucleotides, among other things, can mediate skipping of exon 23, 45, 51, 53, or any other DMD exon.

[00808] In some embodiments, a metabolite of a DMD oligonucleotide has removed from the oligonucleotide an additional moiety (e.g., a lipid or other conjugated moiety).

[00809] In some embodiments, an oligonucleotide of the present disclosure may be a metabolite of another oligonucleotide. For example, several oligonucleotides may be metabolite of WV-3473, for example, WV-4231 (3' n-1, truncated at the 3' end by one nucleotide), WV-4232 (3' n-2), WV-4233 (5' n-1), etc. Example data of such "metabolite" oligonucleotides were presented in Table 9 below (at 1, 3 and 10 uM, in replicates). Generally, an oligonucleotide can be used independently whether or not it can be a metabolite of another oligonucleotide.

Table 9. Example data of certain oligonucleotides.

Results of replicate experiments are shown. Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown. In this and other tables, PMO is a Morpholino oligonucleotide control.

Oligonucleotide	10uM		3uM		1uM	
PMO	2.4	1.6	0.4	1.1	0.4	0.6
WV-3473	78.8	73.5	62.5	59.8	38.8	38.8
WV-4231 (3' n-1)	83.8	71.4	65.0	67.2	44.4	43.0
WV-4232 (3' n-2)	48.5	66.5	42.2	57.5		30.0
WV-4233 (5' n-1)	54.2	45.9	37.1	31.6	18.6	14.5

[00810] In some embodiments, the present disclosure pertains to DMD oligonucleotides corresponding to any DMD oligonucleotide to exon 51 or any other exon listed herein (e.g., in Table A1), but which are truncated by one, two or more nucleotides on the 5' end and/or 3' end.

[00811] In some embodiments, the length of a provided oligonucleotide, e.g., a DMD oligonucleotide, is 15 to 45 bases. In some embodiments, the length of a provided oligonucleotide, e.g., a DMD oligonucleotide, is 20 to 45 bases. In some embodiments, the length of a provided oligonucleotide, e.g., a DMD oligonucleotide, is 20 to 40 bases. In some embodiments, the length of a provided oligonucleotide, e.g., a DMD oligonucleotide, is 35 bases. In some embodiments, the length of a provided oligonucleotide, e.g., a DMD oligonucleotide, is 20 to 25 bases.

[00812] In some experiments, lengths of DMD oligonucleotides for skipping exon 51 are 20 or 25 bases.

Tables 10A and 10B. Example data of certain oligonucleotides.

Table 10A shows data of 20-mers for skipping DMD exon 51; Table 10B shows data of 25-mers for skipping DMD exon 51. Sequences are provided in Table A1. Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

Table 10A. 20-mers

untreated		WV-2313		WV-2314		WV-2315		WV-2316	
0.1	0.1	1.0	1.4	1.7	1.6	2.0	2.0	4.6	2.5
WV-2317		WV-2318		WV-2319		WV-2320		WV-942	
1.7	1.1	4.3	4.3	5.0	6.5	2.9	3.7	3.9	3.4

Table 10B. 25-mers

WV-2223		WV-2224		WV-2225		WV-2226	
15.7	14.8	6.6	7.3	13.4	16.1	7.7	7.7
WV-2227		WV-2228		WV-2229		WV-2230	
9.8	9.7	15.7	15.6	8.5	8.9	12.9	13.4

[00813] Additional data are provided.

Table 10C. Example data of certain oligonucleotides.

Oligonucleotides were tested in vitro at 10, 3 and 1 μM. Results of replicate experiments are shown. Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

	10uM		3uM		1uM	
WV-2531	21.7	25.1	8.7	10.6	3.2	4.6
WV-3152	26.1	21.7	15.3	10.7	5.7	4.1
WV-3472	20.1	16.3	12.4	8.5	7.2	3.8
WV-3473	24.9	38.4	11.4	11.2	7.6	6.5
WV-942	3.3	0.2	2.1		0.7	0.1

Table 10D. Example data of certain oligonucleotides.

Oligonucleotides were tested in vitro at 10, 3 and 1 μM. Results of replicate experiments are shown. Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

	10uM			3uM			1uM		
WV-1714	5.8	6.2	8.1	2.4	3.0	2.7	0.7	0.7	2.0
WV-3030	29.9	27.2	35.2	6.2	5.6	5.6	0.6	0.6	1.6

WV-3032	31.7	29.3	37.9	7.8	6.4	7.7	1.2	1.1	1.1
WV-2669	3.1	3.1	4.1	1.4	1.7	1.7	0.6	0.7	0.8
WV-3035	13.2	16.4	17.6	1.9	2.5	2.8	1.0	1.1	0.8

Table 10E. Example data of certain oligonucleotides.

Oligonucleotides were tested in vitro at 10, 3 and 1 μM. Results of replicate experiments are shown. Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

	10uM		3uM		1uM	
WV-2531	24.7	21.7	11.0	8.7	4.8	3.2
WV-3360		25.1	12.9	10.1		3.3
WV-3363		24.0		7.7		3.4
WV-3364	72.8	45.5	17.2	9.8		4.0

Table 10F. Example data of certain oligonucleotides.

Oligonucleotides were tested in vitro at 10, 3 and 1 μM. Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

	10uM	3uM	1uM
Mock	0.0	0.1	0.0
WV-2531	21.7	8.7	3.2
WV-3360	25.1	10.1	3.3
WV-3363	24.0	7.7	3.4
WV-3364	45.5	9.8	4.0

Table 10G. Example data of certain oligonucleotides.

Oligonucleotides were tested in vitro at 10, 3 and 1 μM. Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

	10uM			3uM			1uM		
WV-1714	5.8	6.2	8.1	2.4	3.0	2.7	0.7	0.7	2.0
WV-3030	29.9	27.2	35.2	6.2	5.6	5.6	0.6	0.6	1.6
WV-3032	31.7	29.3	37.9	7.8	6.4	7.7	1.2	1.1	1.1
WV-2669	3.1	3.1	4.1	1.4	1.7	1.7	0.6	0.7	0.8
WV-3035	13.2	16.4	17.6	1.9	2.5	2.8	1.0	1.1	0.8

Table 10H. Example data of certain oligonucleotides.

Oligonucleotides were tested in vitro at 10 and 3 □M. In this table, in some cases, serum and/or BSA

were added to test the effect on exon skipping. Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

	10uM, 15% serum				10uM 5% serum			
Mock	0.0	0.1			0.0	0.1		
WV-942	1.0	1.0	0.2	0.2	0.7	0.5	0.4	0.4
WV-2578	3.2			2.2	2.4	2.3	2.2	0.9
WV-2579			3.1	2.9			2.5	2.5
WV-2580	2.5	2.9	2.4	3.1	6.8	6.4	2.8	3.2
WV-2581	3.3	3.6	3.9	3.7	4.4	5.8	5.8	5.4

	10uM 5% serum 20mg/ml BSA				10uM 5% serum 4mg/ml BSA			
Mock	0.1	0.1			0.1	0.1		
WV-942	0.7	0.6	1.4	1.3	0.2	0.3	0.6	0.5
WV-2578	0.9	0.5	0.5	0.6	0.6	0.6	0.5	0.7
WV-2579	0.1	0.1	0.5	0.3	0.1	0.1	0.5	0.4
WV-2580	0.4	0.3	0.2	0.2			0.2	0.1
WV-2581	0.2	0.2	0.4	0.4	0.2	0.2	0.1	0.1

	3uM 15% serum				3uM 5% serum			
Mock	0.0	0.0			0.0	0.0		
WV-942	0.1	0.0	0.3	0.3	0.1	0.1	0.2	0.2
WV-2578	0.5	0.3	0.3	0.4	0.3	0.5	0.6	0.2
WV-2579	0.6	0.5	1.8	1.5	0.5	0.4	0.3	0.3
WV-2580	1.0	1.0	0.5	0.6	1.2	1.0	0.5	0.7
WV-2581	0.0	0.0	0.6	0.6	0.4	0.5	0.8	0.7

	3uM 5% serum 20mg/ml BSA				3uM 5% serum 4mg/ml BSA			
Mock	0.0	0.0			0.0	0.0		
WV-942	0.1	0.1	0.1	0.1	0.1	0.1	0.4	0.3
WV-2578	0.2	0.2	0.2	0.3	0.2	0.1	0.1	
WV-2579	0.4	0.4	0.2	0.2	0.1	0.1	0.2	0.2
WV-2580	0.2	0.2	0.2	0.3	0.0	0.0	0.3	0.3
WV-2581	0.0	0.0	0.3	0.3	0.1	0.1	0.1	0.1

	10uM, 15% serum				10uM 5% serum			
Mock	0.0	0.1			0.0	0.1		
WV-942	1.0	1.0	0.2	0.2	0.7	0.5	0.4	0.4
WV-2578	3.2			2.2	2.4	2.3	2.2	0.9
WV-2579			3.1	2.9			2.5	2.5
WV-2580	2.5	2.9	2.4	3.1	6.8	6.4	2.8	3.2
WV-2581	3.3	3.6	3.9	3.7	4.4	5.8	5.8	5.4

	10uM 5% serum 20mg/ml BSA				10uM 5% serum 4mg/ml BSA			
Mock	0.1	0.1			0.1	0.1		
WV-942	0.7	0.6	1.4	1.3	0.2	0.3	0.6	0.5
WV-2578	0.9	0.5	0.5	0.6	0.6	0.6	0.5	0.7
WV-2579	0.1	0.1	0.5	0.3	0.1	0.1	0.5	0.4
WV-2580	0.4	0.3	0.2	0.2			0.2	0.1
WV-2581	0.2	0.2	0.4	0.4	0.2	0.2	0.1	0.1

	3uM 15% serum				3uM 5% serum			
Mock	0.0	0.0			0.0	0.0		
WV-942	0.1	0.0	0.3	0.3	0.1	0.1	0.2	0.2
WV-2578	0.5	0.3	0.3	0.4	0.3	0.5	0.6	0.2
WV-2579	0.6	0.5	1.8	1.5	0.5	0.4	0.3	0.3
WV-2580	1.0	1.0	0.5	0.6	1.2	1.0	0.5	0.7
WV-2581	0.0	0.0	0.6	0.6	0.4	0.5	0.8	0.7

	3uM 5% serum 20mg/ml BSA				3uM 5% serum 4mg/ml BSA			
Mock	0.0	0.0			0.0	0.0		
WV-942	0.1	0.1	0.1	0.1	0.1	0.1	0.4	0.3
WV-2578	0.2	0.2	0.2	0.3	0.2	0.1	0.1	
WV-2579	0.4	0.4	0.2	0.2	0.1	0.1	0.2	0.2
WV-2580	0.2	0.2	0.2	0.3	0.0	0.0	0.3	0.3
WV-2581	0.0	0.0	0.3	0.3	0.1	0.1	0.1	0.1

Table 10I. Example data of certain oligonucleotides.

Oligonucleotides were tested in vitro at 10, 3 and 1 μM. Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

	10uM	3uM	1uM
Mock	0.0	0.1	0.0
WV-2531	21.7	8.7	3.2
WV-3152	26.1	15.3	5.7
WV-2745	24.0	10.7	4.8
WV-3463	6.6	3.0	0.8
WV-3464	16.1	6.2	2.4
WV-3465	16.4	6.0	1.8
WV-3466	13.0	5.7	2.0
WV-3467	12.6	5.8	2.6
WV-3469	14.2	6.0	1.5
WV-3470	24.9	11.9	6.4
WV-3471	4.9	1.6	1.0
WV-3472	20.1	12.4	7.2

WV-3473	24.9	11.4	7.6
WV-942	3.3	2.1	0.7

Table 10J. Example data of certain oligonucleotides.

Oligonucleotides were tested in vitro at 10, 3 and 1 μM. Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

	10uM		3uM		1uM	
WV-2531	32.9	32.0	16.9	16.7	6.2	6.2
WV-3360	27.2	26.5	13.4	14.2	6.0	5.9
WV-3361	28.9	28.0	16.7	16.1	6.3	6.0
WV-3362	34.3	32.9	16.2	15.5	6.1	5.8
WV-3363	33.2	33.6	16.4	16.0	6.7	6.4
WV-3364	47.9	47.6	14.2	14.0	6.4	6.5
WV-3365	25.6	24.2	14.7	14.2	6.9	6.4
WV-3366	34.6	34.0	21.1	19.8	8.0	7.4
WV-942	0.6	0.6	0.3	0.3	0.1	0.1
Mock	0.0	0.0	0.1	0.1	0.1	0.0

Table 10K. Example data of certain oligonucleotides.

Oligonucleotides were tested in vitro at 10 μM. In this table, numbers represent skipping efficiency relative to WV-942 (ave); results from replicate experiments are shown.

	Activity relative to WV-942	
WV-942	1.1	0.9
Mock	0.1	0.0
WV-2526	18.4	15.3
WV-2527	17.0	16.3
WV-2528	34.6	27.2
WV-2529	3.7	2.8
WV-2530	17.0	16.9
WV-2533	4.1	3.6
WV-2534	2.0	1.2
WV-2535	0.4	0.2
WV-2536	0.2	0.1
WV-2537	1.1	1.0

Table 10L. Example data of certain oligonucleotides.

Oligonucleotides were tested in vitro at 10 and 3 μM. In this table, numbers represent skipping efficiency relative to WV-942 (ave); results from replicate experiments are shown.

	Activity relative to WV-942 at 10 uM

WV-942	0.8	1.8	1.2
WV-1709	7.1	10.7	6.5
WV-1710	3.4	5.1	3.9
WV-1711	3.6	4.9	3.1
WV-1712	2.1	3.7	2.6
WV-1713	1.8	2.9	1.9
WV-1714	6.5	8.8	8.5
WV-1715	1.8	3.1	2.7
WV-1716	1.7	2.9	2.0
WV-2444	18.5	22.2	23.8
WV-2445	14.2	17.2	15.6
WV-2528	27.0	28.8	32.7
WV-2529	2.7	4.8	5.1
WV-2530	15.5	17.6	21.2
	Activity relative to WV-942 at 3 uM		
WV-942	0.7	1.7	0.6
WV-1709	10.9	19.5	12.2
WV-1710	3.6	8.3	4.3
WV-1711	3.6	8.1	4.6
WV-1712	3.0	6.7	5.8
WV-1713	2.0	5.3	0.9
WV-1714	7.5	13.8	7.8
WV-1715	2.6	5.8	3.6
WV-1716	3.2	6.1	3.1
WV-2444	30.3	41.9	39.7
WV-2445	23.4	32.3	30.2
WV-2528	56.3	66.3	74.4
WV-2529	7.5	15.0	10.0
WV-2530	25.2	38.4	37.8

[00814] In some embodiments, an oligonucleotide, e.g., a DMD oligonucleotide, can be tested in vivo for capability to skip an exon in a tissue in a live animal; in some embodiments, a tissue is gastrocnemius, triceps, quadriceps, diaphragm, and/or heart. In some embodiments, a live animal is a mouse, rat, monkey, dog, or non-human primate. In some embodiments, an oligonucleotide, e.g., a DMD oligonucleotide, is capable of mediating skipping, e.g., of exon 23, 45, 51, 53, or any other DMD exon. Various DMD oligonucleotides were shown to mediate skipping of DMD exon 51 in a tissue in a non-human primate (NHP), wherein the tissue was gastrocnemius, triceps, quadriceps, diaphragm, or heart.

[00815] In some embodiments, the present disclosure pertains to methods of administering oligonucleotides, e.g., DMD oligonucleotides, wherein the timeline of pre-differentiation (of myoblast cells to myotubules) and treatment with the oligonucleotide are suitably altered. In some embodiments, in

a test in vitro, an oligonucleotide, e.g., a DMD oligonucleotide to exon 51, was tested with treatment of 1 day or 4 day.

Table 11A. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency. PMO is a Morpholino having the sequence of CTCCAACATCAAGGAAGATGGCATTTCTAG.

Oligonucleotide	Group A	Group B	Group C
PMO	1.3	0.6	3.3
WV-3473	29.3	23.1	81.6

Conditions for Groups A to C in Table 11A.

	Group A	Group B	Group C
Pre-differentiation	1 day	2 day	0 day
ASO treatment	1 day	1 day	4 days
Wash-out	2 days	2 days	-

Example 19 describes various timelines for experiments suitable for testing oligonucleotides, e.g., DMD oligonucleotides, e.g., in patient-derived myoblasts in vitro.

Table 11B. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency. PMO is a control oligonucleotide which is a Morpholino corresponding to Eteplirsen. WV-942 is an oligonucleotide corresponding to Drisapersen. Oligonucleotides were delivered gymnotically.

Conc. (uM)	WV-942						PMO		
0.3	0.2	0.0	0.1	0.1		0.5	0.4	0.1	0.0
1	0.6	0.1	0.2	0.1		0.1	0.1	0.1	0.3
3	0.1	0.1	0.1	0.2	0.2	0.5	0.3	0.7	0.2
10	0.5	0.3	0.1	0.8	0.7	1.3	0.8	1.6	0.4
30	0.0	1.0	0.5	2.0	3.4	5.5	2.3	0.9	1.7

Conc. (uM)	WV-3473						WV-3545					
0.3	5.1	4.7	1.9	8.7	1.4	3.9	6.4	3.0	4.2	0.9	1.1	2.9
1	15.6	8.5	13.8	5.7	6.2	12.9	13.9	11.7	2.8	5.6	5.2	12.0
3	24.4	25.1	7.7	14.7	18.5	27.3	22.6	21.3	16.9	16.9		23.5
10	36.8	38.1	17.3	31.9	33.8	46.9	49.0	51.7	42.9	34.1	31.0	42.1
30	67.7		49.0	47.6	51.6	69.4	91.2	88.9	89.9	83.7	79.8	84.7

Conc. (uM)	WV-3546					
0.3	6.0	0.7	1.1	0.7	1.6	7.1
1	8.2	12.2	14.2	4.7	5.4	11.1

3	31.5				15.9	29.6
10	62.1	59.1	74.0	49.9	43.6	65.1
30	98.9	98.8	97.4	97.4	95.6	98.1

Table 11C. Example data of certain oligonucleotides.

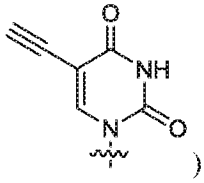
Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency. PMO is a control oligonucleotide which is a Morpholino corresponding to Eteplirsen. WV-942 is an oligonucleotide corresponding to Drisapersen. Oligonucleotides were delivered gymnotically.

Conc. (uM)	WV-942			PMO			WV-3473		
0.3	0.2	0.0	0.1	0.4	0.1	0.0	5.1	4.7	1.9
1	0.6	0.1	0.2	0.1	0.1	0.3	15.6	8.5	13.8
3	0.1	0.1	0.1	0.3	0.7	0.2	24.4	25.1	7.7
10	0.5	0.3	0.1	0.8	1.6	0.4	36.8	38.1	17.3
30	0.0	1.0	0.5	2.3	0.9	1.7	67.7		49.0

Conc. (uM)	WV-3545			WV-3546			WV-3543		
0.3	6.4	3.0	4.2	6.0	0.7	1.1	5.1	2.1	4.6
1	13.9	11.7	2.8	8.2	12.2	14.2	8.2	2.8	9.2
3	22.6	21.3	16.9	31.5			17.9	21.6	18.8
10	49.0	51.7	42.9	62.1	59.1	74.0	26.7	28.9	31.2
30	91.2	88.9	89.9	98.9	98.8	97.4	83.2	82.5	75.5

Conc. (uM)	WV-3544			WV-3554			WV-4107		
0.3	5.6	3.0	3.1	2.2	2.0	4.0	1.1	1.0	0.8
1	12.4	9.8	12.0	12.6	4.5	8.4	3.9	2.3	4.0
3	22.7	23.9	15.7	18.6	15.7	18.3	15.7	14.1	13.5
10	37.8	32.0	35.1	42.3	36.8	33.0	70.0	53.6	64.3
30	80.4	81.3	79.1	86.4	91.1	84.3	93.6	92.0	93.0

[00816] In some embodiments, an oligonucleotide comprises a derivative of U. In some embodiments, an oligonucleotide capable of mediating skipping of an exon of DMD comprises a derivative of U. In some embodiments, an oligonucleotide capable of mediating skipping of an exon of DMD and comprises a derivative of U and at least one chirally controlled internucleotidic linkage. In some embodiments, an oligonucleotide capable of mediating skipping of an exon of DMD and comprises a derivative of U and at least one chirally controlled phosphorothioate internucleotidic linkage. In some



embodiments, a derivative of U is BrU or Acet5U ( ).

[00817] In some embodiments, an oligonucleotide comprises BrU. In some embodiments, an oligonucleotide capable of mediating skipping of an exon of DMD comprises BrU. In some embodiments, an oligonucleotide capable of mediating skipping of an exon of DMD and comprises BrU and at least one chirally controlled internucleotidic linkage. In some embodiments, an oligonucleotide capable of mediating skipping of an exon of DMD and comprises BrU and at least one chirally controlled phosphorothioate internucleotidic linkage.

[00818] In some embodiments, an oligonucleotide comprises Acet5U. In some embodiments, Acet5U is also designated AcetU or acetU. In some embodiments, an oligonucleotide capable of mediating skipping of an exon of DMD comprises Acet5U. In some embodiments, in an oligonucleotide, e.g., DMD oligonucleotide, any U or T can be optionally replaced by Acet5U (e.g., in a first wing, a core, a second wing, or anywhere in the oligonucleotide). In some embodiments, an oligonucleotide capable of mediating skipping of an exon of DMD comprises an Acet5mU nucleoside unit, wherein the base is Acet5U and the sugar is the common natural RNA sugar wherein the 2'-OH is replaced with 2'-OMe. In some embodiments, an oligonucleotide comprises an Acet5fU nucleoside unit, wherein the base is Acet5U and the sugar is the common natural RNA sugar wherein the 2'-OH is replaced with 2'-F. In some embodiments, an oligonucleotide capable of mediating skipping of an exon of DMD and comprises Acet5U and at least one chirally controlled internucleotidic linkage. In some embodiments, an oligonucleotide capable of mediating skipping of an exon of DMD and comprises Acet5U and at least one chirally controlled phosphorothioate internucleotidic linkage.

[00819] As shown in Table 11D, Table 11E, and Table A1, certain oligonucleotides, e.g., DMD oligonucleotides, were designed and constructed comprising BrU or acet5U. In some oligonucleotides, the nucleoside at the 5' end comprises BrU or acet5U. In some embodiments, oligonucleotides comprise a BrfU nucleoside unit, wherein the base is BrU and the sugar is the common natural RNA sugar wherein the 2'-OH is replaced with 2'-F. In some oligonucleotides, the oligonucleotide comprises a BrdU nucleoside unit, wherein the base is BrU and the sugar is 2-deoxyribose (common natural DNA sugar). In some embodiments, any U or T can be replaced by BrU (e.g., in a first wing, a core, a second wing, or anywhere within an oligonucleotide). In some embodiments, in an oligonucleotide, e.g., a DMD oligonucleotide, any number of U or T can be replaced by BrU and/or Acet5U.

[00820] In some embodiments, an oligonucleotide comprises an acet5fU nucleoside unit, wherein the base is acet5U and the sugar is the common natural RNA sugar wherein the 2'-OH is replaced with

2'-F.

[00821] Table 11D shows data of various DMD oligonucleotides which mediate skipping of exon 51, including oligonucleotide WV-7410, which comprises BrfU, and WV-7413, which comprises acet5fU. Percentage was measured using RT-qPCR. Gymnotic delivery of 10 μM and 3 μM oligonucleotides in Δ48-50 patient derived myoblasts (4 days post-differentiation). The experiment was done in technical replicates.

Table 11D. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency. Approximate numbers are provided.

	WV-3152	WV-3516	WV-7410	WV-7413
10 μM	39	10	49	11
3 μM	20	6	34	6

In some embodiments, the present disclosure provides oligonucleotides, e.g., various DMD oligonucleotides, that comprise BrdU at or near the center of the oligonucleotides (e.g., in a core region, middle region, etc.). In some embodiments, example such oligonucleotides include WV-2812, WV-2813, and WV-2814. Certain exon skipping data of these oligonucleotides were presented below.

Table 11E. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 1.000 would represent 100% skipping and 0.0 represents 0% efficiency. Approximate numbers are provided.

	10uM		3uM	
WV-1714	0.035	0.034	0.012	0.013
WV-2812	0.094	0.095	0.023	0.024
WV-942	0.004	0.004	0.001	0.001
WV-2814	0.004	0.005	0.002	0.002
WV-2813	0.041	0.042	0.017	0.017

Table 11F. Example data of certain oligonucleotides.

Additional DMD oligonucleotides for skipping Exon 51 were constructed. Various DMD oligonucleotides comprise BrU. In some cases, a BrU is attached to a sugar which is 2'-F modified (BrfU). D48-50 myoblasts were dosed at 10 uM and 3 uM in differentiation media for 4 days. Percentage of skipping is shown, wherein 100 would represent 100% skipping and 0 would represent 0% skipping.

	10 uM				3 uM			
WV-9738	44.7	44.0	46.1	45.4	26.6	25.9	25.6	24.4
WV-9739	51.8	49.9	53.2	50.9	32.3	35.4	31.0	33.2

WV-9740	49.9	48.8	47.8	46.1	32.5	30.3	29.0	29.6
WV-9741	36.1	37.8	35.0	35.6	23.5	22.3	21.4	24.6
WV-9742	53.4	54.8	59.1	56.8	41.7	40.4	37.6	40.3
WV-7410	64.8	63.9	65.4	67.0	45.1	43.5	43.9	40.6
WV-7410	66.0	67.2	64.7	64.5	44.9	40.3	33.7	31.7
WV-3152	47.0	45.7	47.1	45.0	28.3	30.2	25.3	22.6
WV-3516	12.5	12.5	9.7	10.4	5.0	4.9	5.2	4.6
MOCK	0.5	0.3	0.5	0.3	0.5	0.6	0.8	0.4
MOCK	0.6	0.4	0.5	0.5	0.6	0.6	0.3	0.4
MOCK	0.3	0.3	0.6	0.2	0.4	0.4	0.2	0.6

Table 11G. Activity of certain oligonucleotides

Activity of various DMD exon 51 oligonucleotides was tested in vitro.

Numbers indicate amount of skipping DMD exon 23 (as a percentage of total mRNA, where 100 would represent 100% skipped).

Amounts tested were: 10, 3.3 and 1.1 uM.

	10	3.3	1.1		10	3.3	1.1
WV-3152	20.8	9	4.1	WV-14522	36.9	10.4	4.7
	22	10	4.9		27.4	10.4	4.2
	17.3	9.3	3.2		21	12.6	5.6
	21.3	7.2	4.4		26.5	10.4	5.7
WV-15860	27.4	13.2	12.7	WV-14523	27.2	8.1	6.2
	30.4	15.4	9		28.3	8.5	4.9
	33	14.2	6		18.4	9.1	3.6
	33.4	16.9	5.9		18.7	9.6	4.4
WV-15861	26.6	9.2	5.6	Mock	0.21		
	28.5	6.1	5.4		0.35		
	34.1	8.2	5.2		0.48		
	29.9	11.1	4		0.24		
WV-15862	30.7		7.8				
	33.3		7.2				
	21.9	15.1	6.8				
	26.4	13.2	7.2				

Table 11H. Activity of certain oligonucleotides

Oligonucleotides for skipping DMD exon 51 were tested in vitro.

Numbers indicate amount of skipping DMD exon 23 (as a percentage of total mRNA, where 100

would represent 100% skipped).

Concentrations of oligonucleotides used: 10, 3.3 and 1.1 uM.

	10uM	3.3uM	1.1uM		10uM	3.3uM	1.1uM
Mock	0.2	0.3	0.2	WV-17861	37.6	22.6	9
	0.3	0.2	0.3		38.8	22.5	8.9
	0.2	0	0.2		40.7	24.4	13.2
	0.2	0.6	0.2		41.7	25.4	11.6
WV-7336	3.1	1.6	0.7	WV-17862	38.4	18.9	8.1
	8.9	1.8	0.1		34.1	19.6	9
	5.4	1.4	0.9		34.8	26	10
	4.9	1.5	0.7		36.1	21.4	9.5
WV-3152	32.4	26.5	7.5	WV-17863	32.7	18.2	9.2
	27.2	22.2	8.4		35.1	18.9	9.3
	28	14.5	7.6		34.8	18.2	8.6
	26.8	14.8	7.3		30.7	17	9
WV-15860	43.3	25.7	10.2	WV-17864	37.3	23.6	11.7
	37.9	23.8	9.6		41.4	23.3	10.6
	38.4	24.5	11.2		39.9	20.6	17.5
	42.4	21.9	11		38.8	21.7	10.2
WV-17859	42.3	26.7	16.3	WV-17865	35.9	16.5	9.3
	41.3	26	16.8		34	16.7	7.5
	39.9	22.9	15.5		34.4	17.5	11.9
	48.6	23.6	14.9		34.1	17.8	9.8
WV-17860	38.1	19.3	11.7	WV-17866	48.7	28.4	17.7
	35.3	19.2	12		43.3	28.6	13.1
	41	28.2	16.4		44.5	24.8	15.4
	40.4	21.9	11.1		45.1	30.5	16.3

Table 11I. Activity of certain oligonucleotides

Oligonucleotides for skipping DMD exon 51 were tested in vitro.

Numbers indicate amount of skipping DMD exon 23 (as a percentage of total mRNA, where 100 would represent 100% skipped).

Concentrations of oligonucleotides used: 10 and 3.3 uM.

	10uM	3.3uM		10uM	3.3uM
	0	0		14.6	4.8
	0	0			
	0	0	WV-20058	12	3.7
Mock	0	0		12.6	3.5
WV-	15.9	7	WV-	35.8	26.5

20034	17.1	8.4	20061		
	16.1	7.3		39.3	24.2
	15.3	7.2		39.9	22.8
	29.7	18.3		26.5	17.6
	27.2	17.5			
WV-20037	26.6	19.4	WV-20064	24.5	16.4
	29.2	18.4		27.5	17.1
	9.6	4.9		15.7	8.3
	9.1	5.2		16.8	9.3
WV-20040	11.4	3.5	WV-20067	17.3	8.6
	10.9	2.9		16.3	8.7
	20.2	9.6		41.3	26.4
	20.4	9.8		31.7	22.3
WV-20043	18.9	9.8	WV-20070	39.7	27.2
	21	10.4		38.4	26.9
	28.5	14.7		30.9	21.1
	29.8	14.2		26.9	17.9
WV-20046	29.2	15.8	WV-20073	31.1	20.2
	26.6	14.5		30.7	22.2
	20.9	11.6		23.2	16.8
				18.9	11.4
WV-20049	18.6	12.2	WV-20076	21.8	16.9
	18.4	11.7		22.8	15.8
	28.8	18.8		35.7	24.8
WV-20052	30.1	18.6	WV-3152	33.5	24.9
	29.6	20.1		32.1	25.3
	26.8	17		41.9	27.5
WV-20055	25.3	16.6	WV-15860	43.6	30.7
	24.1	17		42.4	30

Table 11J. Activity of certain oligonucleotides

Oligonucleotides for skipping DMD exon 51 were tested in vitro.

Oligonucleotides were dosed 4d at 10uM.

Numbers indicate amount of skipping DMD exon 51 (as a percentage of total mRNA, where 100 would represent 100% skipped).

WV-3152	19	20	12	14	WV-20093	35	34	35	38
WV-15860	29	31	26	23	WV-20092	25	26	25	25
WV-20140	1	1	1	1	WV-20091	28	27	30	32

WV-20139	3	3	2	2	WV-20090	21	19	22	22
WV-20138			2	3	WV-20089	8	7	8	9
WV-20137	4	5			WV-20088	22	21	26	25
WV-20136					WV-20087	28	28	33	32
WV-20135	5	5	5	5	WV-20086	25	25	27	26
WV-20134	5	6	5	4	WV-20085	33	31	30	31
WV-20133	17	17	13	13	WV-20084	21	22	21	21
WV-20132	8	8	6	6	WV-20083	21	21	19	17
WV-20131	14	16	12	12	WV-20082	42	37	32	30
WV-20130	10	9	8	8	WV-20081	41	41	30	30
WV-20129	12	14	11	11	WV-20080	49	44	26	25
WV-20128	9	9	8	8	WV-20079	42	38	53	51
WV-20127			8	8	WV-20078	27	28	36	35
WV-20126	7	8	8	7	WV-20077	10	10	10	10
WV-20125	8	8	8	8	WV-20076	45	45	45	41
WV-20124	22	21	21	21	WV-20075	40	31	37	42
WV-20123	13	13	14	12	WV-20074	55	57	53	56
WV-20122	11	12	12	11	WV-20073	51	55	51	50
WV-20121	21	22	22	21	WV-20072	41	36	37	36
WV-20120	28	30	32	33	WV-20071	42	40	44	46
WV-20119	52	50			WV-20070	18	18	25	25
WV-20118	39	37	27	26	WV-20069	11	11	10	9
WV-20117	18	17	15	18	WV-20068	20	17	20	18
WV-20116	20	20	17	17	WV-20067	12	9	11	11
WV-20115	8	8	8	6	WV-20066	12	11	13	12
WV-20114	19	20	15	14	WV-20065	16	15	16	14
WV-20113	20	18	17	15	WV-20064	37	35	37	36
WV-20112	16	15	12	12	WV-20063	19		24	22
WV-20111	31	30	33	31	WV-20062	6	6	7	7
WV-20110	14	14	14	12	WV-20061	24	23	26	24
WV-20109	20	21	25	24	WV-20060	16	17	16	17
WV-20108	27	25	22	22	WV-20059	55	42	62	67
WV-20107	20	19	16	14	WV-20058	28	30	33	33
WV-20106	44	42	34	37	WV-20057	37	38	37	34
WV-20105	23	22	18	18	WV-20056	35	34	33	35
WV-20104	41	40	33	28	WV-20055			40	40
WV-20103	48	52	53	53	WV-20054	25	25	35	36
WV-20102	54	52	55	59	WV-20053	43	45	46	46
WV-20101	38	39	38	43	WV-20052	47	47	53	46
WV-20100	52	51	48	50	WV-20051	30	33	30	30
WV-20099	53	51	47	48	WV-20050	29	28	28	26

WV-20098	46	44	45	46	WV-20049	41	41	38	38
WV-20097	47	46	51	48	WV-20049	24	23	22	21
WV-20096	45	41	42	43					
WV-20095	43	41	50	47					
WV-20094	55	50	57	55					

Example Dystrophin Oligonucleotides and Compositions Which Target Exon 52

[00822] In some embodiments, the present disclosure provides oligonucleotides, oligonucleotide compositions, and methods of use thereof for targeting exon 52 and/or mediating skipping of exon 52 in human DMD. Non-limiting examples include oligonucleotides and compositions of Exon 52 oligos include: WV-13733, WV-13734, WV-13735, WV-13736, WV-13737, WV-13738, WV-13739, WV-13740, WV-13741, WV-13742, WV-13743, and WV-13744, WV-13782, and WV-13783, and other oligonucleotides having a base sequence which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

Table 12A. Example data of certain oligonucleotides.

Skipping efficiency of various DMD oligonucleotides, tested for skipping of DMD exon 52.

WV-13733	0.3	0.2
WV-13734	0.0	0.0
WV-13735	1.6	0.3
WV-13736	3.9	1.3
WV-13737	0.7	0.4
WV-13738	0.0	0.0
WV-13739	28.3	29.3
WV-13740	29.9	33.3
WV-13741	1.6	1.6
WV-13742	12.9	14.1
WV-13743	0.9	1.0
WV-13744	0.6	0.7
WV-13782	0.1	0.1
WV-13783	0.8	0.0
Mock	0.0	0.0
Mock	0.1	0.1

Example Dystrophin Oligonucleotides and Compositions for Exon Skipping of Exon 53

[00823] In some embodiments, the present disclosure provides oligonucleotides, oligonucleotide compositions, and methods of use thereof for mediating skipping of exon 53 in DMD (e.g., of mouse, human, etc.).

[00824] In some embodiments, an oligonucleotide, e.g., a human DMD exon 53 skipping oligonucleotide can be tested in a mouse which has been modified to comprise a DMD gene comprising the human exon 53 sequence.

[00825] In some embodiments, an oligonucleotide, e.g., a DMD oligonucleotide, is capable of mediating skipping of exon 53. Non-limiting examples of such oligonucleotides include: WV-10439, WV-10440, WV-10441, WV-10442, WV-10443, WV-10444, WV-10445, WV-10446, WV-10447, WV-10448, WV-10449, WV-10450, WV-10451, WV-10452, WV-10453, WV-10454, WV-10455, WV-10456, WV-10457, WV-10458, WV-10459, WV-10460, WV-10461, WV-10462, WV-10463, WV-10464, WV-10465, WV-10466, WV-10467, WV-10468, WV-10469, WV-10470, WV-10487, WV-10488, WV-10489, WV-10490, WV-10491, WV-10492, WV-10493, WV-10494, WV-10495, WV-10496, WV-10497, WV-10498, WV-10499, WV-10500, WV-10501, WV-10502, WV-10503, WV-10504, WV-10505, WV-10506, WV-10507, WV-10508, WV-10509, WV-10510, WV-10511, WV-10512, WV-10513, WV-10514, WV-10515, WV-10516, WV-10517, WV-10518, WV-10519, WV-10520, WV-10521, WV-10522, WV-10523, WV-10524, WV-10525, WV-10526, WV-10527, WV-10528, WV-10529, WV-10530, WV-10531, WV-10532, WV-10533, WV-10534, WV-10535, WV-10536, WV-10537, WV-10538, WV-10539, WV-10540, WV-10541, WV-10542, WV-10543, WV-10544, WV-10545, WV-10546, WV-10547, WV-10548, WV-10549, WV-10550, WV-10551, WV-10552, WV-10553, WV-10554, WV-10555, WV-10556, WV-10557, WV-10558, WV-10559, WV-10560, WV-10561, WV-10562, WV-10563, WV-10564, WV-10565, WV-10566, WV-10567, WV-10568, WV-10569, WV-10570, WV-10571, WV-10572, WV-10573, WV-10574, WV-10575, WV-10576, WV-10577, WV-10578, WV-10579, WV-10580, WV-10581, WV-10582, WV-10583, WV-10584, WV-10585, WV-10586, WV-10587, WV-10588, WV-10589, WV-10590, WV-10591, WV-10592, WV-10593, WV-10594, WV-10595, WV-10596, WV-10597, WV-10598, WV-10599, WV-10600, WV-10601, WV-10602, WV-10603, WV-10604, WV-10605, WV-10606, WV-10607, WV-10608, WV-10609, WV-10610, WV-10611, WV-10612, WV-10613, WV-10614, WV-10615, WV-10616, WV-10617, WV-10618, WV-10619, WV-10620, WV-10621, WV-10622, WV-10623, WV-10624, WV-10625, WV-10626, WV-10627, WV-10628, WV-10629, WV-10630, WV-10670, WV-10671, WV-10672, WV-11340, WV-11341, WV-11342, WV-11544, WV-11545, WV-11546, WV-11547, WV-13835, WV-13864, WV-14344, WV-4698, WV-4699, WV-4700, WV-4701, WV-4702, WV-4703, WV-4704, WV-4705, WV-4706, WV-4707, WV-4708, WV-4709, WV-4710, WV-4711, WV-4712, WV-4713, WV-4714, WV-4715, WV-4716, WV-4717, WV-4718, WV-4719, WV-4720, WV-4721, WV-4722, WV-4723, WV-4724, WV-4725, WV-4726, WV-4727, WV-4728, WV-4729, WV-4730, WV-4731, WV-4732, WV-4733, WV-4734, WV-4735, WV-4736, WV-4737, WV-4738, WV-4739, WV-4740, WV-4741, WV-4742, WV-4743, WV-4744, WV-4745, WV-4746, WV-4747, WV-

4748, WV-4749, WV-4750, WV-4751, WV-4752, WV-4753, WV-4754, WV-4755, WV-4756, WV-4757, WV-4758, WV-4759, WV-4760, WV-4761, WV-4762, WV-4763, WV-4764, WV-4765, WV-4766, WV-4767, WV-4768, WV-4769, WV-4770, WV-4771, WV-4772, WV-4773, WV-4774, WV-4775, WV-4776, WV-4777, WV-4778, WV-4779, WV-4780, WV-4781, WV-4782, WV-4783, WV-4784, WV-4785, WV-4786, WV-4787, WV-4788, WV-4789, WV-4790, WV-4791, WV-4792, WV-4793, WV-9067, WV-9068, WV-9069, WV-9070, WV-9071, WV-9072, WV-9073, WV-9074, WV-9075, WV-9076, WV-9077, WV-9078, WV-9079, WV-9080, WV-9081, WV-9082, WV-9083, WV-9084, WV-9085, WV-9086, WV-9087, WV-9088, WV-9089, WV-9090, WV-9091, WV-9092, WV-9093, WV-9094, WV-9095, WV-9096, WV-9097, WV-9098, WV-9099, WV-9100, WV-9101, WV-9102, WV-9103, WV-9104, WV-9105, WV-9106, WV-9107, WV-9108, WV-9109, WV-9110, WV-9111, WV-9112, WV-9113, WV-9114, WV-9115, WV-9116, WV-9117, WV-9118, WV-9119, WV-9120, WV-9121, WV-9122, WV-9123, WV-9124, WV-9125, WV-9126, WV-9127, WV-9128, WV-9129, WV-9130, WV-9131, WV-9132, WV-9133, WV-9134, WV-9135, WV-9136, WV-9137, WV-9138, WV-9139, WV-9140, WV-9141, WV-9142, WV-9143, WV-9144, WV-9145, WV-9146, WV-9147, WV-9148, WV-9149, WV-9150, WV-9151, WV-9152, WV-9153, WV-9154, WV-9155, WV-9156, WV-9157, WV-9158, WV-9159, WV-9160, WV-9161, WV-9162, WV-9422, WV-9423, WV-9424, WV-9425, WV-9426, WV-9427, WV-9428, WV-9429, WV-9511, WV-9512, WV-9513, WV-9514, WV-9515, WV-9516, WV-9517, WV-9518, WV-9519, WV-9520, WV-9521, WV-9522, WV-9523, WV-9524, WV-9525, WV-9534, WV-9535, WV-9536, WV-9537, WV-9538, WV-9539, WV-9680, WV-9681, WV-9682, WV-9683, WV-9684, WV-9685, WV-9686, WV-9687, WV-9688, WV-9689, WV-9690, WV-9691, WV-9699, WV-9700, WV-9701, WV-9702, WV-9703, WV-9704, WV-9709, WV-9710, WV-9711, WV-9712, WV-9713, WV-9714, WV-9715, WV-9743, WV-9744, WV-9745, WV-9746, WV-9747, WV-9748, WV-9749, WV-9750, WV-9751, WV-9752, WV-9753, WV-9754, WV-9755, WV-9756, WV-9757, WV-9758, WV-9759, WV-9760, WV-9761, WV-9897, WV-9898, WV-9899, WV-9900, WV-9901, WV-9902, WV-9903, WV-9904, WV-9905, WV-9906, WV-9907, WV-9908, WV-9909, WV-9910, WV-9911, WV-9912, WV-9913, WV-9914, WV-7436, WV-7437, WV-7438, WV-7439, WV-7440, WV-7441, WV-7442, WV-7443, WV-7444, WV-7445, WV-7446, WV-7447, WV-7448, WV-7449, WV-7450, WV-7451, WV-7452, WV-7453, WV-7454, WV-7455, and WV-7456, and other DMD oligonucleotides having a base sequence which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

[00826] Additional examples of such DMD oligonucleotides include: WV-9422, WV-9425, WV-9426, WV-9517, WV-9519, WV-9521, WV-9522, WV-9524, WV-9710, WV-9714, WV-9715, WV-9743, WV-9744, WV-9745, WV-9746, WV-9747, WV-9748, WV-9749, WV-9750, WV-9751, WV-9756, WV-9757, WV-9758, WV-9759, WV-9760, WV-9761, WV-9897, WV-9898, WV-9899, WV-

9900, WV-9906, and WV-9912, and other DMD oligonucleotides having a base sequence which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

[00827] Non-limiting examples of such DMD oligonucleotides also include: WV-12123, WV-12124, WV-12125, WV-12126, WV-12127, WV-12128, WV-12129, WV-12553, WV-12554, WV-12555, WV-12556, WV-12557, WV-12558, WV-12559, WV-12872, WV-12873, WV-12876, WV-12877, WV-12878, WV-12879, WV-12880, WV-12881, WV-12882, and WV-12883, and other DMD oligonucleotides having a base sequence which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

[00828] Results of various experiments for skipping Dystrophin exon 53 are described in the present disclosure. For example, data from a sequence identification screen are shown below, in Table 13A.

Table 13A. Example data of certain oligonucleotides.

Skipping efficiency of various DMD oligonucleotides, tested for skipping of DMD exon 53 in vitro in Delta 52 human myoblast cells. Oligonucleotides tested were 6-8-6 gapmers (2'-F-2'-OMe-2'-F), wherein each internucleotidic linkage is a stereorandom phosphorothioate. Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

Oligonucleotide	Replicate 1	Replicate 2	Oligonucleotide	Replicate 1	Replicate 2
WV-4698	1.9	2.1	WV-4747	2.5	3.5
WV-4699	2.0	2.2	WV-4748	2.1	1.7
WV-4700	2.8	3.0	WV-4749	2.4	2.4
WV-4701	3.7	2.9	WV-4750	2.3	2.9
WV-4702	2.9	2.7	WV-4751	1.9	2.5
WV-4703	1.8	2.4	WV-4752	2.2	1.6
WV-4704	3.2	3.4	WV-4753	1.6	2.0
WV-4705	3.7	4.3	WV-4754	1.7	2.0
WV-4706	2.6	2.6	WV-4755	1.7	1.9
WV-4707	3.2	3.6	WV-4756	1.7	1.5
WV-4708	4.8	6.0	WV-4757	1.6	1.9
WV-4709	6.6	5.2	WV-4758	1.6	2.0
WV-4710	3.9	4.6	WV-4759	1.6	1.6
WV-4711	5.4	6.7	WV-4760	1.8	1.8
WV-4712	5.3	6.4	WV-4761	1.9	1.6
WV-4713	5.8	8.0	WV-4762	1.2	1.3
WV-4714	2.9	3.6	WV-4763	0.9	2.0
WV-4715	3.3	4.3	WV-4764	3.0	2.7
WV-4716	3.8	4.3	WV-4765	3.4	3.2

WV-4717	6.8	7.0	WV-4766	2.5	2.3
WV-4718	4.3	5.0	WV-4767	2.5	2.7
WV-4719	5.5	6.0	WV-4768	2.3	2.7
WV-4720	7.7	8.6	WV-4769	2.4	2.4
WV-4721	2.7	3.8	WV-4770	2.8	2.8
WV-4722	3.8	4.6	WV-4771	2.3	2.9
WV-4723	3.4	5.6	WV-4772	4.0	2.5
WV-4724	3.5	4.7	WV-4773	3.2	1.8
WV-4725	4.9	6.3	WV-4774	3.0	2.3
WV-4726	4.2	4.4	WV-4775	4.4	3.3
WV-4727	2.7	4.9	WV-4776	3.1	3.8
WV-4728	2.6	5.6	WV-4777	4.5	2.1
WV-4729	3.9	4.1	WV-4778	0.0	2.0
WV-4730	2.4	3.3	WV-4779	2.8	3.4
WV-4731	1.8	2.5	WV-4780	3.2	3.5
WV-4732	1.8	2.3	WV-4781	2.9	3.2
WV-4733	2.3	2.1	WV-4782	1.8	2.9
WV-4734	2.0	2.0	WV-4783	2.1	2.6
WV-4735	2.5	2.7	WV-4784	2.4	2.4
WV-4736	2.7	3.0	WV-4785	3.4	3.6
WV-4737	3.2	3.1	WV-4786	1.8	1.6
WV-4738	3.1	3.5	WV-4787	2.9	2.7
WV-4739	2.6	2.4	WV-4788	2.8	3.1
WV-4740	4.4	3.6	WV-4789	4.3	4.0
WV-4741	3.7	4.1	WV-4790	3.9	2.6
WV-4742	4.5	4.9	WV-4791	2.2	2.2
WV-4743	5.0	5.2	WV-4792	2.5	3.2
WV-4744	3.6	4.7	WV-4793	2.4	2.6
WV-4745	4.1	0.0	Mock	1.3	1.6
WV-4746	2.9	2.0			

[00829] A number of oligonucleotides were generated and tested for efficacy in skipping DMD Exon 53 in vitro in human patient-derived myoblast cells; certain results are shown below in Tables 13B to 21 (A and B). Oligonucleotides were used at concentrations of 3 and 10 uM, in two replicates (R1 and R2). Numbers indicate the percentage of skipping of DMD exon 53, wherein 0.0 would indicate no skipping, and 100.0 would indicate 100% skipping. Several base sequences were tested in combination with a variety of chemical formats. For example, in some embodiments, a base sequence is GUACUUCAUCCCACUGAUUC, GUGUUCTTGTACTTCAUCCC, UUCUGAAGGTGTTCUUGUAC, or CUCCGGTTCTGAAGGUGUUC, wherein U is optionally substituted with T and vice versa. Various chemical formats were utilized, including, e.g., gapmers (for example, 6-8-6 wing-core-wing gapmers). In some embodiments, both wings are 2'-F, while the core

was all 2'-MOE, alternating 2'-MOE/2-OMe, alternating 2'-OMe/2'-MOE, alternating 2'-MOE/2'-F, alternating 2'-F/2'-MOE, alternating 2'-OMe/2'-F, and alternating 2'-F/2'-OMe, etc. In some embodiments, the first wing was 2'-MOE or 2'-OMe and the second wing was 2'-F (a type of asymmetrical gapmers). In some embodiments, each internucleotidic linkage is a stereorandom phosphorothioate. In some embodiments, some alternating phosphorothioate linkages are replaced by phosphodiester linkages. In some embodiments, 5'-methyl 2'-MOE C is used. Descriptions of certain oligonucleotides tested are provided in **Table A1**.

Table 13B. Example data of certain oligonucleotides.

Efficacy of DMD Exon 53 skipping of various DMD oligonucleotides in vitro. Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency. Results from replicate experiments are shown.

Oligonucleotide	Replicate 1		Replicate 2	
	10 uM	3 uM	10 uM	3 uM
WV-9067	6.6		1.9	1.8
WV-9068	6.5		1.5	1.6
WV-9069	6.9	1.8	1.7	1.5
WV-9070	2.9	3.2	2.6	1.9
WV-9071	2.9	1.9	2.0	1.4
WV-9072	9.6	2.4	2.4	1.5
WV-9073	8.6	3.3	2.7	2.1
WV-9074	8.3	2.4	2.5	1.9
WV-9075	7.0	2.1	2.1	2.0
WV-9076	9.6	3.0	3.1	2.0
WV-9077	6.3	1.7	2.0	1.5
WV-9078	6.1	2.3	2.2	1.9
WV-9079	10.0	3.9	3.6	2.3
WV-9080	7.6	3.1	2.8	2.6
WV-9081	5.7	2.2	1.9	1.6
WV-9082	11.2	6.1	6.4	3.2
WV-9083	6.0	1.9	2.1	1.6
WV-9084	6.6	2.4	2.9	2.1
WV-9085	0.0	7.5	7.6	3.4
WV-9086	7.5	3.4	3.1	2.0
WV-9087	7.1	2.4	2.1	1.7
WV-9088	9.0	3.0	2.6	1.6
WV-9089	8.2	2.5	2.3	1.9
WV-9090	0.0	2.3	2.2	1.6
WV-9091	9.9	4.7	3.7	3.2
WV-9092	9.0	3.4	3.4	2.0
WV-9093	8.7	2.9	3.2	2.0

WV-9094	11.9	6.0	5.2	3.1
WV-9095	7.5	3.4	2.6	2.5
WV-9096	10.1	4.0	4.0	2.9
WV-9097	10.7	5.7	4.5	2.8
WV-9098	8.5	3.6	2.9	2.3
WV-9099	8.1	2.9	2.4	2.4
WV-9100	12.7	6.0	4.7	2.9
WV-9101	7.6	2.9	3.1	2.0
WV-9102	9.9	4.0	3.6	2.5
WV-9103	12.6	6.9	6.1	3.0
WV-9104	11.3	3.7	4.3	2.1
WV-9105	6.5	2.9	2.3	2.4
WV-9106	15.1	7.7	5.5	4.3
WV-9107	7.8	2.5	2.2	2.6
WV-9108	11.3	3.3	3.5	2.2
WV-9109	16.1	10.6	8.9	4.1
WV-9110	8.8	3.5	3.4	1.7
WV-9111	7.3	3.4	2.5	1.7
WV-9112	11.5	4.6	3.4	2.2
WV-9113	10.6	4.2	3.1	2.3
WV-9114	10.8	4.9	4.1	2.6
WV-9115	8.4	0.0	2.5	2.1
WV-9116	7.5	0.0	1.6	1.8
WV-9117	6.8	0.0	2.0	1.5
WV-9118	9.3	0.0	2.7	2.1
WV-9119	7.2	0.6	2.0	2.0
WV-9120	8.5	6.1	2.5	2.0
WV-9121	11.8	5.7	3.9	2.5
WV-9122	8.6	4.0	2.4	2.4
WV-9123	10.7	5.2	2.0	2.0
WV-9124	11.0	5.3	3.6	3.2
WV-9125	8.7	3.5	2.3	2.2
WV-9126	10.5	3.4	3.4	2.4
WV-9127	8.5	3.4	2.7	2.5
WV-9128	8.2	2.9	2.0	2.2
WV-9129	7.5	2.6	1.6	1.7
WV-9130	12.6	0.0	5.4	2.7
WV-9131	7.6	2.3	2.2	1.8
WV-9132	8.4	0.7	3.4	2.3
WV-9133	16.2	7.0	6.9	3.2
WV-9134	8.5	3.9	3.0	1.9
WV-9135	12.5	2.8	2.9	1.7
WV-9136	8.7	4.1	3.1	2.2

WV-9137	7.5	2.5	1.7	1.6
WV-9138	7.2	2.7	2.1	1.7
WV-9139	9.3	5.3	5.1	2.8
WV-9140	8.0	3.1	2.5	2.1
WV-9141	7.7	3.3	2.9	1.8
WV-9142	11.9	6.4	6.0	3.2
WV-9143	7.0	3.2	3.9	1.8
WV-9144	9.8	4.0	3.6	2.7
WV-9145	13.0	6.6	5.3	2.6
WV-9146	7.9	3.7	3.4	1.9
WV-9147	8.2	3.9	3.1	2.0
WV-9148	15.0	8.8	6.4	3.3
WV-9149	6.9	2.9	2.3	3.1
WV-9150	10.8	6.9	5.6	1.9
WV-9151	12.9	7.2	5.1	2.7
WV-9152	8.4	3.4	2.6	1.5
WV-9153	7.2	3.9	2.9	1.7
WV-9154	21.5	14.1	12.4	4.3
WV-9155	6.9	3.3	2.5	1.6
WV-9156	11.0	6.4	4.9	2.4
WV-9157	16.7	10.5	9.7	3.9
WV-9158	7.7	3.7	2.3	1.7
WV-9159	7.7	3.1	3.3	1.5
WV-9160	8.0	3.1	2.8	1.8
WV-9161	8.4	4.5	3.2	2.2
WV-9162	8.9	4.5	4.7	2.2
Mock	2.4			
Mock	2.1			

WV-9746	2.5	2.5	4.6	3.4
WV-9747	3.0	3.1	5.5	4.8
WV-9748	4.9	2.5	4.3	4.0
WV-9749	2.9	2.7	4.5	4.1
WV-9750	3.2	2.5	4.4	3.8
WV-9751	3.5	2.7	4.7	4.8
WV-9758	1.7	1.9	2.1	3.5
WV-9759	2.6	3.6	2.8	6.1
WV-9760	3.1	3.9	3.4	4.8
WV-9761	3.0	4.8	4.6	7.2
WV-9756	3.9	4.4	5.3	8.4
WV-9757	3.7	4.3	6.8	8.1
WV-9517	3.3	2.7	7.1	5.3
WV-9519	2.4	2.1	5.1	4.6

WV-9521	2.4	2.5	6.3	4.9
WV-9522	2.6	2.3	5.8	4.3
WV-9715	4.6	5.7	10.5	4.2
WV-9714	4.5	3.4	9.0	8.5
WV-9422	2.1	2.0	6.2	4.3
WV-9743	4.1	2.4	7.3	6.2
WV-9744	3.4	1.9	4.4	5.1
WV-9745	2.7	2.4	5.6	6.2
Mock	2.4	1.8	1.7	2.5

Table 14. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments (R1 and R2) are shown.

	3 uM-R1	3 uM-R2	10 uM-R1	10 uM-R2
WV-9746	2.5	2.5	4.6	3.4
WV-9747	3.0	3.1	5.5	4.8
WV-9748	4.9	2.5	4.3	4.0
WV-9749	2.9	2.7	4.5	4.1
WV-9750	3.2	2.5	4.4	3.8
WV-9751	3.5	2.7	4.7	4.8
WV-9758	1.7	1.9	2.1	3.5
WV-9759	2.6	3.6	2.8	6.1
WV-9760	3.1	3.9	3.4	4.8
WV-9761	3.0	4.8	4.6	7.2
WV-9756	3.9	4.4	5.3	8.4
WV-9757	3.7	4.3	6.8	8.1
WV-9517	3.3	2.7	7.1	5.3
WV-9519	2.4	2.1	5.1	4.6
WV-9521	2.4	2.5	6.3	4.9
WV-9522	2.6	2.3	5.8	4.3
WV-9715	4.6	5.7	10.5	4.2
WV-9714	4.5	3.4	9.0	8.5
WV-9422	2.1	2.0	6.2	4.3
WV-9743	4.1	2.4	7.3	6.2
WV-9744	3.4	1.9	4.4	5.1
WV-9745	2.7	2.4	5.6	6.2
Mock	2.4	1.8	1.7	2.5

Table 15. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency.

	10uM	3uM
WV-9897	7.4	4.8
WV-9898	11.8	4.6
WV-9899	10.1	4.1
WV-9900	10.3	4.7
WV-9901	5.7	2.5
WV-9902	8.8	3.5
WV-9903	7.3	3.4
WV-9904	6.9	3.0
WV-9905	6.7	3.1
WV-9906	12.1	5.0
WV-9907	11.1	3.8
WV-9908	12.6	5.1
WV-9909	11.3	3.9
WV-9910	9.8	4.3
WV-9911	3.5	4.0
WV-9912	11.3	4.7
WV-9913	10.3	3.9
WV-9914	9.4	2.8
WV-9747	7.6	3.4
WV-9749	6.4	3.6
WV-9750	6.0	3.5
WV-9758	3.5	2.5
WV-9517	9.6	4.1
Mock	2.5	2.6

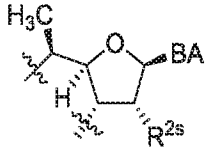
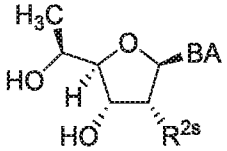
[00830] Additional oligonucleotides were generated and tested for skipping DMD exon 53 in vitro in cells. Certain data are shown below in Table 16. Oligonucleotides were used at concentrations of 3 and 10 uM, in two replicates. Numbers indicate the percentage of skipping of DMD exon 53. As shown, oligonucleotides can have different base sequences in combination with a variety of chemical formats. In some embodiments, oligonucleotides tested were 20-mers, each having a gapmer format of wing-core-wing, wherein each wing was 2'-F, and the core was 2'-OMe or a mixture of 2'-OMe and 2'-F. In some embodiments, each internucleotidic linkage was a chirally controlled phosphorothioate internucleotidic linkage in Sp configuration. In some embodiments, oligonucleotides comprise one or more natural phosphate linkages. In some embodiments, oligonucleotides of the present disclosure comprise one or more 5'-methyl 2'-F C (5MSfC,  , nucleoside is  , wherein BA is nucleobase C, R^{2s} is −F).

Table 16. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

	Group A (3 uM)		Group B (10 uM)	
WV-9746	8.0	7.5	13.7	7.5
WV-9747	10.2	9.3	17.4	9.3
WV-9748	8.8	8.2	14.1	8.2
WV-9749	9.9	8.7	15.8	8.7
WV-9750	10.0	9.3	17.3	9.3
WV-9751	9.3	8.4	14.5	8.4
WV-9758	6.9	6.1	8.8	6.1
WV-9759	7.5	7.7	11.3	7.7
WV-9760	8.1	7.3	10.2	7.3
WV-9761	7.3	8.2	12.7	8.2
WV-9756	10.9	10.3	20.2	10.3
WV-9757	22.7	10.1	32.1	10.1
WV-9517	10.3	9.2	20.1	9.2
WV-9519	8.8	8.1	16.2	8.1
WV-9521	9.2	8.0	16.0	8.0
WV-9522	9.5	8.8	17.7	8.8
WV-9715	14.3	12.3	26.9	12.3
WV-9714	13.2	11.3	23.7	11.3
WV-9422	8.3	7.3	16.6	7.3
WV-9743	9.8	7.8	20.1	7.8
WV-9744	7.6	6.7	12.9	6.7
WV-9745	9.6	7.4	17.0	7.4
Mock	4.7	4.9	5.2	

[00831] A number of DMD oligonucleotides were also designed, constructed and tested for efficacy in skipping DMD Exon 53 in vitro in differentiated myoblast cells. Certain data are shown below in Table 17. Oligonucleotides were delivered gymnotically at concentrations of 3 and 10 μM, in two biological replicates (R1 and R2). Numbers indicate the percentage of skipping of DMD exon 53, as determined by RT-qPCR.

Table 17. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments (R1 and R2) are shown.

	3 uM-R1	3 uM-R2	10 uM-R1	10 uM-R2
WV-9422	2.1	2.0	6.2	4.3
WV-9743	4.1	2.4	7.3	6.2
WV-9744	3.4	1.9	4.4	5.1

WV-9745	2.7	2.4	5.6	6.2
Mock	2.4	1.8	1.7	2.5

[00832] A number of oligonucleotides were designed, constructed and tested for efficacy in skipping DMD Exon 53 in vitro in Δ52 differentiated myoblast cells. Certain data were shown below in Table 18. In an example procedure, cells were pre-differentiated for 4 days and oligonucleotides were delivered gymnotically for 4 days. Differentiation medium was DMEM, 2% horse serum and 10μg/ml insulin. In some embodiments, with certain oligonucleotides, without pre-differentiating these cells, skipping efficiency was relatively low. Oligonucleotides were delivered gymnotically at concentrations of 1, 3 and 10 μM, in biological replicates (R1 and R2). Numbers indicate the percentage of skipping of DMD exon 53, as determined by RT-qPCR. PMO53 is an oligonucleotide also designated as WV-13405, HumDMDEx53, or PMO (in DMD exon 53 experiments), or PMO SR, which has a base sequence of GTTGCCTCCGGTTCTGAAGGTGTTC and is fully PMO (Morpholino).

"-" indicates that no data were available for that particular sample.

Table 18. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping relative to control and 0.0 would represent 0% efficiency; results from replicate experiments (R1 and R2) are shown.

	30uM -R1	30uM -R2	10uM -R1	10uM -R2	3uM -R1	3uM -R2	1uM -R1	1uM -R2
WV-9714	-	-	52.1	31.0	25.0	21.7	7.9	9.2
WV-9715	-	-	-	-	12.6	7.3	11.1	8.7
WV-9517	-	-	-	-	20.5	20.4	7.3	6.9
WV-9519	-	-	39.0	30.5	15.1	13.3	5.3	6.6
WV-9521	-	-	43.2	10.2	16.9	15.1	5.1	5.2
WV-9747	83.0	87.5	50.7	46.6	17.0	19.5	6.4	6.2
WV-9748	66.4	68.2	42.9	33.2	14.5	10.2	4.8	3.9
WV-9749	76.8	80.2	39.2	35.4	18.5	13.0	5.7	23.5
WV-9897	-	-	-	-	26.0	25.3	8.3	8.4
WV-9898	-	-	-	-	22.8	23.6	8.5	7.9
WV-9900	-	-	46.7	45.7	25.5	21.8	7.4	7.9
WV-9899	-	-	28.7	-	27.2	26.1	8.8	8.8
WV-9906	-	-	-	-	37.9	-	9.7	9.8
WV-9912	-	-	-	-	22.5	-	8.8	9.7
WV-9524	-	14.6	-	32.9	15.2	14.5	5.4	6.9
PMO53	112.8	105.4	53.7	49.3	20.4	19.9	6.9	10.4
Mock	2.2	1.7	2.2	1.5	1.6	1.8	2.0	2.0

[00833] A number of DMD oligonucleotides were designed, constructed and tested for efficacy in

skipping DMD Exon 53 in vitro in Δ45–52 differentiated myoblast cell. Certain results, normalized to SFSR9, are shown below in Table 19. Oligonucleotides were delivered gymnotically at concentrations of 1, 3 and 10 μM, in biological replicates (R1 and R2). Numbers indicate the percentage of skipping of DMD exon 53, as determined by RT-qPCR.

Table 19. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments (R1 and R2) are shown.

	10 uM-R1	10 uM-R2	3 uM-R1	3 uM-R2	1 uM-R1	1 uM-R2
MOCK	0.8	0.8	0.8	0.8	0.9	0.9
MOCK	0.7	0.7	0.8	0.8	0.8	0.8
PMO	18.0	18.0	5.6	5.7	3.8	4.0
PMO	19.3	17.9	9.6	9.4	3.1	3.1
WV-9517	39.4	42.3	16.0	16.1	5.3	5.2
WV-9517	43.8	42.9	18.5	17.5	5.5	5.7
WV-9519	33.7	28.5	14.3	13.3	4.5	4.5
WV-9519	27.6	27.9	12.4	11.3	4.1	4.1
WV-9897	30.8	31.1	11.7	12.5	3.9	3.8
WV-9897	32.3	30.7	12.0	11.9	4.6	4.7
WV-9714	46.8	42.8	21.5	20.6	4.5	4.1
WV-9714	46.5	48.1	25.4	25.6	4.2	2.9
WV-9747	31.1	31.8	12.0	12.5	4.7	4.7
WV-9747	27.6	28.0	10.5	11.1	3.5	3.7
WV-9748	21.7	21.7	7.9	8.0	3.3	3.2
WV-9748	21.1	20.9	8.5	8.1	3.1	3.1
WV-9749	23.2	24.2	10.1	9.4	3.7	3.7
WV-9749	25.3	24.6	10.7	10.5	3.7	3.9
WV-9897	53.2	53.1	24.5	24.4	5.4	5.5
WV-9897	48.3	48.7	22.8	22.8	4.8	4.8
WV-9898	46.5	46.8	21.1	21.1	5.2	5.4
WV-9898	46.3	46.4	23.4	23.8	5.0	4.6
WV-9899	45.4	44.1	19.5	19.5	4.8	5.0
WV-9899	44.9	44.0	21.4	21.2	5.5	5.6
WV-9900	34.9	35.0	19.5	19.6	5.0	5.3
WV-9900	30.2	31.5	17.6	17.6	4.4	4.4
WV-9906	42.9	44.6	18.0	19.0	2.9	3.1
WV-9906	37.5	36.3	17.5	18.2	2.8	3.2
WV-9912	39.8	41.6	19.6	17.7	5.0	4.4
WV-9912	41.6	40.8	21.3	19.9	4.2	4.2

[00834] Additional testing of oligonucleotides was performed, and the results were shown below

in Tables 20 and 21.

Table 20. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100.0 would represent 100% skipping and 0.0 represents 0% efficiency; results from replicate experiments are shown.

	10 uM	10 uM	3 uM	3 uM	1 uM	1 uM
WV-9517	34.6	35.6	17.0	19.4	6.7	7.8
WV-9897	43.8		26.8	27.3	9.7	9.8
WV-9898	42.7	30.3	22.8	26.7	8.5	9.3
WV-9899	45.0		16.4	26.8	10.0	8.6
WV-10670	32.4	32.9	15.2	18.2	7.2	8.0
WV-10671	28.7	30.9	14.7	16.1	6.7	8.0
WV-10672	25.6	28.1	11.8	12.2	5.0	5.0
PMO	40.8	36.0	19.1	18.6	10.7	11.7
Mock	1.1	1.9	1.8	1.9	1.7	2.5

Table 21. Example data of certain oligonucleotides.

Oligonucleotides were tested in vitro in delta 52 cells. A, Exon skipping at 10 uM is shown. B, protein restoration. Different replicates or experiments are designated as a), b), and c).

A.

WV-9422	WV-9425	WV-9426	WV-9517	WV-9519	WV-9521	WV-9522	WV-9524	WV-9536
a) 8, c) 4	a) 8	a) 3	a) 10, c) 6	a) 9, c) 4	a) 8, c) 5	a) 8, c) 5	a) 9	a) 7

WV-9700	WV-9701	WV-9702	WV-9703	WV-9704	WV-9709	WV-9710	WV-9711	WV-9713
a) 4	a) 4	a) 6	a) 8	a) 7	a) 4	a) 6	a) 6	a) 4

WV-9714	WV-9715	WV-9746	WV-9747	WV-9748	WV-9749	WV-9750	WV-9751	WV-9756
a) 13, c) 9	a) 15, c) 9	c) 4	c) 4	c) 4	c) 4	c) 4	c) 4	c) 7

WV-9757	WV-9758	WV-9759	WV-9760	WV-9761	WV-9743	WV-9744	WV-9745
c) 7	c) 2	c) 4	c) 4	c) 6	c) 6	c) 4	c) 6

B.

WV-9422	WV-9425	WV-9426	WV-9429	WV-9517
b) 4	b) 2	b) 2	b) 1	b) 5

[00835] Additional DMD oligonucleotides were tested for their ability to mediate skipping of a DMD exon, as shown below. Full PMO (Morpholino) oligonucleotides have the following sequences:

PMO SR	WV-13405	GTTGCCTCCGGTTCTGAAGGTGTTC
PMO WV	WV-13406	CTCCGGTTCTGAAGGTGTTC
PMO	WV-13407	TGCCTCCGGTTCTGAAGGTGTTCTTGTA

WV-13407 is also designated PMO NS.

Table 21C. Example data of certain oligonucleotides.

Numbers represent skipping efficiency, wherein 100 would represent 100% skipping and 0 would represent 0% skipping. Replicate data is shown.

	10 uM				3 uM			
Mock	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1
PMO SR	1.8	1.6	1.1	0.9	0.5	0.5	0.5	0.4
PMO WV	0.8	1.0	1.0	1.1	0.4	0.4	0.5	0.3
PMO	2.3	2.5	1.8	1.8	1.0	0.9	0.6	0.6
WV-10454	5.5	6.1	4.5	3.9	1.3	1.3	0.9	0.7
WV-10455	10.5	13.8	7.3	7.8	2.1	2.8	2.0	2.5
WV-10456	7.2	7.4	5.6	5.0	1.4	1.5	1.7	1.3
WV-10457	9.8	14.2	8.4	9.0	3.8	2.9	3.2	2.9
WV-10458	6.6	5.4	5.6	5.2	1.2	1.1	1.1	1.2
WV-10459	2.4	2.8	2.7	2.5	1.0	1.0	0.5	0.5
WV-10460	7.9	6.0	7.6	7.5	1.9	1.8	1.4	1.4
WV-10461	14.9	11.3			5.7	6.0	2.4	3.7
WV-10462	1.6	2.4	3.4	3.1	0.8	0.8	0.7	0.9
WV-10463	2.6	3.2	2.9	2.7	0.7	0.7	0.7	0.7
WV-10464	1.2	1.1	0.2	0.1	0.4	0.3	0.2	0.3
WV-10465	2.3	1.8			0.6	0.7	0.7	0.7
WV-10466	8.6	9.1	3.9	2.6	1.8	1.6	1.9	1.6
WV-10467	3.2	0.8	1.4	1.1	4.1	4.3	3.3	2.9
WV-10468					2.1	2.0		
WV-10469	3.2	3.1	4.8	4.2	0.6	0.6	1.0	0.0
WV-9699	4.6	3.2	2.8	2.4	0.8	0.9	0.7	0.5
WV-9898	19.4	19.0	17.6	18.2	5.4	6.2	5.9	5.4

In some embodiments, oligonucleotides, e.g., DMD oligonucleotides, are designed to target Intronic Splice Enhancer elements, e.g., for DMD oligonucleotides for exon 53 skipping, elements within 4kb of Exon53. In some embodiments, provided oligonucleotides are 30-mers. Example data for certain such oligonucleotides are presented in Table 21D.

Table 21D. Example data of certain oligonucleotides.

Results: Gymnotic delivery of 10μM Intron ASO's in Δ45-52 patient derived myoblasts (4 days post-differentiation). Done in biological replicates. Numbers represent percentage of exon skipping, as

determined by RT-qPCR.

WV-10490	1.6	1.6	1.8	1.9
WV-10491	1.6	1.7	1.7	1.5
WV-10492	1.4	1.5	1.6	1.4
WV-10493			0.9	0.6
WV-10494	1.4	1.5	1.3	1.6
WV-10495				
WV-10496	1.8	1.5	1.8	1.7
WV-10497	1.6	1.6	1.5	1.7
WV-10498	0.7	0.7	2.0	1.8
WV-10499	1.5	1.4	1.7	1.6
WV-10500	0.8	1.3	0.9	0.6
WV-10501	1.2	1.7	1.3	1.4
WV-10502	1.4	1.4	1.5	1.4
WV-10503		1.5	1.0	1.7
WV-10504			1.6	1.8
WV-10505	1.5	1.2	1.9	1.5
WV-10506	0.8	0.8	1.4	1.3
WV-10507	1.4	1.1	0.9	1.4
WV-10508	1.5	1.4	1.8	1.7
WV-10509	1.2	1.5	1.4	1.6
WV-10510	1.3	1.7	1.0	1.6
WV-10511	0.5	0.9	0.8	1.2
WV-10512	1.3	1.5	1.7	1.7
WV-10513	1.5	1.6	1.6	1.7
WV-10514	1.1		1.7	1.8
WV-10515	2.0	1.9	1.9	1.9
WV-10516	8.3	8.7	9.1	8.0
WV-10517	0.5	0.5	1.7	1.5
WV-10518	1.7	1.5	1.5	1.7
WV-10519	1.8	1.6	1.8	1.8
WV-10520	2.1	1.8	1.8	1.7
WV-10521	3.3	3.1	2.6	3.4
WV-10522	1.9	2.0	1.7	2.1
WV-10523	2.3	2.1	1.9	1.9
WV-10524	1.8	1.9	2.1	2.0
WV-10525	2.0	2.1	1.1	1.6
WV-10526	1.7	1.9	1.8	1.7
WV-10527	1.1	1.3	1.4	1.5
WV-10528	1.6	1.6	1.7	1.4

WV-10529	1.6	1.1		
WV-10530	0.9	1.7	1.7	1.6
WV-10531	1.2	1.5	1.0	1.3
WV-10532	1.4	1.6	1.6	1.5
WV-10533	1.4	0.5	1.5	1.5
WV-10534	1.3	1.4	1.7	1.6
WV-10535	0.9	0.6	1.7	1.6
WV-10536	1.5	1.0	1.4	1.3
WV-10537	1.4	1.6	1.6	1.4
WV-9517	44.5	42.5	41.6	43.2
WV-9699	13.0	12.7	9.8	9.3
Mock	1.6	1.7	1.4	1.3

Table 21E. Example data of certain oligonucleotides.

Δ45-52 DMD patient derived myoblasts, with 7d of pre-differentiation, were treated with oligonucleotides in muscle differentiation medium at indicated concentrations under free uptake condition before being collected and analyzed for RNA skipping efficiency (4d dosing) by qPCR. Relative (SRSF9 normalization) quantification. Oligonucleotides were tested at a concentration of 0 to 10 μM. Results of replicate experiments are shown. Some of the oligonucleotides tested comprise a non-negatively charged internucleotidic linkage (WV-12887 and WV-12880).

Conc.	**10**	**3.33**	**1.11**	**0.3704**	**0.1235**	**0**
	35.2	23.1	9.0	4.0	2.2	1.0
	36.3	23.1	8.7	4.0	2.3	1.2
	33.1	20.6	8.3	3.3	2.1	1.0
WV-13405 (PMO)	33.7	20.7	8.3	3.2	2.2	1.2
	31.2	22.2	8.6	1.7	1.3	1.1
	30.4	22.5	10.3	1.5	1.2	0.9
	49.6	23.3	6.2	1.7	1.4	1.2
WV-9898	48.3	22.3	5.5	1.5	1.6	1.5
	73.1	53.5	38.4	10.3	4.5	1.0
	72.1	54.3	37.6	10.3	4.8	1.1
	69.3	51.5	24.4	5.5	3.5	1.2
WV-12880	69.6	52.6	23.7	6.2	3.2	1.0
	40.4	28.1	3.5	2.1	1.4	1.0
	39.8	28.2	1.2	2.1	1.3	1.0
	29.3	18.1	5.5	1.8	1.3	1.6
WV-9517	28.9	17.4	4.9	1.7	1.3	1.4
WV-9897	21.2	20.0	3.9	1.6	2.1	1.3

	23.6	18.5	3.7	1.9	2.1	1.2
	39.5	18.7	5.1	1.7	2.0	1.5
	40.9	18.5	5.2	1.6	1.8	1.0
	79.7	59.4	44.2	9.6	5.5	0.9
	78.7	58.8	44.1	9.6	5.6	0.9
	76.1	61.0	38.1	12.3	6.7	1.1
WV-12887	75.0	61.3	31.9	9.8	5.1	1.1

Table 21F. Example data of certain oligonucleotides.

Δ45-52 DMD patient derived myoblasts were treated with oligos in muscle differentiation medium at indicated concentrations for 4d under free uptake conditions and analyzed for RNA skipping efficiency by qPCR.

	10uM				3.3uM			
Mock	0.3	0.3	0.3	0.4	0.3	0.3	0.3	0.3
WV-13405 (PMO)	4.3	4.5	4.2	4.7	1.2	1.1	1.8	1.9
WV-9517	15.0	14.2			5.6	5.8	8.7	9.3
WV-11340	32.4	33.7	35.9	36.9	15.4	13.0	15.9	15.0
WV-12873	38.7	37.5	39.6	39.2	13.6	11.7	17.0	14.5
WV-12872	44.9	41.9	44.1	46.5	15.7	17.5	15.7	19.5
WV-13408	49.0	48.7	50.2	50.3	21.6	22.0	23.0	24.5
WV-12553	18.3	20.7	18.7	24.1	7.4	7.6	9.7	8.4
WV-12557	40.0	39.2	33.8	35.9	15.3	15.5	23.6	23.9
WV-12554	38.8	39.0	43.5	44.9	15.1	14.0	20.5	20.3
WV-13409	34.6	38.4	39.1	40.3	14.7	12.9	18.9	16.5
WV-9898	24.1	22.0			7.9	7.7	9.9	8.5
WV-11342	30.4	34.5	31.3	31.9	14.3	14.4	14.1	13.3
WV-12559	44.3	41.8			16.6	16.5	17.4	19.4
WV-12556	42.5	43.0	39.7	43.3	16.1	17.1	18.8	17.1
WV-9897	20.8	17.9			6.0	5.4	6.8	4.8
WV-11341	36.6	39.4			17.8	16.8	18.2	19.3
WV-12558	41.5	39.4	36.0		18.2	15.1	18.5	16.7
WV-12555	44.3	43.6			20.5	19.0	20.2	22.1
WV12880	41.1	43.2	46.1	45.1	27.4	24.6	25.9	29.1
WV-12877	51.5	53.3			26.2	27.1	30.2	30.7
WV-12125	47.3	49.4	37.8	35.1	21.3	20.6	24.0	23.5
WV-12127	40.0	40.6	41.2	39.7	19.9	15.5	18.3	18.0
WV-12129	33.5	35.0	24.4	24.4	13.9	10.7	14.4	13.7

Table 21G. Example data of certain oligonucleotides.

Δ45-52 DMD patient derived myoblasts, with 7d of pre-differentiation, were treated with oligos in muscle differentiation medium at indicated concentrations for 4d under free uptake conditions and analyzed for RNA skipping efficiency by qPCR.

Oligo Conc [uM]	10uM				3.3uM			
Mock	0.6	0.6	0.6	0.8	0.7	0.6	1.0	0.8
WV-13405 (PMO)	6.9	7.4	10.1	10.9	2.2	1.9	4.1	4.4
WV-9517	24.2	22.0	11.5	33.7	9.3	9.8	19.8	20.6
WV-11340	50.8	54.1	61.6	63.9	30.1	22.0	33.2	30.6
WV-12872	70.6	66.4	71.0	74.6	24.7	29.2	27.9	38.9
WV-12873	60.8	59.5	62.9	62.8	20.4	15.3	33.5	24.5
WV-13408	73.5	72.3	75.8	75.6	35.6	35.7	42.2	46.3
WV-12553	32.7	39.1	38.0	51.3	13.7	14.6	22.7	18.9
WV-12557	65.2	64.4	76.7	80.4	26.3	27.1	45.3	45.6
WV-12554	61.0	61.5	69.5	71.7	27.0	22.9	38.5	37.6
WV-13409	57.2	63.6	66.2	69.3	23.6	18.9	34.4	28.4
WV-9898	45.1	40.3	16.3	14.4	13.2	12.1	20.8	16.1
WV-11342	49.9	58.1	57.9	60.0	27.4	27.8	30.3	27.4
WV-12559	72.4	68.4	50.8	56.1	33.3	32.8	35.5	42.5
WV-12556	70.5	71.0	68.4	73.5	31.0	33.5	42.0	37.0
WV-9897	42.0	34.9		41.2	10.2	8.0	17.9	9.4
WV-11341	61.6	67.2	74.1	74.4	37.0	33.8	40.8	42.9
WV-12558	71.6	68.0	66.3		35.6	27.1	40.5	35.5
WV-12555	70.2	68.9	56.0	61.7	35.2	32.4	40.1	45.0
WV12880	58.8	63.0	68.5	66.5	44.4	36.6	44.8	52.1
WV-12877	77.9	80.2	69.5	75.6	46.3	48.2	55.8	58.4
WV-12125	71.1	74.1	83.6	80.4	36.5	34.8	45.6	44.3
WV-12127	61.9	64.0	67.8	66.2	35.0	23.3	35.5	34.7
WV-12129	52.7	55.8	63.1	63.6	23.8	14.7	26.5	24.1

Table 21H. Example data of certain oligonucleotides.

Full length oligonucleotide stability at 5 day timepoint in Human Liver homogenate was tested. Numbers are replicates and represent percentage of full-length oligonucleotide remaining, wherein 100 would represent 100% oligonucleotide remaining (complete stability) and 0 would represent 0% oligonucleotide remaining (complete instability). Some nucleotides tested comprise a non-negatively charged internucleotidic linkage.

WV-	27.2	WV-	74.4	WV-	45.0

12553	30.1	12124	67.6	12127	42.3
	32.1		67.7		43.2
WV-11341	63.6	WV-12125	65.8	WV-12129	50.2
	55.0		74.2		53.3
	55.7		92.6		51.2
WV-11342	51.7	WV-12126	65.8	WV-12882	60.6
	54.0		57.9		66.9
	50.8		55.8		68.6
WV-12555	81.1	WV-12880	65.2	WV-12878	76.0
			63.9		75.1
	76.2		60.9		78.1
WV-12556	73.4	WV-12881	61.9	WV-12876	67.0
	75.1		60.3		62.0
	66.9		57.7		66.4
WV-12558	59.9	WV-12123	59.5		
	78.8		55.1		
	66.0		49.9		
WV-12559	68.3	WV-12877	78.9		
	76.3		78.0		
	73.3		83.1		

WV-9897	59.9
	59.6
	58.6
WV-9898	44.7
	39.1
	46.3

Table 21I. Example data of certain oligonucleotides.

Numbers indicate amount of skipping relative to control.

Oligo Conc [uM]	WV-9517	WV-13826	WV-13827	WV-13835	Mock
10uM	45.7	46.5	23.1	40.5	1.2
	46.3	45.8	22.9	58.8	1.1
	49.3	46.8	26.8	54.5	1.3
	48.5	50.3	28.1	55.2	1.2
3.3uM	18.1	20.3	7.9	24.6	1
	17	19.5	8.3	25.3	1.1
	22.6	19.7	8.8	26.6	1.1

	22.8	20.2	8.3	27.2	1.1
1.1uM	6	7	2.9	7.9	1
	6	6.2	2.7	7.4	1.2
	6.9	7.3	0.7	9.6	0.9
	6.6	6.8	0.9	9.1	0.7

	WV-9517	WV-12880	WV-13864	WV-14344	MOCK
10uM	36.1	60.2	66.8	47.9	0.9
	38.3	62.0	67.0	46.8	1.0
	44.5	60.9	68.7	56.8	1.2
	43.9	59.2	69.6	56.3	1.0
3.3uM	15.4	38.3	45.3	25.1	0.9
	15.8	37.3	45.6	27.0	0.9
	18.8	37.9	50.5	39.2	1.0
	18.8	39.6	49.3	38.9	1.0
1.1uM	4.7	15.8	21.5	12.2	0.6
	4.9	14.4	22.6	12.4	0.9
	6.4	18.5	24.9	17.2	1.1
	6.2	16.2	13.2	17.1	0.9
0.3uM	2.2	5.0	6.6	5.7	0.8
	1.8	5.0	5.9	5.7	0.9
	2.7	7.4	8.2	7.2	1.0
	2.7	7.5	8.2	6.9	1.0

Table 21I.1. Example data of certain oligonucleotides.

Skipping efficiency of various DMD oligonucleotides, tested for skipping of DMD exon 53. Numbers represent skipping of exon 53.

Δ45-52 patient myoblasts were differentiated for 7days, then treated with oligonucleotide for 4d under gymnotic conditions in differentiation media. RNA was harvested by Trizol extraction and skipping analyzed by TaqMan.

	10uM	3.3uM	1.1uM	0.3uM	0.1uM
	1.1	1.2		0.8	1.0
	1.0	1.1	2.0	0.9	1.0
	1.1	0.7	1.1	1.0	1.1
Mock	1.2	0.7	1.1	0.9	1.0
	44.8	28.6	18.1	9.5	4.0
	44.8	23.4	17.4	8.7	4.0
Wv-13405	51.2	26.5	11.4	5.1	3.7
(PMO)	50.8	25.6	11.2	5.5	3.6
WV-	35.9	18.3	6.5	2.2	1.9

9517	36.6	17.3	6.4	2.1	1.9
	40.2	23.4	5.5	2.7	1.7
	38.7	25.6	5.9	2.2	1.8
Wv-12880	57.3	36.3	16.4	4.8	7.5
	55.8	37.0	18.1	2.8	4.7
	57.5	35.9	16.6	8.0	7.4
	58.9	33.0	16.5	7.2	6.8
WV-13864	68.1	45.1	22.6	10.5	7.4
	68.0	44.5	23.0	12.0	5.6
	67.5	43.1	24.3	8.4	6.0
	64.8	44.5	19.9	3.3	6.1
WV-13835	40.2	21.5	6.3	2.8	2.0
	39.4	20.3	9.7	2.5	2.0
	50.0	21.0	5.5	3.2	2.0
	47.7	20.6	6.0	3.3	2.2
WV-14791	41.4	25.9	7.4	4.7	0.7
	40.3	24.8	5.8	4.0	0.5
	40.1	24.9	9.1	4.3	3.9
	41.3	27.2	8.9	4.6	3.5
WV-14344	50.1	28.6	13.6	6.4	3.8
	47.4	28.6	8.8	5.8	4.7
	54.9	46.1	18.0	11.4	6.6
	55.7	38.3	18.7	11.8	6.0

Table 21I.2. Example data of certain oligonucleotides.

Skipping efficiency of various DMD oligonucleotides, tested for skipping of DMD exon 53. Numbers represent skipping of exon 53.

Δ45-52 patient myoblasts were treated with oligonucleotide for 4d (4 days) under gymnotic conditions in differentiation media. RNA was harvested by Trizol extraction and skipping analyzed by TaqMan.

	10uM	3.3uM	1.1uM	0.3uM	0.1uM
Mock	0.7	0.6	0.6	0.6	0.7
	0.7	0.7	0.6	0.6	0.7
	0.6	0.6	0.6	0.7	0.7
	0.5	0.5	0.7	0.6	0.7
Wv-13405 (PMO)	9.4	1.5	3.4	1.1	0.8
	9.3	1.4	3.1	1.1	0.8
	6.6	2.8	1.5	0.9	0.8
	6.3	2.6	1.5	1.0	0.8
WV-	29.3	8.4	2.6	1.0	0.7

9517	28.7	9.2	3.0	1.1	0.8
	16.6	6.6	2.3	1.1	0.7
	16.9	6.8	2.2	1.1	0.9
WV-12880	37.9	17.7	9.6	3.4	1.3
	38.8	19.9	9.1	3.3	1.4
	31.4	16.1	7.9	3.3	1.6
	31.6	16.8	8.0	3.0	1.5
WV-13864	55.9	28.6	11.7	4.3	2.0
	54.3	27.8	11.6	4.6	2.0
	43.4	22.2	10.7	4.2	2.0
	43.0	22.7	9.8	3.8	2.1
WV-13835	38.7	11.6	2.9	1.3	0.9
	37.2	11.0	2.9	1.3	0.8
	42.3	13.1	3.5	1.2	0.9
	41.5	10.0	3.1	1.3	0.9
WV-14791	26.3	12.1	5.2	1.9	1.3
	24.8	11.2	4.7	2.1	1.1
	28.0	13.0	5.2	2.2	1.2
	27.6	12.4	4.9	2.1	1.4
WV-14344	36.2	17.8	8.0	2.7	1.7
	37.4	17.0	7.1	2.7	1.8
	37.4	22.3	9.8	3.7	1.7
	36.6	22.6	9.9	3.7	1.5

Several oligonucleotides (including WV-9517, WV-13864, WV-13835, and WV-14791) were tested at various concentrations up to 30 uM for TLR9 activation in vitro in HEK-blue-TLR9 cells (16 hour gymnotic uptake). WV-13864 and WV-14791 comprise a chirally controlled non-negatively charged internucleotidic linkage in the Rp configuration. WV-9517, WV-13864, WV-13835, and WV-14791 did not exhibit significant TLR9 activation (less than 2-fold TLR9 induction; data not shown). WV-13864 and WV-14791 also exhibited negligible signal up to 30uM in PBMC cytokine release assay compared to water (data not shown).

Example Dystrophin Oligonucleotides and Compositions Which Target Exon 54

[00836] In some embodiments, the present disclosure provides oligonucleotides, oligonucleotide compositions, and methods of use thereof for targeting exon 54 and/or mediating skipping of exon 54 in human DMD. Non-limiting examples include oligonucleotides and compositions of Exon 54 oligos include: WV-13745, WV-13746, WV-13747, WV-13748, WV-13749, WV-13750, WV-13751, WV-

13752, WV-13753, WV-13754, WV-13755, WV-13756, WV-13757, WV-13758, WV-13759, WV-13760, WV-13784, and WV-13785, and other oligonucleotides having a base sequence which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

Table 21J. Example data of certain oligonucleotides.

Skipping efficiency of various DMD oligonucleotides, tested for skipping of DMD exon 54.

WV-13745	0.2	0.3	0.2	0.0
WV-13746	0.6	0.6	0.4	0.4
WV-13747	0.4	0.5	0.4	0.4
WV-13748	1.1	1.2	0.7	0.9
WV-13749	2.5	2.1	1.7	1.8
WV-13750	1.9	2.1	1.4	1.4
WV-13751	4.3	5.1	4.4	5.7
WV-13752	0.0	0.0	3.1	3.9
WV-13753	0.0	0.0	0.0	0.0
WV-13754	6.0		1.4	1.7
WV-13755	1.1	1.2	0.5	0.5
WV-13756	4.7	5.0	2.3	2.4
WV-13757	1.9	2.1	1.1	1.4
WV-13758	2.0	2.2	0.9	1.2
WV-13759	0.7	0.7	0.4	0.2
WV-13760	0.7	0.6	0.3	0.5
WV-13784	0.0	0.0	0.0	0.0
WV-13785	0.0	0.0	0.0	0.0
Mock	0.0		0.0	
Mock	0.0		0.0	

Example Dystrophin Oligonucleotides and Compositions Which Target Exon 55

[00837] In some embodiments, the present disclosure provides oligonucleotides, oligonucleotide compositions, and methods of use thereof for targeting exon 55 and/or mediating skipping of exon 55 in human DMD. Non-limiting examples include oligonucleotides and compositions of Exon 55 oligos include: WV-13761, WV-13762, WV-13763, WV-13764, WV-13765, WV-13766, WV-13767, WV-13768, WV-13769, WV-13770, WV-13771, WV-13772, WV-13773, WV-13774, WV-13775, WV-13776, WV-13777, WV-13778, WV-13779, WV-13786, and WV-13787, and other oligonucleotides having a base sequence (naked sequence) which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

[00838] In some embodiments, two or more oligonucleotides capable of skipping or targeting exon 44, 46, 47, 51, 52, 53, 54 and/or 55 can be used in any combination to mediate multiple exon

skipping.

Table 21K. Example data of certain oligonucleotides.

Skipping efficiency of various DMD oligonucleotides, tested for skipping of DMD exon 55.

WV-13761	0.5	0.5	0.3	0.4
WV-13762	0.3	0.2	0.1	0.1
WV-13763	0.2	0.2	0.2	0.2
WV-13764	0.1	0.1	0.1	0.1
WV-13765	1.0	1.0	0.4	0.4
WV-13766	2.6	2.7	1.7	1.8
WV-13767	0.2	0.0	1.4	1.6
WV-13768	1.1	1.1	0.7	0.7
WV-13769	1.6	1.8	1.1	1.1
WV-13770	1.4	1.4	0.8	0.9
WV-13771	0.3	0.4	0.2	0.2
WV-13772	1.8	1.7	0.9	0.9
WV-13773	0.0	0.0	0.1	0.1
WV-13774	0.0	0.0	0.0	0.0
WV-13775	1.0	0.8	0.3	0.4
WV-13776	0.7	0.6	0.3	0.7
WV-13777	2.8	2.2	0.4	1.1
WV-13778	0.3	0.3	0.2	0.3
WV-13779	0.0	0.0	0.4	0.4
WV-13786	0.0	0.0	2.0	2.3
WV-13787	0.0	0.0	0.2	0.1
Mock	0.0	0.0	0.0	0.0
Mock	0.0	0.0	0.0	0.0

Example Dystrophin Oligonucleotides and Compositions Which Target Exon 57

[00839] In some embodiments, the present disclosure provides oligonucleotides, oligonucleotide compositions, and methods of use thereof for targeting exon 57 and/or mediating skipping of exon 57 in human DMD. Non-limiting examples include oligonucleotides and compositions of Exon 57 oligos include: WV-18853, WV-18854, WV-18855, WV-18856, WV-18857, WV-18858, WV-18859, WV-18860, WV-18861, WV-18862, WV-18863, WV-18864, WV-18865, WV-18866, WV-18867, WV-18868, WV-18869, WV-18870, WV-18871, WV-18872, WV-18873, WV-18874, WV-18875, WV-18876, WV-18877, WV-18878, WV-18879, WV-18880, WV-18881, WV-18882, WV-18883, WV-18884, WV-18885, WV-18886, WV-18887, WV-18888, WV-18889, WV-18890, WV-18891, WV-18892, WV-18893, WV-18894, WV-18895, WV-18896, WV-18897, WV-18898, WV-18899, WV-

18900, WV-18901, WV-18902, WV-18903, WV-18904, and other oligonucleotides having a base sequence (naked sequence) which comprises at least 15 contiguous bases of any of these DMD oligonucleotides.

Example Dystrophin Oligonucleotides and Compositions for Exon Skipping of Mutiple Exons (Multi-Exon Skipping)

[00840] In some embodiments, the present disclosure provides oligonucleotides, compositions, and methods for splicing modulation, including skipping of multiple exons. In some embodiments, a DMD oligonucleotide or composition thereof is capable of mediating skipping of multiple exons in the human or mouse Dystrophin gene.

[00841] In some embodiments, in a patient with muscular dystrophy, the symptoms of muscular dystrophy can at least be partially relieved and/or the disorder at least partially treated by administration of a DMD oligonucleotide capable of skipping one exon or multiple exons. Without wishing to be bound by any particular theory, the present disclosure notes that BMD patients with a deletion of exons 45 to 55 of DMD showed a milder or asymptomatic phenotype.

[00842] A non-limiting example of a scheme for multiple exon skipping is shown in Figure 1. In this Figure, various numbers (43 to 57) indicate exons; and the shapes of the exons (e.g., <, > or |) indicate which reading frame is represented at the 5' and 3' end of each exon. Normally exon 44 is joined to exon 45. In a non-limiting example of multiple exon skipping, exons 45 to 55 are skipped, allowing exon 44 to join to exon 56. The 3' end of exon 44 is represented by the same reading frame (<) as the 5' end of exon 56; thus skipping exons 45 to 55 maintains or restores the correct reading frame. In some embodiments, skipping multiple exons restores the reading frame if one of the skipped exons comprises a mutation which alters the reading frame (in many cases, for example, producing a missense or prematurely truncated protein).

[00843] Among other things, the present disclosure notes that various exons represent at their 5' and/or 3' ends different reading frames; thus, some combinations of skipping adjacent reading frames but not other combinations are capable of maintaining or restoring the reading frame. In some embodiments, provided compositions and methods for multiple exon skipping skip, as non-limiting examples, exons 45-46, 45-47, 45-48, 45-49, 45-51, 45-53, 45-55, 47-48, 47-49, 47-51, 47-53, 47-55, 48-49, 48-51, 48-53, 46-55, 50-51, 50-53, 50-55, 49-51, 49-53, 49-55, 52-53, 52-55, 44-45, 44-54, or 44-56, wherein in each case multiple exon skipping maintains or restores the correct reading frame. In some embodiments, skipping of non-overlapping sets of exons is capable of maintaining or restoring reading frame, e.g., skipping of exons 45-46 and exons 49-55; skipping of exons 45-47 and 49-55; skipping of exons 45-49 and 52-55; etc.

[00844] Without wishing to be bound by any particular theory, the present disclosure notes that some DMD exons may be spliced transcriptionally, while others are spliced post-transcriptionally. For example, each of exons 45 to 55 are reportedly not simultaneously spliced, but rather first as three groups: exons 45 to 49, 50 to 52, and 53 to 55, the individual exons within each group being spliced transcriptionally. Reportedly, the remaining introns (between exons 44/45, 49/50, 52/53, and 55/56) are later spliced post-transcriptionally. Without wishing to be bound by any particular theory, the present disclosure notes that this lag in the timing of splicing may be exploited by oligonucleotides capable of increasing the splicing between exons whose adjacent introns are spliced post-transcriptionally, such as exon 44 and 56. It is reported that in nature, such multi-exon skipping joining exon 44 to exon 56 occurs at a low but detectable frequency (approximately 1/600). Without wishing to be bound by any particular theory, the present disclosure pertains in part to DMD oligonucleotides capable of skipping multiple exons at a therapeutically and clinically significant level.

[00845] In some embodiments, a composition capable of mediating multiple exon skipping comprises a DMD oligonucleotide. In some embodiments, a composition capable of mediating multiple exon skipping comprises a combination of (e.g., two or more different) DMD oligonucleotides. In some embodiments, a composition capable of mediating multiple exon skipping comprises a combination of (e.g., two or more different) DMD oligonucleotides, wherein at least one oligonucleotide recognizes a target associated with skipping the 5' exon to be skipped, and at least one oligonucleotide recognizes a target associated with skipping the 3' exon to be skipped. In some embodiments, a composition capable of mediating multiple exon skipping comprises a oligonucleotide capable of recognizes both (1) a target associated with skipping the 5' exon to be skipped and (2) a target associated with skipping the 3' exon to be skipped.

[00846] In some embodiments, an advantage of a composition capable of multiple exon skipping is that it is useful for treatment of dystrophy associated with a mutation in any individual exon included in the group of exons which is skipped. As a non-limiting example, a DMD oligonucleotide capable of mediating skipping of exon 48 is only capable of treating mutations within that exon (or, in some cases, an adjacent or nearby exon) but not mutations within other exons. However, a composition capable of mediating skipping of exons 45 to 55 is capable of treating mutations in any of exons 45, 46, 47, 48, 49, 50, 51, 52, 53, 54 or 55. Thus, both a patient with a mutation in exon 48 and a patient with a mutation in exon 54 can be treated with a composition capable of skipping exons 45 to 55. In some embodiments, a composition capable of mediating skipping of exons 45 to 55 is capable of treating up to about 63% of DMD patients.

[00847] In some embodiments, a composition comprises one or more DMD oligonucleotides, wherein the composition is capable of mediating skipping of multiple (two or more) DMD exons.

[00848] In some embodiments,, a MESO (a composition comprising one or more oligonucleotides, which composition is capable of mediating multiple exon skipping) has an advantage over a DMD oligonucleotide capable of skipping only one exon. In some embodiments, a composition which is capable of mediating skipping of a single exon, is only useful for treating patients treatable by skipping that exon (e.g., patients having a genetic lesion in that exon). In some embodiments, a MESO is useful for treating patients treatable by skipping any of the exons which the MESO is able to skip, which is likely a larger percentage of the patient population. In some embodiments, double or multiple exon skipping can potentially be applicable to 90% of patients.

[00849] In addition, in some embodiments, because the 5' and 3' ends of an exon are sometimes not in the same frame, deletion of such an exon would cause a frameshift. Skipping of multiple exons, in various such cases, can restore the reading frame.

[00850] In some embodiments, multiple exon skipping is useful to treat DMD patients with deletion, duplication, and nonsense mutations.

[00851] In addition, in some embodiments, skipping of multiple exons can mimic the genetics of the milder Becker muscular dystrophy. In some embodiments, the more severe Duchenne muscular dystrophy, mediated by a genetic lesion in one exon, can be converted into a milder Becker muscular dystrophy, mediated by an in-frame deletion of multiple exons. It is reported that some BMD patients and an asymptomatic person have in-frame deletions of exons 48 to 51 or 45 to 51. Singh et al. 1997 Hum. Genet. 99: 206-208; Melacini et al. 1993 J. Am. Col.. Cardiol. 22: 1927-1934; Melis et al. 1998 Eur. J. Paediatr. Neurol. 2: 255-261; and Aartsma-Rus et al. 2003 Hum. Mol. Genet. 8: 907-914.

[00852] In some embodiments, certain exons may be more challenging than others to skip. In some embodiments, the present disclosure provides technologies to skip such exons, e.g., through chemical modifications, linkage phosphorus stereochemistry, and combinations thereof. In some embodiments, the present disclosure encompasses the recognition that multiple exon skipping can be useful for skipping such challenging exons. In some embodiments, the present disclosure provides multiple exon skipping technologies for skipping such challenging exons.

[00853] In some embodiments, exon skipping, e.g., DMD exon skipping, can be used to treat patients, e.g., DMD patients, with circular or circularized RNA transcripts (e.g., those of DMD). Circular DMD transcripts are reported in, as a non-limiting example: Gualandi et al. 2003 J. Med. Gen. 40:e100.

[00854] In some embodiments, a composition capable of mediating multiple exon skipping (MESO) comprises one DMD oligonucleotide capable of mediating skipping of multiple exons. In some embodiments, a composition capable of mediating multiple exon skipping (MESO) comprises two DMD oligonucleotides which are together (e.g., when used in combination) capable of mediating skipping of multiple exons. In some embodiments, a composition capable of mediating multiple exon skipping

(MESO) comprises a cocktail of (e.g., a mixture of three or more) DMD oligonucleotides which are together (e.g., when used in combination as a cocktail) capable of mediating skipping of multiple exons. Combinations or cocktails of oligonucleotides capable of mediating skipple of multiple exons have been reported by, for example, Yokota et al. 2009 Arch. Neurol. 66: 32; Yokota et al. 2012 Nucl. Acid Ther. 22: 306; Adkin et al. 2012 Neur. Dis. 22: 297-305; Echigoya et al. 2013 Nucl. Acid. Ther.; and Echigoya et al. 2015 Molecular Therapy—Nucleic Acids 4: e225. Among other things, the present disclosure provides more effective combinations, through, e.g., selected sequences, chemical modifications, and/or linkage phosphorus chemistry, etc.

[00855] In some embodiments, the present disclosure provides oligonucleotides that, when combined with other oligonucleotides, can provide dramatically increased activities compared to either oligonucleotides individually prior to combination. For example, in some embodiments, the present disclosure provides DMD oligonucleotides which are individually incapable of mediating efficient skipping of a particular exon; when combined with other oligonucleotides, such oligonucleotides are capable of mediating skipping of multiple exons. Among other things, the present disclosure provides combination therapy, wherein two or more oligonucleotides are used together to provide desired and/or enhanced properties and/or activities. When used in combination therapy, the two or more agents, e.g., oligonucleotides, may be administered concurrently, or separately in suitable ways for them to achieve their combination effects. In some embodiments, two or more oligonucleotides in a combination are all (primarily) for skipping of the same exon, and their combination provides enhanced skipping of such exon, in some embodiments, significantly more than the addition of their separate effects. In some embodiments, two or more oligonucleotide in a combination are for skipping of difference exons, and their combination provides effective skipping, sometimes more than the oligonucleotides individually can achieve, of two or more exons. In some embodiments, the present disclosure provide combinations of oligonucleotides with synergies between two or more different oligonucleotides. In some embodiments, the present disclosure provides combinations of different oligonucleotides wherein one or more, or each oligonucleotide by itself is not effective for exon skipping. Certain combinations are described in Adams et al. 2007 BMC Mol. Biol. 8:57. Among other things, the present disclosure provides more effective combinations, through, e.g., designed control of one or more or all structural elements of oligonucleotides. In some embodiments, a provided combination provides exon skipping of DMD exon 45. In some embodiments, a provided combination provides exon skipping of another DMD exon, including those described herein or otherwise desirable for skipping (e.g., for prevention or treatment of one or more conditions, diseases or disorders etc.) as known in the art.

[00856] In some embodiments, cocktails, combinations and mixtures of oligonucleotides, e.g., for multiple exon skipping may have disadvantages compared to single oligonucleotides which can perform

the same or comparable functions, such as higher costs of goods, complications in manufacturing and delivery, increased regulatory burden, etc. In accordance with FDA regulations, each component in a combination may need to be separately tested for toxicity, as well as the entire combination. In some embodiments, the present disclosure provides single oligonucleotides that can achieve the same or comparable functions of oligonucleotide combinations, and may be utilized to replace oligonucleotide combinations, through precise and designed control of one or more structural elements of oligonucleotides, e.g., chemical modifications, stereochemistry, and combinations thereof.

[00857] Various technologies are suitable for assessing multiple exon skipping in accordance with the present disclosure. Non-limiting examples are described in Example 20 and Figure 2.

[00858] In some embodiments, a composition for skipping multiple DMD exons comprises a DMD oligonucleotide capable of skipping DMD exon 45. Various DMD oligonucleotides were tested for their capability to skip exon 45, as shown in Table 1A. Various DMD oligonucleotides for skipping exon 45 were also tested for their ability to skip multiple exons, as shown in Table 22A. Among other things, the present disclosure demonstrates that several oligonucleotides, including WV-11088 and WV-11089, can provide low levels of skipping of exons 45-55 (creating a junction between exon 44 and exon 56 or 44-56).

[00859] In another experiment, oligonucleotides WV-11047, WV-11051 to WV-11059 did not demonstrate significant skipping under the specific tested condition, and oligonucleotides WV-11062 to WV-11069 each exhibited detectable levels of skipping which were <1% under the specific tested condition. Oligonucleotides WV-11091 to WV-11096, WV-11098, and WV-11100 to WV-11105 exhibited <.5% skipping of exon 45 under the specific tested condition.

Table 22A. Example data of certain oligonucleotides.

Oligonucleotides were tested for their ability to skip DMD exon 45 in Δ48-50 cells.

Numbers indicate skipping level, wherein 100 would represent 100% skipping and 0 would represent 0% skipping.

WV-11070	1.6
WV-11071	.3
WV-11072	.2
WV-11073	.7
WV-11074	2.2
WV-11075	.2
WV-11076	1.2
WV-11077	1.3
WV-11078	3.3
WV-11079	7.5
WV-11080	1.3
WV-11081	7.2

WV-11082	2.8
WV-11083	3.1
WV-11084	10.1
WV-11085	1.5
WV-11086	15.8
WV-11087	1.1
WV-11088	13
WV-11089	15.1
WV-11090	.9

Several oligonucleotides, including WV-11088 and WV-11089, showed detectable levels of multiple exon skipping (specifically exons 45-55) (approximately 0.1% skipping).

[00860] In another experiment, various DMD oligonucleotides targeting exon 45 were tested in Δ48-50 for an ability to skip multiple exons (specifically 45 to 53, creating a junction between exon 44 and exon 54 or 44-54). Oligonucleotides tested were: WV-11047, WV-11051, WV-11052, WV-11053, WV-11054, WV-11055, WV-11056, WV-11057, WV-11058, WV-11059, WV-11062, WV-11063, WV-11064, WV-11065, WV-11066, WV-11067, WV-11068, WV-11069, WV-11070, WV-11071, WV-11072, WV-11073, WV-11074, WV-11075, WV-11076, WV-11077, WV-11078, WV-11079, WV-11080, WV-11081, WV-11082, WV-11083, WV-11084, WV-11085, WV-11086, WV-11087, WV-11088, WV-11089, WV-11090, WV-11091, WV-11092, WV-11093, WV-11094, WV-11095, WV-11096, WV-11098, WV-11100, WV-11101. All these oligonucleotides, in one experiment, demonstrated on average about 0.05% or less skipping of exons 44-54 (data not shown).

[00861] Oligonucleotides targeting exon 45 were also tested for skipping of exons 45 to 57, as shown in Table 22A.1.

Table 22A.1. Example data of certain oligonucleotides.

Oligonucleotides were tested in Δ48-50 for their ability to skip DMD exons 45 to 57, creating a junction between exon 44 and exon 58 or 44-58. Numbers indicate skipping level, wherein 100 would represent 100% skipping and 0 would represent 0% skipping. Replicate data in this and other tables are shown.

WV-11047	0.064	0.118	0.048	0.099
WV-11051	0.044	0.101	0.034	0.079
WV-11052	0.076	0.089	0.078	0.090
WV-11053	0.082	0.076	0.078	0.072
WV-11054	0.126	0.083	0.110	0.100
WV-11055	0.037	0.071	0.048	0.073
WV-11056	0.133	0.102	0.116	0.092
WV-11057	0.000	0.001	0.000	0.097
WV-11058	0.102	0.030	0.071	0.042

WV-11059	0.171	0.100	0.157	0.075
WV-11062	0.070	0.112	0.081	0.088
WV-11063	0.088	0.078	0.051	0.081
WV-11064	0.085	0.071	0.071	0.075
WV-11065	0.073	0.114	0.077	0.143
WV-11066	0.083	0.100	0.004	0.143
WV-11067	0.115	0.069	0.094	0.068
WV-11068	0.112	0.071	0.125	0.053
WV-11069	0.075	0.075	0.083	0.053
WV-11070	0.062	0.107	0.067	0.101
WV-11071	0.085	0.116	0.073	0.118
WV-11072	0.080	0.097	0.052	0.084
WV-11073	0.052	0.148	0.047	0.118
WV-11074	0.155	0.098	0.116	0.101
WV-11075	0.145	0.079	0.126	0.113
WV-11076	0.000	0.105	0.000	0.111
WV-11077	0.050	0.087	0.080	0.058
WV-11078	0.087	0.095	0.077	0.103
WV-11079	0.076	0.063	0.079	0.062
WV-11080	0.059	0.058	0.052	0.070
WV-11081	0.077	0.086	0.058	0.055
WV-11082	0.117	0.071	0.112	0.080
WV-11083	0.077	0.108	0.091	0.091
WV-11084	0.080	0.102	0.053	0.069
WV-11085	0.047	0.143	0.041	0.140
WV-11086	0.085	0.087	0.084	0.074
WV-11087	0.114	0.034	0.000	0.056
WV-11088	0.134	0.112	0.057	0.063
WV-11089	0.074	0.113	0.109	0.082
WV-11090	0.119	0.076	0.074	0.081
WV-11091	0.000	0.055	0.031	0.054
WV-11092	0.039	0.057	0.068	0.058
WV-11093	0.147	0.061	0.138	0.061
WV-11094	0.108	0.078	0.061	0.080
WV-11095	0.062	0.061	0.056	0.072
WV-11096	0.104	0.071	0.072	0.101
WV-11098	0.072	0.095	0.081	0.065
WV-11100	0.068	0.079	0.078	0.068
WV-11101	0.000	0.058	0.000	0.048

[00862] In some embodiments, a DMD oligonucleotide targets DMD exon 44 or the adjoining intronic region 3' to DMD exon 44 and is capable of mediating multiple exon skipping.

[00863] In some embodiments, a DMD oligonucleotide targets DMD exon 44 or the adjoining intronic region 3' to DMD exon 44, and the oligonucleotide is capable of mediating multiple exon skipping (e.g., of exons 45 to 55, or 45 to 57).

[00864] Reportedly, a phenomenon known as back-splicing can occur, in which, for example, a portion of the 3' end of exon 55 interacts with a portion of the 5' end of exon 45, forming a circular RNA (circRNA), which can thus skip multiple exons, e.g., all exons from exon 45 to 55, inclusive. The phenomenon can also reportedly occur between exon 57 and exon 45, skipping multiple exons, e.g., all exons from exon 45 to 57, inclusive. Back-splicing is described in the literature, e.g., in Suzuki et al. 2016 Int. J. Mol. Sci. 17.

[00865] Without wishing to be bound by any particular theory, the present disclosure suggests that it may be possible for a DMD oligonucleotide targeting DMD exon 44 or the adjoining intronic region 3' to exon 44 may be able to mediate splicing of exons 45 to 55, or of exons 45 to 57, which exons are excised as a single piece of circular RNA (circRNA) designated 45-55 (or 55-45) or 45-57 (or 57-45), respectively.

[00866] Several oligonucleotides were designed to target exon 44 or intron 44, or which straddle exon 44 and intron 44. In some embodiments, oligonucleotides designed to target exon 44 or intron 44, or which straddle exon 44 and intron 44 are tested to determine if they can increase the amount of backslicing and/or multiple-exon skipping.

[00867] As shown in Table 22A.2 and Table 22A.3, below, DMD oligonucleotides targeting Exon44 were tested for the ability to increase circRNA 55-45 (e.g., mediate multiple exon skipping of exons 45 to 55); or for the ability to increase circRNA 57-45 (e.g., mediate multiple exon skipping of exons 45 to 57). Various DMD oligonucleotides comprise various difference including, inter alia, base sequence and length (18 or 20 bases). Numbers indicate relative amount of circRNA 55-45 (Table 22A.2) or circRNA 57-45 (Table 22A.3). In this and various other tables, Rep indicates Replicate.

Table 22A.2. Example data of certain oligonucleotides.

WV-13964	0.9	1	WV-14016	1.2	1.5
WV-13965	1.1	1.1	WV-14017	1.5	1.5
WV-13966	1.1	0.6	WV-14018	0.8	1
WV-13967	1.3	1.2	WV-14019	1.2	1.4
WV-13969	1	0.8	WV-14020	1	1
WV-13971	0.3	0.9	WV-14021	1	1.3
WV-13972	1.1	1.3	WV-14022	1.3	1.5

WV-13973	1.1	1.3	WV-14023	1.3	1.7
WV-13976	1.2	1.2	WV-14024	1.2	1.2
WV-13979	0.5	0.5	WV-14025	1.5	1.6
WV-13980	1.3	0.4	WV-14026	2.4	0.6
WV-13981	0.9	0.7	WV-14027	1.2	1.2
WV-13982	1	1	WV-14028	1.1	1.2
WV-13983	0.9	0.6	WV-14029	1.2	1.4
WV-13984	1.1		WV-14030	1.3	1.6
WV-13985	1.3	0.8	WV-14031	1.3	1.6
WV-13987	1.2	1	WV-14032	1.2	1.5
WV-13988	1.4	0.9	WV-14033	1.3	
WV-13989	1.6	1	WV-14034	1.1	1.2
WV-13990	1.7	1	WV-14035	1.2	1.4
WV-13991	1.4	1	WV-14036	1.1	1.1
WV-13992	1.6	1	WV-14037	1.1	1.2
WV-13993	1.2	1	WV-14038	1.4	1.4
WV-13994	1.2	0.6	WV-14039	1.2	1.2
WV-13995	1.1	0.9	WV-14040	2.2	3
WV-13996	1.4	1	WV-14041	2.3	2.4
WV-13997	1.2	1.3	WV-14042	1.3	1.3
WV-13998	1.2	0.8	WV-14043	1.1	1.4
WV-13999	1.2	1.3	WV-14044	1.3	1.5
WV-14000	0.9	0.9	WV-14045	1.8	2.1
WV-14001	1.1	1.5	WV-14046	1.3	1.6
WV-14002	1	1.1	WV-14047	1.2	1.6
WV-14003	2	2.1	WV-14048	3.8	4.9
WV-14004	1.9	1.2	WV-14049	2.1	2.6
WV-14005	1.1	1	WV-14050	1.4	1.5
WV-14006	1.2	1.4	WV-14051	1.5	1.7
WV-14007	1.3	1.7	WV-14052	1.4	2.2
WV-14008	1.4	1.1	WV-14053	1.5	1.4
WV-14009	1.3	1.3	WV-14054	1.4	1.8
WV-14010	1	1.1	WV-14055	1.3	1.6
WV-14011	3.2	3.7	WV-14056	1.3	1.4
WV-14012	1.8	2	WV-14057	1.7	2.1
WV-14013	1.4	1.8	WV-14058	1.8	1.4
WV-14014	1.1	1.3			
WV-14015	1.1	1.3			

Table 22A.3. Example data of certain oligonucleotides.

	Biological Rep1	Biological Rep2		Biological Rep1	Biological Rep2
mock		0.9	WV-14010	1	0.6
mock	0.8	1	WV-14011	3.1	4.7
mock	1	1.4	WV-14012	1.3	1.7
mock	1	0.5	WV-14013	0.9	1
mock	1.9	1.2	WV-14014	0.9	1.1
mock	0.7	0.7	WV-14015	0.4	1.2
mock	0.9	0.6	WV-14016	0.4	2.1
mock	0.3	1.6	WV-14017	1.4	1.3
WV-13964	0.8	1	WV-14018	0.8	0.7
WV-13965	0.8	0.7	WV-14019	1.3	1.5
WV-13966	1	0.7	WV-14020	0.6	1.2
WV-13967	1.2	0.9	WV-14021	1.2	1.4
WV-13969	1.2	1.3	WV-14022	1.6	1.6
WV-13971		0.5	WV-14023	1.2	1.3
WV-13972	0.9	1.3	WV-14024	1.4	1.1
WV-13973	0.6	1.4	WV-14025	0.5	1.6
WV-13976	1.3	1.6	WV-14026	1.9	
WV-13979	0.5	0.3	WV-14027	1.1	0.9
WV-13980	1.4	0.6	WV-14028	0.8	1
WV-13981	0.8	1.3	WV-14029	1.1	1.3
WV-13982	1.1	1	WV-14030	1.2	1.4
WV-13983	1	0.8	WV-14031	1.2	1.5
WV-13984	0.8	0.4	WV-14032	0.9	1.7
WV-13985	1.3	1.6	WV-14033	0.9	
WV-13987	1.4	1.1	WV-14034	0.8	1.1
WV-13988	1.4	1	WV-14035	1.3	1.1
WV-13989	1.5	0.7	WV-14036	0.7	0.9
WV-13990	1.3	0.6	WV-14037	1.2	1
WV-13991	1.3	0.8	WV-14038	1.4	1.6
WV-13992	1.6	2.4	WV-14039	1.1	0.5
WV-13993	0.9	0.9	WV-14040	2.5	4.4
WV-13994	0.6	1	WV-14041	2	2.8
WV-13995	0.9	1.6	WV-14042	1.4	1.2
WV-13996	1.2	0.8	WV-14043	1.4	1.4
WV-13997	1.4	0.7	WV-14044	1.7	1.2
WV-13998	1.2	0.8	WV-14045	1.7	2
WV-13999	0.9	0.9	WV-14046	1.1	1.9

WV-14000	0.6	0.3	WV-14047	1.3	2
WV-14001	0.8	0.9	WV-14048	3.1	7.1
WV-14002	0.6	1.3	WV-14049	1.9	2.5
WV-14003	2.1	2	WV-14050	1.6	1.4
WV-14004	2.1	0.7	WV-14051	1.8	1.7
WV-14005	0.9	0.8	WV-14052	0.9	2.6
WV-14006	1.3	1.1	WV-14053	1.1	1.8
WV-14007	0.9	1.6	WV-14054	1.2	2
WV-14008	1.3	1.1	WV-14055	1.2	2
WV-14009	0.9	1	WV-14056	1.4	0.9
WV-14010	1	0.6	WV-14057	1.5	1.9
WV-14011	3.1	4.7	WV-14058	1.3	1

[00868] In some embodiments, a composition capable of mediating exon skipping of a particular DMD exon comprises two or more oligonucleotides targeting a particular exon. In some embodiments, a combination of two or more oligonucleotides provides skipping levels significantly higher than the addition of the skipping level of each oligonucleotide individually. In some embodiments, a combination of two or more oligonucleotides provides significant (1%, 5%, 10%, or more) and/or detectable levels of skipping while each oligonucleotide individually does not provide detectable levels of skipping. Combinations of traditional oligonucleotides (e.g., stereorandom oligonucleotide and/or oligonucleotides without non-negatively charged internucleotidic linkages described in the present disclosure) has been reported to provide certain improved effects, e.g., in Wilton et al. 2007 Mol. Ther. 7: 1288-1296 (exons 10, 20, 34, 65, etc.). Among other things, provided combinations comprise at least one oligonucleotide comprising one or more chirally controlled internucleotidic linkages and/or one or more non-negatively charged internucleotidic linkages, and can provide significantly increased levels of exon skipping.

[00869] Among other things, the present disclosure recognizes that certain exons are particularly challenging for skipping. For example, in one report, for exons 47 and 57. individual DMD oligonucleotides were not capable of mediating exon skipping, but pairs of oligonucleotides were capable of mediating exon skipping. In one report, effective skipping of exon 45 was mediated by combining two DMD oligonucleotides which were individually not effective in skipping of this exon. Aartsma-Rus et al. 2006 Mol. Ther. 14: 401. Aartsma-Rus et al. 2006 Mol. Ther. 14: 401. In some embodiments, the present disclosure provides oligonucleotides (e.g., chirally controlled oligonucleotides), and compositions and methods of use thereof, for exon skipping of such challenging exons. With chemistry modifications and/or stereochemistry technologies described herein, the present disclosure provides technologies with greatly improved exon skipping efficiency. In some embodiments, the present disclosure provides single

oligonucleotide (e.g., a chirally controlled oligonucleotide) and compositions thereof (e.g., a chirally controlled oligonucleotide composition) for exon skipping of one or more exons that are challenging to skip. In some embodiments, the present disclosure provides combinations of oligonucleotides (e.g.,, chirally controlled oligonucleotides) and compositions thereof (e.g., chirally controlled oligonucleotide compositions) for exon skipping of one or more exons that are challenging to skip. In some embodiments, combinations of DMD oligonucleotides targeting the same exon mediate increased exon skipping levels relative to individual DMD oligonucleotides.

[00870] In some embodiments, a composition comprises two or more DMD oligonucleotides, wherein each individual DMD oligonucleotide mediates low levels of exon skipping, while the combination mediates a higher level of skipping (higher than the addition of levels achieved by each oligonucleotide individually).

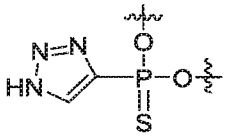
[00871] In some embodiments, a composition comprises two or more DMD oligonucleotides, wherein the oligonucleotides target different exons.

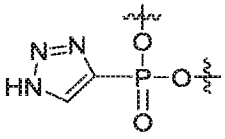
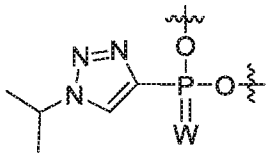
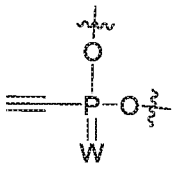
[00872] In some embodiments, a combination of multiple DMD oligonucleotides targeting different exons is capable of mediating skipping of two or more (e.g., multiple) exons.

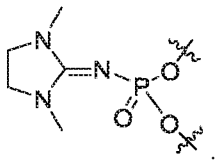
[00873] In some embodiments, a composition comprises two or more DMD oligonucleotides. In some embodiments, a composition comprises two or more DMD oligonucleotides, at least one of which is described herein or has a base sequence, stereochemistry or other chemical characteristic described herein.

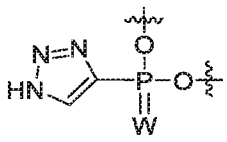
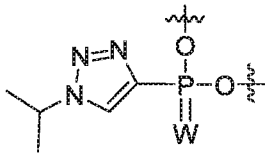
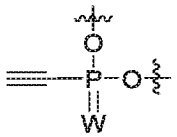
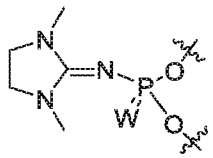
Oligonucleotides Comprising Non-Negatively Charged Internucleotidic Linkages Can Provide Significantly Improved Activities.

[00874] In some embodiments, the present disclosure provides oligonucleotides comprising one or more non-negatively charged internucleotidic linkages. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, the present disclosure provides oligonucleotides comprising one or more neutral internucleotidic linkages. In some embodiments, a non-negatively charged internucleotidic linkage has the structure of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof.

[00875] In some embodiments, a non-negatively charged internucleotidic linkage comprises a triazole moiety. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted triazolyl group. In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged

internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage comprises a substituted triazolyl group. In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  , wherein W is O or S. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted alkynyl group. In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  , wherein W is O or S.

[00876] In some embodiments, the present disclosure provides oligonucleotides comprising an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, which comprises a cyclic guanidine moiety. In some embodiments, an internucleotidic linkage comprises a cyclic guanidine and has the structure of:  . In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, comprising a cyclic guanidine is stereochemically controlled.

[00877] In some embodiments, a non-negatively charged internucleotidic linkage, or a neutral internucleotidic linkage, is or comprising a structure selected from  ,  ,  , or  , wherein W is O or S. In some embodiments, a non-negatively charged internucleotidic linkage is a chirally controlled internucleotidic linkage. In some embodiments, a neutral internucleotidic linkage is a chirally controlled internucleotidic linkage. In some embodiments, a nucleic acid or an oligonucleotide comprising a modified internucleotidic linkage comprising a cyclic guanidine moiety is a siRNA, double-straned siRNA, single-stranded siRNA, gapmer, skipmer, blockmer, antisense oligonucleotide, antagomir, microRNA, pre-

microRNs, antimir, supermir, ribozyme, Ul adaptor, RNA activator, RNAi agent, decoy oligonucleotide, triplex forming oligonucleotide, aptamer or adjuvant.

[00878] In some embodiments, an oligonucleotide comprises a neutral internucleotidic linkage and a chirally controlled internucleotidic linkage. In some embodiments, an oligonucleotide comprises a neutral internucleotidic linkage and a chirally controlled internucleotidic linkage which is a phosphorothioate in the Rp or Sp configuration. In some embodiments, the present disclosure provides an oligonucleotide comprising one or more non-negatively charged internucleotidic linkages and one or more phosphorothioate internucleotidic linkage, wherein each phosphorothioate internucleotidic linkage in the oligonucleotide is independently a chirally controlled internucleotidic linkage. In some embodiments, the present disclosure provides an oligonucleotide comprising one or more neutral internucleotidic linkages and one or more phosphorothioate internucleotidic linkage, wherein each phosphorothioate internucleotidic linkage in the oligonucleotide is independently a chirally controlled internucleotidic linkage. In some embodiments, a provided oligonucleotide comprises at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more chirally controlled phosphorothioate internucleotidic linkages.

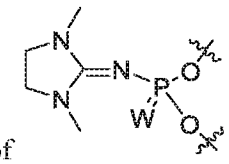
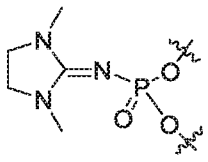
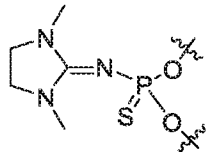
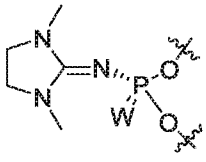
[00879] Without wishing to be bound by any particular theory, the present disclosure notes that a neutral internucleotidic linkage is more hydrophobic than a phosphorothioate internucleotidic linkage (PS), which is more hydrophobic than a phosphodiester linkage (natural phosphate linkage, PO). Typically, unlike a PS or PO, a neutral internucleotidic linkage bears less charge. Without wishing to be bound by any particular theory, the present disclosure notes that incorporation of one or more neutral internucleotidic linkages into an oligonucleotide may increase oligonucleotides' ability to be taken up by a cell and/or to escape from endosomes. Without wishing to be bound by any particular theory, the present disclosure notes that incorporation of one or more neutral internucleotidic linkages can be utilized to modulate melting temperature between an oligonucleotide and its target nucleic acid.

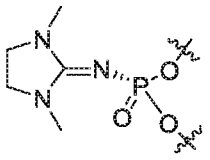
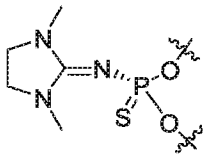
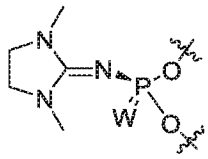
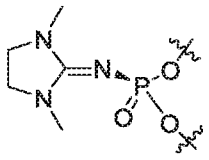
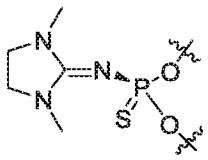
[00880] Without wishing to be bound by any particular theory, the present disclosure notes that incorporation of one or more non-negatively charged internucleotidic linkages, e.g., neutral internucleotidic linkages, into an oligonucleotide may be able to increase the oligonucleotide's ability to mediate a function such as exon skipping or gene knockdown. In some embodiments, an oligonucleotide capable of altering skipping of one or more exons in a target gene comprises one or more neutral internucleotidic linkages. In some embodiments, an oligonucleotide capable of mediating skipping of an exon(s) in a target gene comprises one or more neutral internucleotidic linkages. In some embodiments, an oligonucleotide capable of mediating skipping of one or more DMD exon(s) comprises one or more neutral internucleotidic linkages.

[00881] In some embodiments, an oligonucleotide capable of mediating knockdown of level of a

nucleic acid or a product encoded thereby comprises one or more non-negatively charged internucleotidic linkages. In some embodiments, an oligonucleotide capable of mediating knockdown of expression of a target gene comprises one or more non-negatively charged internucleotidic linkages. In some embodiments, an oligonucleotide capable of mediating knockdown of expression of a target gene comprises one or more neutral internucleotidic linkages.

[00882] In some embodiments, a non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, a non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, a non-negatively charged internucleotidic linkage is chirally controlled and its linkage phosphorus is *Rp*. In some embodiments, a non-negatively charged internucleotidic linkage is chirally controlled and its linkage phosphorus is *Sp*.

[00883] In some embodiments, a provided oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more non-negatively charged internucleotidic linkages. In some embodiments, a provided oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more neutral internucleotidic linkages. In some embodiments, each of non-negatively charged internucleotidic linkage and/or neutral internucleotidic linkages is optionally and independently chirally controlled. In some embodiments, each non-negatively charged internucleotidic linkage in an oligonucleotide is independently a chirally controlled internucleotidic linkage. In some embodiments, each neutral internucleotidic linkage in an oligonucleotide is independently a chirally controlled internucleotidic linkage. In some embodiments, at least one non-negatively charged internucleotidic linkage/neutral internucleotidic linkage has the structure of  , wherein W is O or S. In some embodiments, at least one non-negatively charged internucleotidic linkage/neutral internucleotidic linkage has the structure of  . In some embodiments, at least one non-negatively charged internucleotidic linkage/neutral internucleotidic linkage has the structure of  . In some embodiments, at least one non-negatively charged internucleotidic linkage/neutral internucleotidic linkage has the structure of  , wherein W

is O or S. In some embodiments, at least one non-negatively charged internucleotidic linkage/neutral internucleotidic linkage has the structure of  . In some embodiments, at least one non-negatively charged internucleotidic linkage/neutral internucleotidic linkage has the structure of  . In some embodiments, at least one non-negatively charged internucleotidic linkage/neutral internucleotidic linkage has the structure of  , wherein W is O or S. In some embodiments, at least one non-negatively charged internucleotidic linkage/neutral internucleotidic linkage has the structure of  . In some embodiments, at least one non-negatively charged internucleotidic linkage/neutral internucleotidic linkage has the structure of  . In some embodiments, a provided oligonucleotide comprises at least one non-negatively charged internucleotidic linkage wherein its linkage phosphorus is in *Rp* configuration, and at least one non-negatively charged internucleotidic linkage wherein its linkage phosphorus is in *Sp* configuration.

[00884] In some embodiments, an oligonucleotide capable of increasing the frequency of skipping of an exon of a target gene comprises a non-negatively charged internucleotidic linkage. In some embodiments, an oligonucleotide capable of increasing the frequency of skipping of an exon of a target gene comprises a non-negatively charged internucleotidic linkage and is useful for treatment of a disease wherein the exon comprises a deleterious or disease-associated mutation. A non-limiting example is the DMD gene, wherein the skipping of an exon comprising a mutation contributes to muscular dystrophy.

[00885] Various oligonucleotides, including DMD oligonucleotides, that comprise one or more non-negatively charged internucleotidic linkages/neutral internucleotidic linkages were designed and/or constructed and/or tested, for example, WV-11343, WV-11344, WV-11345, WV-11346, WV-11347, WV-11237, WV-11238, WV-11239, WV-12130, WV-12131, WV-12132, WV-12133, WV-12134, WV-

12135, WV-12136, WV-11340, WV-11341, WV-11342, WV-12123, WV-12124, WV-12125, WV-12126, WV-12127, WV-12128, WV-12129, WV-12553, WV-12554, WV-12555, WV-12556, WV-12557, WV-12558, WV-12559, WV-12872, WV-12873, etc. Example DMD oligonucleotides for skipping exon 23 and comprising a non-negatively charged internucleotidic linkage (e.g., a neutral internucleotidic linkage) include: WV-11343, WV-11344, WV-11345, WV-11346, and WV-11347. Example DMD oligonucleotides for skipping exon 51 and comprising a non-negatively charged internucleotidic linkage (e.g., a neutral internucleotidic linkage) include: WV-11237, WV-11238, WV-11239, WV-12130, WV-12131, WV-12132, WV-12133, WV-12134, WV-12135, and WV-12136. Example DMD oligonucleotides for skipping exon 53 and comprising a non-negatively charged internucleotidic linkage (e.g., a neutral internucleotidic linkage) include: WV-11340, WV-11341, WV-11342, WV-12123, WV-12124, WV-12125, WV-12126, WV-12127, WV-12128, WV-12129, WV-12553, WV-12554, WV-12555, WV-12556, WV-12557, WV-12558, WV-12559, WV-12872, and WV-12873. Certain oligonucleotides are in Table A1.

[00886] Additional DMD oligonucleotides comprising a non-negatively charged internucleotidic linkage were designed and/or constructed. These include DMD oligonucleotides for skipping DMD exon 45, WV-14528, WV-14529, WV-14532, and WV-14533.

[00887] The efficacy of various DMD oligonucleotides comprising a non-negatively charged internucleotidic linkage in skipping DMD exon 45 is shown in Table 1B.1 and Table 1B.2 herein.

[00888] The efficacy of various DMD oligonucleotides comprising a non-negatively charged internucleotidic linkage in skipping DMD exon 53 is shown in Table 21E, Table 21F, Table 21G, and Table 21H herein.

[00889] In some embodiments, a non-negatively charged internucleotidic linkage may be designated as nX if stereorandom, or nS chirally controlled and linkage phosphorus in the Sp configuration, or nR if chirally controlled and the linkage phosphorus in the Rp configuration.

[00890] In some embodiments, a non-negatively charged internucleotidic linkage may be designated as n001 if stereorandom, or n001S chirally controlled and linkage phosphorus in the Sp configuration, or n001R if chirally controlled and the linkage phosphorus in the Rp configuration (e.g., in Table A1).

[00891] Various DMD oligonucleotides comprising a non-negatively charged internucleotidic linkage in the Rp configuration were constructed, including WV-12872, WV-13408, WV-12554, WV-13409, WV-12555, and WV-12556.

[00892] Various DMD oligonucleotides comprising a non-negatively charged internucleotidic linkage in the Sp configuration were constructed, including WV-12557, WV-12558, and WV-12559.

[00893] Data showing activity and stability of various oligonucleotides comprising a non-

negatively charged internucleotidic linkage in the Rp or Sp configuration are shown in Table 21H Table 21I, Table 21I.1, and Table 21I.2

[00894] Several oligonucleotides (including WV-9517, WV-13864, WV-13835, and WV-14791) were tested at various concentrations up to 30 uM for TLR9 activation in HEK-blue-TLR9 cells (16 hour gymnotic uptake). WV-13864 and WV-14791 comprise a chirally controlled non-negatively charged internucleotidic linkage in the Rp configuration. WV-9517, WV-13864, WV-13835, and WV-14791 did not exhibit significant TLR9 activation (data not shown).

[00895] Several oligonucleotides which target a gene other than DMD were designed and/or constructed which comprise a non-negatively charged internucleotidic linkage.

[00896] Below are presented oligonucleotides comprising a cyclic guanidine moiety which target DMD or Malat-1 (Malat1). The DMD oligonucleotides are designed to mediate skipping of exon 23 (in mouse) or exon 51 or exon 53 (in human). The Malat-1 oligonucleotides are designed to for Malat1 mRNA knockdown, e.g., mediated through RNase H.

Table 22B. Example Malat-1 oligonucleotides comprising a neutral backbone.

All of these oligonucleotides have the base sequence of UGCCAGGCTGGTTATGACUC.

Oligonucleotide	**Description**	**Stereochemistry**
WV-11533	mU * SGeon001m5Ceon001 m5Ceo n001mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	SnXnXnXSSRSSR SSRSSSSSS
WV-12504	Mod001L001mU * SGeon001 m5Ceon001 m5Ceon001mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	OSnXnXnXSSRSS RSSRSSSSSS
WV-12505	L001mU * SGeon001m5Ceon001 m5Ceon001mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	OSnXnXnXSSRSS RSSRSSSSSS

[00897] Oligonucleotides comprising non-negatively charged internucleotidic linkages and targeting other gene targets were also designed, constructed and/or tested for their properties and activities, including activities for reducing levels of target mRNAs and/or proteins, e.g., via RNaseH-mediated knockdown. Such oligonucleotides are active in reducing target levels.

[00898] Various Malat1 oligonucleotides were designed, constructed and tested which comprise a non-negatively charged internucleotidic linkage. Various Malat1 oligonucleotides comprise 1, 2 or 3 non-negatively charged internucleotidic linkages in a wing and/or a core.

Table 22C. Malat1 oligonucleotides

All of the oligonucleotides in this table have the base sequence of UGCCAGGCTGGTTATGACUC.

Oligo-	**Sequence**	**Stereochemistry**

nucleotide		
WV-8587	mU * SGeo m5Ceo m5Ceo mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	SOOOSSRSSR SSRSSSSSS
WV-14733	mU * SGeo m5Ceo m5Ceo mA * SG * SG * SC * ST * SG * SG * ST * ST * SA * ST * S mG * S mA * S mC * S mU * S mC	SOOOSSSSSS SSSSSSSSS
WV-15351	mU * SGeo m5Ceo m5Ceo mA * SG * SGn001C * ST * SGn001G * ST * STn001A * ST * S mG * S mA * S mC * S mU * S mC	SOOOSSnXSS nXSSnXSSSSSS
WV-15352	mU * SGeo m5Ceo m5Ceo mA * SG * SGn001C * ST * SG * RG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	SOOOSSnXSS RSSRSSSSSS
WV-15353	mU * SGeo m5Ceo m5Ceo mA * SG * SG * RC * ST * SGn001G * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	SOOOSSRSSnX SSRSSSSSS
WV-15354	mU * SGeo m5Ceo m5Ceo mA * SG * SG * RC * ST * SG * RG * ST * STn001A * ST * S mG * S mA * S mC * S mU * S mC	SOOOSSRSSRSS nXSSSSSS
WV-15356	mU * SGeo m5Ceo m5Ceo mA * SG * SG * RCn001Tn001G * RG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	SOOOSSRnXnX RSSRSSSSSS
WV-15357	mU * SGeo m5Ceo m5Ceo mA * SG * SG * RC * ST * SG * RGn001Tn001T * RA * ST * S mG * S mA * S mC * S mU * S mC	SOOOSSRSSR nXnXRSSSSSS
WV-15358	mU * SGeo m5Ceo m5Ceo mA * SG * SG * RC * ST * SG * RG * ST * ST * RAn001Tn001 mG * S mA * S mC * S mU * S mC	SOOOSSRSSRS SRnXnXSSSS
WV-8582	mU * SGeo m5Ceo m5Ceo mA * SG * SG * SC * ST * SG * SG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	SOOOSSSSSSS SRSSSSSS
WV-15359	mU * SGeo m5Ceo m5Ceo mA * SG * SG * SC * ST * SG * SG * ST * STn001An001Tn001 mG * S mA * S mC * S mU * S mC	SOOOSSSSSSS SnXnXnXSSSS
WV-15360	mU * SGeo m5Ceo m5Ceo mA * SG * SG * SC * ST * SG * SG * ST * STn001A * ST * S mG * S mA * S mC * S mU * S mC	SOOOSSSSSSS SnXSSSSSS
WV-15361	mU * SGeo m5Ceo m5Ceo mA * SG * SG * SC * ST * SG * SG * ST * ST * RA * STn001 mGn001 mA * S mC * S mU * S mC	SOOOSSSSSSS SRSnXnXSSS
WV-15362	mU * SGeo m5Ceo m5Ceo mA * SG * SG * SC * ST * SG * SG * ST * ST * RAn001T * S mG * S mA * S mC * S mU * S mC	SOOOSSSSSSS SRnXSSSSS
WV-15363	mU * SGeo m5Ceo m5Ceo mA * SG * SG * SC * ST * SG * SG * ST * ST * RA * STn001 mG * S mA * S mC * S mU * S mC	SOOOSSSSSSS SRSnXSSSS
WV-14556	mUn001Geon001 m5Ceon001 m5Ceo mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	nXnXnXOSSRS SRSSRSSSSS
WV-14557	mUn001Geon001 m5Ceo m5Ceon001 mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	nXnXOnXSSRS SRSSRSSSSS
WV-14558	mUn001Geon001 m5Ceo m5Ceo mAn001G * SG * RC * ST * SG * RG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	nXnXOOnXSRS SRSSRSSSSS
WV-14559	mUn001Geo m5Ceon001 m5Ceon001 mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	nXOnXnXSSRSS RSSRSSSSS
WV-14560	mUn001Geo m5Ceon001 m5Ceo mAn001G * SG * RC * ST * SG * RG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	nXOnXOnXSRSS RSSRSSSSS
WV-14561	mUn001Geo m5Ceo m5Ceon001 mAn001G * SG * RC * ST *	nXOOnXnXSRSS

	SG * RG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	RSSRSSSSSS
WV-11533	mU * SGeon001 m5Ceon001 m5Ceon001 mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	SnXnXnXSSRSS RSSRSSSSSS
WV-14562	mU * SGeon001 m5Ceon001 m5Ceo mAn001G * SG * RC * ST * SG * RG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	SnXnXOnXSRSS RSSRSSSSSS
WV-14563	mU * SGeon001 m5Ceo m5Ceon001 mAn001G * SG * RC * ST * SG * RG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	SnXOnXnXSRSS RSSRSSSSSS
WV-14564	mU * SGeo m5Ceon001 m5Ceon001 mAn001G * SG * RC * ST * SG * RG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	SOnXnXnXSRSS RSSRSSSSSS
WV-14349	Mod098L001 mU * SGeo m5Ceo m5Ceo mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * S mG * S mA * S mC * S mU * S mC	OSOOOSSRSSRS SRSSSSSS

Table 22D. Data of Malat1 oligonucleotides

Numbers represent knockdown of Malat1 mRNA relative to HPRT1, wherein 1.000 would represent no (0.0%) knockdown and 0.000 represents 100.0% knockdown; results from replicate experiments are shown. WV-9491 is a negative control that is not designed to target Malat1.

	0.004uM			0.02uM			0.1uM		
WV-8587	1.23	1.21	0.94	0.95	0.84	0.81	0.54	0.53	0.61
WV-14733	1.81	1.06	1.36	1.47	1.12	1.17	0.98	0.97	0.72
WV-15351	1.27	0.92	1.00	0.89	0.95	0.92	0.74	0.66	0.71
WV-15352	1.49	1.78	1.52	0.88	0.83	0.91	0.50	0.52	0.73
WV-15353	0.85	0.91	1.10	0.65	0.59	0.68	0.44	0.42	0.40
WV-15354	1.31	1.00	0.90	0.69	0.94	0.79	0.56	0.87	0.74
WV-15356	0.77	0.87	0.68	0.49	0.67	0.63	0.30	0.35	0.31
WV-15357	0.91	1.02	1.13	0.66	0.75	0.79	0.37	0.32	0.36
WV-15358	0.80	0.82	0.90	0.83	0.85	0.85	0.36	0.45	0.43
WV-8582	1.11	1.06	1.15	1.30	1.15	1.14	0.67	0.85	1.06
WV-15359	1.16	1.26	1.02	0.92	0.83	0.83	0.85		0.90
WV-15360	1.57	1.38	1.31	1.05	0.99	0.83	1.03	0.91	0.80
WV-15361	0.92	1.11	1.00	0.71	0.63	0.68	0.74	1.09	0.73
WV-15362	1.23	1.22	1.07	0.90	0.83	0.82	0.99	0.97	0.80
WV-15363	1.16	1.03	0.85	0.89	0.87	0.90	1.10	1.18	1.01
WV-14556	0.81	0.84	0.91	0.46	0.42	0.58	0.15	0.23	0.17
WV-14557	0.75	1.10	0.96	0.46	0.40	0.54	0.19	0.19	0.21
WV-14558	0.96	1.11	0.90	0.77	1.08	0.78	1.27	0.40	0.45
WV-14559	0.80	0.62	0.75	0.35	0.36	0.37	0.12	0.17	0.13

WV-14560	1.11	0.99	1.03	0.44	0.48	0.60	0.29	0.31	0.15
WV-14561	0.71	0.73	1.04	0.47	0.41	0.48	0.22	0.24	0.16
WV-11533	0.74	0.75	0.87	0.40	0.37	0.41	0.14	0.14	0.09
WV-14562	0.79	0.60	0.60	0.53	0.45	0.64	0.22	0.33	0.24
WV-14563	0.76	0.96	0.79	0.57	0.51	0.53	0.23	0.23	0.24
WV-14564	0.72	0.65	0.70	0.58	0.47	0.50	0.17	0.20	0.21
WV-9491	1.02	0.96	1.28	0.82	0.93	1.27	0.88	0.91	1.06
WV-14349	1.07	1.34	1.03	0.86	0.77	1.11	0.63	0.60	0.79

[00899] Various Malat1 oligonucleotides were designed, constructed and tested which comprise one or more non-negatively charged internucleotidic linkages in a core. In various embodiments of a Malat1 oligonucleotide, a phosphorothioate in the Rp configuration is replaced by a non-negatively charged internucleotidic linkage.

Table 22E. Data of Malat1 oligonucleotides

Numbers represent knockdown of Malat1 mRNA relative to HPRT1, wherein 1.000 would represent no (0.0%) knockdown and 0.000 represents 100.0% knockdown; results from replicate experiments are shown.

	WV-8587	WV-15351	WV-15352	WV-15353	WV-15354	WV-9491
0.004uM	1.23	1.27	1.49	0.85	1.31	1.02
	1.21	0.92	1.78	0.91	1.00	0.96
	0.94	1.00	1.52	1.10	0.90	1.28
0.02uM	0.95	0.89	0.88	0.65	0.69	0.82
	0.84	0.95	0.83	0.59	0.94	0.93
	0.81	0.92	0.91	0.68	0.79	1.27
0.1uM	0.54	0.74	0.50	0.44	0.56	0.88
	0.53	0.66	0.52	0.42	0.87	0.91
	0.61	0.71	0.73	0.40	0.74	1.06

[00900] Various Malat1 oligonucleotides were designed, constructed and tested which comprise a non-negatively charged internucleotidic linkage. Various Malat1 oligonucleotides comprise 1 or more non-negatively charged internucleotidic linkages.

Table 22F. Data of certain oligonucleotides.

Numbers represent knockdown of Malat1 mRNA relative to HPRT1, wherein 1.000 would represent no (0.0%) knockdown and 0.000 represents 100.0% knockdown; results from replicate experiments are shown.

	WV-8587	WV-15356	WV-15357	WV-15358	WV-9491
0.004uM	1.23	0.77	0.91	0.80	1.02

	1.21	0.87	1.02	0.82	0.96
	0.94	0.68	1.13	0.90	1.28
0.02uM	0.95	0.49	0.66	0.83	0.82
	0.84	0.67	0.75	0.85	0.93
	0.81	0.63	0.79	0.85	1.27
0.1uM	0.54	0.30	0.37	0.36	0.88
	0.53	0.35	0.32	0.45	0.91
	0.61	0.31	0.36	0.43	1.06

[00901] Various Malat1 oligonucleotides were designed, constructed and tested which comprise a non-negatively charged internucleotidic linkage. Various Malat1 oligonucleotides comprise 1 or more non-negatively charged internucleotidic linkages. In various tables and throughout the text herein, the presence or absence of a hyphen in the designation of an oligonucleotide is irrelevant. For example, WV8582 is equivalent to WV-8582.

Table 22G. Data of certain oligonucleotides.

Numbers represent knockdown of Malat1 mRNA relative to HPRT1, wherein 1.000 would represent no (0.0%) knockdown and 0.000 represents 100.0% knockdown; results from replicate experiments are shown.

	WV-8582	WV-15359	WV-15360	WV-15361	WV-15362	WV-15363	WV-9491
	1.11	1.16	1.57	0.92	1.23	1.16	1.02
	1.06	1.26	1.38	1.11	1.22	1.03	0.96
0.004uM	1.15	1.02	1.31	1.00	1.07	0.85	1.28
	1.30	0.92	1.05	0.71	0.90	0.89	0.82
	1.15	0.83	0.99	0.63	0.83	0.87	0.93
0.02uM	1.14	0.83	0.83	0.68	0.82	0.90	1.27
	0.67	0.85	1.03	0.74	0.99	1.10	0.88
	0.85		0.91	1.09	0.97	1.18	0.91
0.1uM	1.06	0.90	0.80	0.73	0.80	1.01	1.06

[00902] Various Malat1 oligonucleotides were designed, constructed and tested which comprise a non-negatively charged internucleotidic linkage. Various Malat1 oligonucleotides comprise 1 or more non-negatively charged internucleotidic linkages.

Table 22H. Data of certain oligonucleotides.

Numbers represent knockdown of Malat1 mRNA relative to HPRT1, wherein 1.000 would represent no (0.0%) knockdown and 0.000 represents 100.0% knockdown; results from replicate experiments are shown.

	0.004uM	0.02uM

WV-11533	0.74	0.75	0.87	0.40	0.37	0.41
WV-14556	0.81	0.84	0.91	0.46	0.42	0.58
WV-14557	0.75	1.10	0.96	0.46	0.40	0.54
WV-14558	0.96	1.11	0.90	0.77	1.08	0.78
WV-14559	0.80	0.62	0.75	0.35	0.36	0.37
WV-14560	1.11	0.99	1.03	0.44	0.48	0.60
WV-14561	0.71	0.73	1.04	0.47	0.41	0.48
WV-14562	0.79	0.60	0.60	0.53	0.45	0.64
WV-14563	0.76	0.96	0.79	0.57	0.51	0.53
WV-14564	0.72	0.65	0.70	0.58	0.47	0.50
WV-9491	1.02	0.96	1.28	0.82	0.93	1.27

	0.1uM		
WV-11533	0.14	0.14	0.09
WV-14556	0.15	0.23	0.17
WV-14557	0.19	0.19	0.21
WV-14558	1.27	0.40	0.45
WV-14559	0.12	0.17	0.13
WV-14560	0.29	0.31	0.15
WV-14561	0.22	0.24	0.16
WV-14562	0.22	0.33	0.24
WV-14563	0.23	0.23	0.24
WV-14564	0.17	0.20	0.21
WV-9491	0.88	0.91	1.06

[00903] In some embodiments, oligonucleotides were designed, constructed and tested in vitro against suitable reference oligonucleotides which do not comprise any non-negatively charged internucleotidic linkages, e.g., in iCell Astrocytes, at several suitable doses (e.g., 0,0.014,0.041,0.123,0.37,1.11,3.33,10 uM) gymnotic for a suitable period of time, e.g., 2 days.

[00904] Tables 23, 24 and 25 present experimental results.

Table 23. Data of certain oligonucleotides.

Numbers represent knockdown of Malat1 mRNA, wherein 1.000 would represent no (0.0%) knockdown and 0.000 represents 100.0% knockdown; results from replicate experiments are shown.

Dose (uM)	**Oligonucleotide tested (Relative fold change Malat1/HPRT1)**					
	WV-8587			**WV-9696**		
0	0.924	0.970	1.106	1.162	1.040	0.799

0.013717	0.833	0.930	0.730	0.997	0.844	0.918
0.041152	1.186	0.868	0.874	1.076	0.957	0.844
0.123457	0.772	0.827	0.658	0.970	0.756	0.821
0.37037	0.610	0.610	0.553	0.821	0.520	0.681
1.111111	0.394	0.360	0.425	0.431	0.419	0.402
3.333333	0.157	0.136	0.162	0.225	0.214	0.220
10	0.051	0.052	0.065	0.090	0.086	0.091

Dose (uM)	**Oliogonucleotide tested (Relative fold change Malat1/HPRT1)**					
	WV-11114			**WV-11533**		
0	0.761	0.881	1.212	0.958	0.985	1.056
0.013717	1.048	1.027	1.187	0.900	0.932	1.020
0.041152	0.912	0.958	1.108	0.453	0.503	0.479
0.123457	0.971	1.063	1.238	0.356	0.387	0.332
0.37037	0.706	0.846	0.692	0.105	0.107	0.096
1.111111	0.429	0.486	0.574	0.048	0.051	0.049
3.333333	0.181	0.196	0.203	0.033	0.032	0.030
10	0.080	0.075	0.087	0.026	0.034	0.031

Table 24. IC50 of certain Malat1 oligonucleotides.

Oligonucleotide	**IC50**
WV-8587	757nM
WV-9696	806nM
WV-11114	894nM
WV-11533	49nM

[00905] Among other things, the present disclosure demonstrates that oligonucleotides comprising one or more non-negatively charged internucleotidic linkages can provide dramatically improved activities - as illustrated in Table 24, more than 15-fold improvement can be achieved in terms of IC50.

[00906] In another experiment, several Malat1 oligonucleotides including WV-11533, which comprises three neutral internucleotidic linkages, were assessed for knockdown of Malat1, measured by a decrease in the abundance of a Malat1 RNA, WV-7772, which is complementary to the tested oligonucleotides, in the presence of RNaseH.

Oligo-nucleotide	**Description**	**Naked Sequence**	**Linkage / Stereochemistry**
WV-11533	mU * SGeon001m5Ceo n001m5Ceo n001mA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTG GTTATGACUC	SnXnXnXSSRSSRS SRSSSSSS
WV-8556	mU * Geom5Ceom5CeomA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTGG TTATGACUC	XOOOXXXXXX XXXXXXXXX

WV-8587	mU * SGeom5Ceom5CeomA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTGG TTATGACUC	SOOOSSRSSRSS RSSSSSS
WV-7772	rC rU rG rA rG rU rC rA rU rA rA rC rC rA rG rC rC rU rG rG rC rA	CUGAGUCAUAAC CAGCCUGGCA	OOOOOOOOOOOO OOOOOOOOO
WV-9696	L001mU * SGeom5Ceom5CeomA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCT GGTTATGACUC	OSOOOSSRSSRS SRSSSSS
WV-11114	Mod091L001mU * SGeom5Ceom5CeomA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCT GGTTATGACUC	OSOOOSSRSSRS SRSSSSS

[00907] At a time point of 45 minutes, less than 20% of the Malat1 RNA remained in the presence of RNase H and WV-11533 or WV-8587, indicating greater than 80% knockdown; and about 60% of the Malat1 RNA remained in the presence of RNase H and WV-8556, which is stereorandom and does not comprise a neutral backbone. Among other things, the present disclosure demonstrates that oligonucleotides comprising non-negatively charged internucleotidic linkages and/or chirally controlled internucleotidic linkages showed significantly improved activities in reducing levels of target nucleic acids, e.g., through RNase H-mediated knockdown.

[00908] Certain oligonucleotides were also tested for stability in rat liver homogenate at 0, 1 and 2 days. For both WV-11533 and WV-8587, over 80% of the full-length oligonucleotide remained at 2 days; about 40% of the stereorandom WV-8556 remained.

[00909] Oligonucleotides were also tested for Tm with the Malat1 RNA, WV-7772. One example set of test conditions: 1 μM Duplex in 1X PBS (pH 7.2); Temperature Range: 15°C-90°C; Temperature Rate: 0.5°C/min; Measurement Interval: 0.5°C. The results showed the following duplex Tm (°C) with WV-7772: WV-8556, 73.52; WV-8587, 69.57; and WV-11533, 68.67.

[00910] In some embodiments, oligonucleotides comprising non-negatively charged internucleotidic linkages provide improved splicing modulation activities. Various oligonucleotides for mediating skipping of an exon in DMD were prepared and/or tested, wherein the oligonucleotides comprise non-negatively charged internucleotidic linkages. Certain oligonucleotides comprising non-negatively charged internucleotidic linkages are listed in Table A1.

Table 25A. Example data of certain oligonucleotides.

Numbers indicate the level of exon skipping; e.g., 27.13 in column 2, row 2, represents 27.13% skipping of a DMD exon. Oligonucleotides were tested in vitro on cells at 10 or 3 uM.

Oligonucleotide	10 uM		3 uM	
WV-9898	27.13	13.38	11.27	9.69
WV-9897	33.61	31.46	11.82	9.52

WV-9517	20.21	12.08	6.72	6.89
WV-11342	44.84	41.17	19.22	18.43
WV-11341	38.85	44.85	18.95	20.63
WV-11340	41.51	43.08	17.79	16.4
PMO	3.89	4.05	2.08	1.52
Mock	0.49	0.53	0.45	0.52

Table 25B. Example data of certain oligonucleotides.

Numbers indicate the level of exon skipping relative to control; numbers are approximate.

Oligonucleotides were tested in vitro on cells at 10 or 3 uM.

PMO indicates an all-PMO oligonucleotide.

	Mock	WV-11237	WV-3152	WV-3516	PMO
10 uM	1	49	35	7	3
3 uM	1	22	16	3	2

[00911] Various DMD oligonucleotides for skipping exon 23 in mouse were constructed, several of which comprise a non-negatively charged internucleotidic linkage, including WV-11343, WV-11344, WV-11345, WV-11346, and WV-11347. These oligonucleotides were tested and demonstrated skipping of exon 23, as shown in the table below.

Table 25C.1. Example data of certain oligonucleotides.

Numbers represent exon 23 skipping level relative to control.

	10 uM	3.3 uM
WV-7684	5	2
WV-10256	25	13
WV-11343	44	33
WV-10257	16	10
WV-11344	42	29
WV-10258	22	20
WV-11345	48	39
WV-10259	24	10
WV-11346	43	32
WV-10260	23	14
WV-11347	43	32

[00912] In some experiments, del45-52 cells (patient derived myoblasts) were treated with various oligonucleotides, including WV-13405 (PMO), WV-9517 and WV-9898, in muscle differentiation medium at 15, 10, 3.3, 1.1, .3, .1 and 0 uM under free uptake conditions for 6 days before being collected and analyzed for dystrophin protein restoration by Western blot. WV-9517 and WV-9898 demonstrated significant DMD production at concentrations of 3.3 uM and higher; WV-13405 did not show significant DMD product at a concentration of 3.3 uM, but did show DMD production at

concentrations of 10 and 15 uM. Control was Vinculin.

[00913] As shown in Table 25D, additional oligonucleotides were constructed which were capable of mediating skipping of exon 53 and which comprise at least one neutral internucleotidic linkage.

[00914] Various additional DMD oligonucleotides for skipping exon 23 in mouse were constructed. These oligonucleotides were tested and demonstrated skipping of exon 23, as shown in the table below.

Table 25C.2. Example data of certain oligonucleotides.

DMD oligonucleotides were tested in vitro for their ability to skip DMD exon 23 in H2K murine cells. Oligonucleotide delivery was gymnotic, and 4 day treatment was used.

Numbers represent exon 23 skipping level relative to control. 100.0 would represent 100% of transcripts skipped; 0 would represent 0% of transcripts skipped. Data from replicates are shown.

	WV-11345		WV-24092		WV-24098		Mock	
10uM	37.8	39.8	30.2	32.4	41.5	40.2	0	0
3.3uM	22.4	22.9	13.4	14.5	24.3	23.5	0	0
1.1uM	9.2	8.1	3	3.1	10.5	9.9	0	0

Table 25C.3. Example data of certain oligonucleotides.

DMD oligonucleotides were tested in vitro for their ability to skip DMD exon 23 in H2K murine cells. Oligonucleotide delivery was gymnotic, and 4 day treatment was used.

Numbers represent exon 23 skipping level relative to control. 100.0 would represent 100% of transcripts skipped; 0 would represent 0% of transcripts skipped. Data from replicates are shown.

	10uM	3.3uM	1.1uM
WV-10258	22.9	11.6	3.8
WV-12885	34.2	17.8	6.1
	32.4	18.6	6.9
WV-23576	23.7	10.6	3.8
	25.6	11.5	3.3
WV-23577	23.3	13.9	6.6
WV-23578	22	11.8	4.9
	16.1	13.9	7.1
WV-23579	19.2	8.3	6.7
	20.7	29.8	5.5
WV-23937	18.8	9.2	3.5
	6.3	4.2	1.3

WV-23938	26.4	16	6.9
	30.3	16.7	7.3
WV-23939	35.2	23.3	11.8
	33.6	22	12.9
Mock	0	0	0
	0	0	0

Table 25C.4. Example data of certain oligonucleotides.

DMD oligonucleotides were tested in vitro for their ability to skip DMD exon 23 in H2K murine cells. Oligonucleotide delivery was gymnotic, and 4 day treatment was used. Some of the tested oligonucleotides comprise one or more LNA.

Numbers represent exon 23 skipping level relative to control. 100.0 would represent 100% of transcripts skipped; 0 would represent 0% of transcripts skipped. Data from replicates are shown.

	WV-10258	WV-25536		WV-25537		WV-25539		Mock	
10uM	22.9	2.3	10.7	11.8	15.1	12.5	8.1	0	0
3.3uM	11.6	1.5	3.6	7.3	9.9	5.6	3.8	0	0
1.1uM	3.8	1.1	1.3	2.7	4.2	1.8	2.3	0	0

Table 25C.5. Example data of certain oligonucleotides.

DMD oligonucleotides were tested in vitro for their ability to skip DMD exon 23 in H2K murine cells. Oligonucleotide delivery was gymnotic, and 4 day treatment was used. Some of the tested oligonucleotides comprise one or more non-negatively charged internucleotidic linkage.

Numbers represent exon 23 skipping level relative to control. 100.0 would represent 100% of transcripts skipped; 0 would represent 0% of transcripts skipped. Data from replicates are shown.

	10uM	3.3uM	1.1uM		10uM	3.3uM	1.1uM
WV-10258	22.9	11.6	3.8	WV-23939	35.2	23.3	11.8
					33.6	22	12.9
WV-11345	37.8	22.4	9.2	WV-24092	30.2	13.4	3
	39.8	22.9	8.1		32.4	14.5	3.1
WV-12885	34.2	17.8	6.1	WV-24098	41.5	24.3	10.5
	32.4	18.6	6.9		40.2	23.5	9.9
WV-23576	23.7	10.6	3.8	WV-25536	2.3	1.5	1.1
	25.6	11.5	3.3		10.7	3.6	1.3
WV-23577	23.3	13.9	6.6	WV-25537	11.8	7.3	2.7
					15.1	9.9	4.2
WV-23578	22	11.8	4.9	WV-25539	12.5	5.6	1.8
	16.1	13.9	7.1		8.1	3.8	2.3
WV-23579	19.2	8.3	6.7	Mock	0	0	0
	20.7	29.8	5.5		0	0	0

WV-23937	18.8	9.2	3.5	
	6.3	4.2	1.3	
WV-23938	26.4	16	6.9	
	30.3	16.7	7.3	

Table 25C.6. Example data of certain oligonucleotides.

Oligonucleotides targeting Malat-1, wherein the oligonucleotides comprise a non-negatively charged internucleotidic linkage, were tested for their ability to knock down Malat-1 in GABA neurons in vitro, with 4 day treatment. Numbers represent Malat-1 level relative to HPRT1 control and water, wherein 1.0 would represent 100% Malat-1 level (0% knockdown) and 0 would represent 0% Malat-1 level (100% knockdown). Concentrations (Conc.) tested are provided as [Log (dose uM)].

Data from replicates are shown.

Conc.	WV-24104		WV-24109	
-4.70927	0.891	0.837	0.814	1.059
-4.40824	0.942	1.052	0.765	1.208
-4.10721	0.948	1.030	0.754	1.104
-3.80618	0.855	1.143	0.792	1.059
-3.50515	1.067	1.234	0.831	0.891
-3.20412	0.797	0.968	0.760	1.045
-2.90309	0.968	0.825	0.675	1.067
-2.60206	0.825	1.016	0.765	1.135
-2.30103	1.059	0.872	0.648	0.613
-2	0.988	1.067	0.413	0.548
-1.70927	0.754	0.955	0.357	0.362
-1.69897	0.922	0.797	0.313	0.340
-1.40824	0.666	0.739	0.220	0.227
-1.10721	0.548	0.604	0.162	0.170
-0.80618	0.404	0.427	0.096	0.098
-0.50515	0.352	0.427	0.062	0.053
-0.20412	0.272	0.206	0.027	0.027
0.09691	0.132	0.103	0.013	0.014
0.39794	0.061	0.058	0.008	0.011
0.69897	0.028	0.032	0.007	0.008
1	0.018	0.019	0.008	0.009
1.30103	0.016	0.015	0.009	0.010

IC50 of WV-24104 was 132 nM; and IC50 of WV-24109 was 12 nM.

Table 25D. Example data of certain oligonucleotides.

D45-52 myoblasts were treated for 4 days with 10 and 3uM oligonucleotide.

Numbers in this and various other tables indicate amount of skipping relative to control.

	10 uM				3 uM			
mock	0.9	1.0	0.5	0.8	0.9	0.9	1.0	1.0
WV-9517	20.1	18.9	18.3	19.3	9.0	8.9	7.7	7.6
WV-11340	28.9	29.4	26.7	26.7	12.8	12.6	11.5	11.4
WV-11342	18.7	17.9	20.4	20.0	8.3	8.3	7.6	7.7
WV-12553	17.0	19.2	20.0	18.6	8.1	8.1	7.8	8.3
WV-12123	21.7	22.7	21.6	22.4	9.5	9.6	9.9	9.6
WV-12124	17.6	17.5	16.5	17.6	6.7	6.9	7.2	7.0
WV-12125	39.5	38.6	40.6	39.4	18.5	16.8	17.9	17.6
WV-12126	31.2	31.1	32.3	32.2	14.7	14.3	14.1	14.7
WV-12127	36.8	38.0	37.0	38.3	17.4	16.9	17.0	16.9
WV-12128	27.0	26.3	26.3	26.8	10.1	10.8	10.1	10.0
WV-12129	32.9	33.5	35.1	35.3	14.8	14.9	16.0	16.0

	10 uM				3 uM			
Mock	1.6	1.5	1.8	1.8	1.7	1.6	1.5	1.7
WV-9517	30.3	31.1	32.4	29.2	14.1	13.9	13.5	14.5
WV-11340	48.7	50.3	45.1	44.6	24.0	25.8	23.8	23.3
WV-12553	28.7	27.8	27.5	27.0	13.5	13.6	13.1	13.8
WV-9897	39.7	38.5	37.3	35.6	18.8	19.1	18.0	17.7
WV-11341	47.1	47.4			21.8	22.5	22.5	23.1
WV-12555	55.7	54.7	55.7	54.6	27.1	27.7	26.0	26.0
WV-12558	36.0	35.8	49.9	47.3	21.2	19.8	22.1	22.1
WV-9898	43.6	41.7	38.0	38.8	21.1	20.6		
WV-11342	43.7	44.3	42.1	41.8	22.5	20.9	19.0	20.1
WV-12556	46.1	46.4	45.6	44.0	24.2	23.1	21.3	21.0
WV-12559	47.4	45.1	45.6	47.2	21.0	21.7	24.5	22.6

	10 uM				3 uM			
Mock	1.7	1.6	1.8	1.7	1.7	1.7	1.6	1.5
WV-9517	29.8	29.8	28.7	29.2	15.6	15.4	16.0	16.2
WV-11340	45.7	44.5	46.1	47.3	25.7	24.0	23.8	24.4
WV-11342	44.6	46.6	45.3	44.2	21.5	21.0	19.8	20.3
WV-12876	42.4	43.3	41.2	41.0	26.2	26.3	24.5	26.0
WV-12877	53.7	53.8	52.4	52.3	37.8	36.5	34.3	32.9
WV-12878	48.5	48.3	45.1	46.2	31.4	30.9	29.3	30.0
WV-12879	34.1	34.9	33.2	34.0	19.7	19.8	21.4	21.1
WV-12880	50.4	50.1	51.4	52.1	33.0	32.5	32.9	32.0
WV-12881	41.6	42.9	38.8	39.4	26.1	25.6	24.3	22.7
WV-12882	29.6	29.7	32.3	31.3	15.3	15.1	15.5	15.2

WV-12129	57.8	57.0	55.5	55.6	33.1	32.2		

[00915] Various DMD oligonucleotides comprising a chirally controlled neutral backbone were constructed, including WV-12555, which comprises a neutral internucleotidic linkage in the Rp configuration, and WV-12558, which comprises a neutral internucleotidic linkage in the Sp configuration. These were also tested for skipping a DMD exon, as shown in Table 25E.

Table 25E. Example data of certain oligonucleotides.

D45-52 myoblasts were treated for 4 days with 10 and 3uM oligonucleotide. Oligonucleotides were delivered gymnotically. Numbers represent amount of skipping relative to control.

	MOCK	WV-9517	WV-11340	WV-9897	WV-11341	WV-12555	WV-12558
	1.6	30.3	48.7	39.7	47.1	55.7	36.0
	1.5	31.1	50.3	38.5	47.4	54.7	35.8
	1.8	32.4	45.1	37.3		55.7	49.9
10 uM	1.8	29.2	44.6	35.6		54.6	47.3
	1.7	14.1	24.0	18.8	21.8	27.1	21.2
	1.6	13.9	25.8	19.1	22.5	27.7	19.8
	1.5	13.5	23.8	18.0	22.5	26.0	22.1
3 uM	1.7	14.5	23.3	17.7	23.1	26.0	22.1

[00916] In some embodiments, >2 fold increase in exon skipping efficiency was achieved.

Table 25F. Example data of certain oligonucleotides.

Various DMD oligonucleotides for skipping exon 53 or 51 were incuted in tissue lysate for 5-days; full length oligonucleotides detected by LC-MS. Numbers represent percentage of full-length oligonucleotide remaining. Greater than 75% oligonucleotide remains in human and MDX muscle lysates at 5d incubation. Data was from a previous experiment performed for WV-3473, with 2d incubation in MDX muscle lysate. ND: Not determined; WV-3473 stability in human muscle lysate was not performed.

	MDX mouse Muscle	**Human Liver**	**Human Muscle**	**Human Kidney**
WV-9517	82.4	77.8	84	73.7
	3.08	7.9	2.01	3.59
WV-9897	88.3	82	96.1	75.2
	9.12	4.2	5.5	3.8
WV-9898	74	75.8	96.8	81.5
	5.07	6.4	8.9	5
WV-3473	69.8	69.8	ND	24
	5.91	5.91	ND	0.15

[00917] In some embodiments, an oligonucleotide comprising a neutral internucleotidic linkage (e.g., a cyclic guanidine type) demonstrated a higher level of exon skipping than a corresponding

oligonucleotide which did not comprise such a neutral internucleotidic linkage.

[00918] In some embodiments, the present disclosure pertains to an oligonucleotide or an oligonucleotide composition which is capable of mediating single-stranded RNA interference, wherein the oligonucleotide or oligonucleotide composition comprises a non-negatively charged internucleotidic linkage.

[00919] As described herein, various oligonucleotides comprising a non-negatively charged internucleotidic linkage and targeting any of several different genes, with different base sequences, patterns of sugar modifications, backbone chemistry, and patterns of stereochemistry of backbone internucleotidic linkages were constructed, including but not limited to various oligonucleotides which target C9orf72 (a different gene than DMD, or Malat1).

[00920] Described herein are various non-limiting examples of oligonucleotides which target C9orf72 (which is a gene different from the other genes mentioned herein) and which comprise a non-negatively charged internucleotidic linkage.

[00921] A hexanucleotide repeat expansion in the C9orf72 gene (Chromosome 9, open reading frame 72) is reportedly the most frequent genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). C9orf72 gene variants comprising the repeat expansion and/or products thereof are also associated with other C9orf72-related disorders, such as corticobasal degeneration syndrome (CBD), atypical Parkinsonian syndrome, olivopontocerebellar degeneration (OPCD), primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), Huntington's disease (HD) phenocopy, Alzheimer's disease (AD), bipolar disorder, schizophrenia, and other non-motor disorders. Various oligonucleotides were designed and constructed which comprise a neutral internucleotidic linkage and which target a C9orf72 target (e.g., a C9orf72 oligonucleotide) and are capable of knocking down or decreasing expression, level and/or activity of the C9orf72 target gene and/or a gene product thereof (a transcript, particularly a repeat expansion containing transcript, a protein, etc.).

[00922] Various oligonucleotides designed to target C9orf72 and comprising a non-negatively charged internucleotidic linkage include, but are not limited to: WV-11532, WV-13305, WV-13307, WV-13309, WV-13311, WV-13312, WV-13313, WV-13803, WV-13804, WV-13805, WV-13806, WV-13807, WV-13808, WV-14553, and WV-14555. These are described below in Table 25G.

Table 25G. Oligonucleotides targeting C9orf72 comprising a neutral internucleotidic linkage.

Oligo-nucleo-tide	Sequence	Naked Sequence	Stereochemistry
WV-11532	mC * Sm5Ceon001 Teon001 m5Ceon001 mA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC *	CCTCACTCACCC ACTCGCCA	SnXnXnXSSSRSSR SSSSSSSS

Oligo-nucleo-tide	Sequence	Naked Sequence	Stereochemistry
	SmC * SmA		
WV-13305	m5Ceo * Rm5Ceon001 Teon001 m5Ceon001 Aeo * RC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCC ACTCGCCA	RnXnXnXRSSRSSR SSSSSSSS
WV-13307	m5Ceo * Sm5Ceon001 Teon001 m5Ceon001 Aeo * RC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCC ACTCGCCA	SnXnXnXRSSRSSR SSSSSSSS
WV-13309	m5Ceo * Rm5Ceon001 Teon001 m5Ceon001 Aeo * RC * ST * SC * RA * SC * SC * SC * RA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCC ACTCGCCA	RnXnXnXRSSRSSS RSSSSSSS
WV-13311	m5Ceo * Sm5Ceon001 Teon001 m5Ceon001 Aeo * RC * ST * SC * RA * SC * SC * SC * RA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCC ACTCGCCA	SnXnXnXRSSRSSS RSSSSSSS
WV-13312	mC * Sm5Ceon001 Teon001 m5Ceon001 mA * SC * ST * SC * RA * SC * SC * SC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCC ACTCGCCA	SnXnXnXSSSR SSSSSSSSSS
WV-13313	m5Ceo * Rm5Ceon001 Teon001 m5Ceon001 Aeo * RC * ST * SC * RA * SC * SC * SC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCC ACTCGCCA	RnXnXnXRSSR SSSSSSSSSS
WV-13803	Teo * Geon001 m5Ceon001 m5Ceon001 Geo * C * C * T * C * C * T * C * A * C * T * mC * mA * mC * mC * mC	TGCCGCCTCCT CACTCACCC	XnXnXnXXXXXXX XXXXXXXXX
WV-13804	Teo * Geom5Ceom 5CeoGeo * C * C * T * C * C * T * C * A * C * T * mCn001 mAn001 mCn001 mC * mC	TGCCGCCTCCT CACTCACCC	XOOOXXXXXXXXX XXnXnXnXX
WV-13805	Teo * Geon001 m5Ceon001 m5Ceon001 Geo * C * C * T * C * C * T * C * A * C * T * mCn001 mAn001 mCn001 mC * mC	TGCCGCCTCCT CACTCACCC	XnXnXnXXXXXXXX XXXXnXnXnXX
WV-13806	Geo * m5Ceon001 Geon001 m5Ceon001 Geo * A * C * T * C * C * T * G * A * G * T * Teom5Ceom5CeoAeo * Geo	GCGCGACTCCT GAGTTCCAG	XnXnXnXXXXXXXX XXXXOOOX
WV-13807	Geo * m5CeoGeom5CeoGeo * A * C * T * C * C * T * G * A * G * T * Teon001 m5Ceon001 m5Ceon001 Aeo * Geo	GCGCGACTCCT GAGTTCCAG	XOOOXXXXXXXXX XnXnXnXX
WV-13808	Geo * m5Ceon001 Geon001 m5Ceon001 Geo * A * C * T * C * C * T * G * A * G * T * Teon001 m5Ceon001 m5Ceon001	GCGCGACTCCT GAGTTCCAG	XnXnXnXXXXXXXXX XXXnXnXnXX

Oligo-nucleo-tide	Sequence	Naked Sequence	Stereochemistry
	Aeo * Geo		
WV-14553	m5Ceo * Rm5Ceon001 Teon001 m5Ceon001 Aeo * RC * ST * SC * RA * SC * SC * RC * SA * SC * ST * Rm5Ceo * SmG * SmC * SmC * SmA	CCTCACTCACCC ACTCGCCA	RnXnXnXRSSRSSR SSSRSSSS
WV-14555	m5Ceo * Rm5Ceon001 Teon001 m5Ceon001 Aeo * RC * ST * SC * RA * SC * SC * SC * RA * SC * ST * Rm5Ceo * SmG * SmC * SmC * SmA	CCTCACTCACCC ACTCGCCA	RnXnXnXRSSRSSS RSSRSSSS

Several variants of a C9orf72 mRNA are produced from the C9orf72 gene: V2 (which does not comprise the deleterious hexanucleotide repeat and which comprises about 90% of all transcripts); V3 (which comprises the hexanucleotide repeat and comprises about 9% of all transcripts); and V1 (which comprises the hexanucleotide repeat and comprises about 1% of all transcripts).

Hexanucleotide repeats reportedly elicit gain of function toxicities, at least partially mediated by the dipeptide repeat proteins and foci formation by, for example, repeat-expansion containing transcripts and/or spliced-out repeat-expansion containing introns and/or antisense transcription of the repeat-expansion containing region and various nucleic-acid binding proteins.

Both WV-8008 and WV-11532 have the same base sequence (or naked sequence), CCTCACTCACCCACTCGCCA. They differ, inter alia, in that the latter comprises 3 contiguous neutral internucleotidic linkages (Xn), but the former does not comprise any neutral internucleotic linkages. The structures of these oligonucleotides is provided below, in Table 25H.

Table 25H. C9orf72 oligonucleotides.

Oligo-nucleotide	Sequence	Stereochemistry
WV-8008	m5Ceo * Rm5CeoTeom5CeoAeo * RC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	ROOORSSRSSRS SSSSSSS
WV-11532	mC * Sm5Ceon001Teon001m5Ceon001mA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	SnXnXnXSSSRSS RSSSSSSSS

WV-8008 and WV-11532 were tested for their ability to knock down expression of hexanucleotide-comprising (i.e., disease-associated) transcript V3 compared to total transcripts (all V), as shown below in Table 25I.

Table 25I and J. Activity of various c9orf72 oligonucleotides.

In Tables 25I to 25J, various c9orf72 oligonucleotides were tested in motor neurons, with oligonucleotides delivered gymnotically at concentrations from 0.003 to 10 μM (Concentrations are provided as exp10). Tested c9orf72 oligonucleotide WV-11532 comprises three neutral internucleotidic linkages. In Tables 14A and 14B, shown are residual levels of c9orf72 transcriptions [e.g., all transcripts (all V) or only V3] relative to HPRT1, after treatment with c9orf72 oligonucleotides, wherein 1.000 would represent 100% relative transcript level (no knockdown) and 0.000 would represent 0% relative transcript level (e.g., 100% knockdown). Results from replicate experiments are shown.

Table 25I. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts)

Conc.	WV-8008			WV-11532		
-2.495	0.999	0.958	0.913	1.006	0.894	0.900
-1.796	0.965	0.864	0.882	0.972	0.829	0.858
-1.097	1.006	0.900	0.932	0.907	0.888	0.858
-0.398	0.800	0.742	0.806	0.795	0.747	0.742
0.301	0.624	0.611	0.687	0.562	0.554	0.554
1	0.524	0.500	0.521	0.409	0.411	0.387

Table 25J. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

Conc.	WV-8008			WV-11532		
-2.495	0.947	0.871	1.014	0.927	0.853	0.908
-1.796	0.877	0.841	0.908	0.836	0.769	0.841
-1.097	0.665	0.743	0.871	0.620	0.633	0.717
-0.398	0.555	0.427	0.707	0.421	0.415	0.427
0.301	0.210	0.178	0.304	0.096	0.105	0.094
1	0.056	0.071	0.083	0.012	0.015	0.015

[00923] As described herein and in data not shown, various oligonucleotides comprising a non-negatively charged internucleotidic linkage and targeting different genes, with different base sequences, patterns of sugar modifications, backbone chemistries, and patterns of stereochemistry of backbone internucleotidic linkages were constructed, including but not limited to various oligonucleotides which target DMD, Malat1, or C9orf72.

[00924] Oligonucleotides comprising a non-negatively charged internucleotidic linkage were also constructed to target six other genes not described herein (wherein the six genes were not DMD, Malat1, or C9orf72); these oligonucleotides include oligonucleotides designed to target these genes and reduce the expression, level and/or activity of the gene or its gene product. These and various oligonucleotides comprising a neutral internucleotidic linkage described herein are capable of performing various

functions, including reducing the level, expression and/or activity of a gene or its gene product (e.g., via a RNaseH- or steric-hindrance-mediated mechanism, or via a single-stranded RNA interference-mediated mechanism) and inducing skipping of an exon (e.g., skipping modulation).

[00925] Without wishing to be bound by any particular theory, Applicant notes that a non-negatively charged and/or neutral internucleotidic linkage can improve an oligonucleotide's entry into a cell and/or escape from an endosome.

Oligonucleotides Which Comprise a Non-Negatively Charged Internucleotidic Linkage Can Provide Desired Levels of TLR9 Activation

[00926] Among other things, oligonucleotides comprising non-negatively charged internucleotidic linkages can provide desired levels of properties and/or activities, *e.g.*, TLR9 antagonist or agonist activities. In some embodiments, oligonucleotides comprising non-negatively charged internucleotidic linkages demonstrate lower levels of TLR9 activation in human and/or an animal model (*e.g.*, a mouse) compared to certain comparable oligonucleotides of the same base sequences but having no non-negatively charged internucleotidic linkages. In some embodiments, oligonucleotides comprising non-negatively charged internucleotidic linkages have lower toxicity compared to certain oligonucleotides of the same base sequences but having no non-negatively charged internucleotidic linkages. In some embodiments, a non-negatively charged internucleotidic linkage is within a CpG motif and is the internucleotidic linkage between the C and G.

[00927] In an experiment, several oligonucleotides to target gene C were constructed. Gene C is a different gene than DMD, or SMalat-1. The sequence of these oligonucleotides comprises a CpG, a motif known to activate TLR9.

[00928] Table 25K.

[00929] This experiment represents a test of induction of human TLR9 or mouse TLR9 in HEK293 cells. Numbers represent relative inductive relative to negative control, water. Concentrations tested: 0.93uM, 2.77uM, 8.33uM, 25uM, 75uM. Positive control: WV-BZ21. The experiment was performed in biological duplicates.

[00930] Table 25K. Oligonucleotides used in this study

Oligo-nucleotide	Sequence	Stereochemistry
WV-HZ12	mN * Sm5NeoNeom5NeomN * SN * SN * SN * RN * SN * SN * RN * SN * SN * SN * SmC * SmG * SmN * SmN * SmN	SOOOS SSRSS RSSSSSSSS
WV-BZ761	mN * Sm5NeoNeom5NeomN * SN * SN * SN * RN * SN * SN * RN * SN * SN * SN * SmCmG * SmN * SmN * SmN	SOOOS SSRSS RSSSSOSSS
WV-BZ762	mN * Sm5NeoNeom5NeomN * SN * SN * SN * RN * SN * SN *	SOOOS SSRSS

	RN * SN * SN * SN * Sm5CeomG * SmN * SmN * SmN	RSSSSOSSS
WV-BZ763	mN * Sm5NeoNeom5NeomN * SN * SN * SN * RN * SN * SN * RN * SN * SN * SN * Sm5Ceo * SmG * SmN * SmN * SmN	SOOOS SSRSS RSSSSSSSS
WV-BZ764	mN * Sm5NeoNeom5NeomN * SN * SN * SN * RN * SN * SN * RN * SN * SN * SN * Rm5CeomG * SmN * SmN * SmN	SOOOS SSRSS RSSSROSSS
WV-BZ765	mN * Sm5NeoNeom5NeomN * SN * SN * SN * RN * SN * SN * RN * SN * SN * SN * Rm5Ceo * SmG * SmN * SmN * SmN	SOOOS SSRSS RSSSRSS SS
WV-BZ766	mN * Sm5NeoNeom5NeomN * SN * SN * SN * RN * SN * SN * RN * SN * SN * SN * Sm5mC * SmG * SmN * SmN * SmN	SOOOS SSRSS RSSSSSSSS
WV-BA207	mN * Sm5NeoNeom5NeomN * SN * SN * SN * RN * SN * SN * SN * RN * SN * SN * SmCn001mG * SmN * SmN * SmN	SOOOS SSRSS SRSSSnXSSS
WV-BA208	m5Neo * Rm5NeoNeom5NeoNeo * RN * SN * SN * RN * SN * SN * RN * SN * SN * SN * SmCn001mG * SmN * SmN * SmN	ROOOR SSRSS RSSSSnXSSS
WV-BA209	m5Neo * Rm5NeoNeom5NeoNeo * RN * SN * SN * RN * SN * SN * SN * RN * SN * SN * SmCn001mG * SmN * SmN * SmN	ROOOR SSRSS SRSSSnXSSS
WV-BZ21	T * C * G * T * C * G * T * T * T * T * G * T * C * G * T * T * T * T * G * T * C * G * T * T	XXXXX XXXXX XXXXX XXXXX XXX

Table 25L. Activity of certain oligonucleotides.

All the tested oligonucleotides (WV-HZ12, WV-BZ761, WV-BZ762, WV-BZ763, WV-BZ764, WV-BZ765, WV-BZ766, WV-BA207, WV-BA208, and WV-BA209) target gene C and all have the same base sequence, wherein each base is indicated generically by N, except that the single CpG motif is indicated. WV-BZ21, positive control, has a base sequence of TCGTCGTTTTGTCGTTTTGTCGTT, which comprises several CpG motifs, and is not designed to target gene C. Numbers indicate relative induction of hTLR9 activity relative to water.

	0.93uM	2.77uM	8.33uM	25uM	75uM
WV-HZ12	1.0	1.0	1.0	1.0	0.9
	1.1	1.0	1.1	1.0	1.0
WV-BZ761	1.0	1.0	1.0	1.0	1.0
	1.1	1.0	1.1	1.0	0.9
WV-BZ762	1.0	1.0	1.0	1.1	1.0
	1.0	1.1	1.0	1.0	1.0
WV-BZ763	1.0	1.0	1.1	1.1	1.1
	1.1	1.1	1.1	1.1	1.0
WV-BZ764	1.0	1.0	1.0	0.9	1.0
	1.0	1.0	1.0	1.0	1.0
WV-BZ765	1.0	0.9	1.1	1.0	1.0
	1.0	1.1	1.0	0.9	0.9
WV-BZ766	1.1	1.3	1.5	1.5	1.5
	1.2	1.3	1.3	1.4	1.4
WV-BA207	1.0	1.0	1.0	1.0	1.0

	1.1	1.1	1.0	1.0	1.0
WV-BA208	1.0	1.0	1.0	1.0	1.0
	1.0	1.1	1.0	0.9	1.0
WV-BA209	1.0	1.0	1.0	0.9	1.0
	1.1	1.0	0.9	1.0	1.0
WV-BZ21 (positive control)	10.0	12.0	12.0	11.4	11.0
	9.4	10.4	11.4	11.5	11.1

Table 25M. Activity of certain oligonucleotides.

These oligonucleotides were also tested for induction of mouse TLR9.

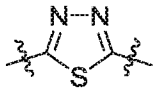
Numbers indicate relative induction of mTLR9 activity relative to water.

	0.93uM	2.77uM	8.33uM	25uM	75uM
WV-HZ12	2.9	4.4	4.7	5.0	4.9
	3.0	4.1	4.8	5.1	5.2
WV-BZ761	1.2	1.5	1.8	2.1	2.1
	1.2	1.4	1.8	2.1	2.2
WV-BZ762	1.0	1.0	1.0	1.0	1.0
	1.0	1.1	1.1	0.9	1.0
WV-BZ763	1.0	1.1	1.1	1.1	1.0
	1.1	1.0	1.1	1.1	1.1
WV-BZ764	1.0	1.1	1.1	1.1	1.1
	1.0	1.1	1.1	1.1	1.1
WV-BZ765	1.0	1.2	1.3	1.3	1.2
	1.1	1.2	1.3	1.3	1.3
WV-BZ766	1.1	1.3	1.4	1.6	1.6
	1.1	1.2	1.4	1.6	1.6
WV-BA207	1.1	1.1	1.1	1.1	1.1
	1.0	1.0	1.1	1.1	1.2
WV-BA208	1.0	1.1	1.1	1.2	1.1
	1.0	1.0	1.1	1.2	1.2
WV-BA209	1.0	1.2	1.1	1.2	1.1
	1.0	1.1	1.2	1.2	1.3
WV-BZ21 (positive control)	21.4	22.4	22.9	21.2	18.1
	22.9	24.0	23.8	22.3	18.9

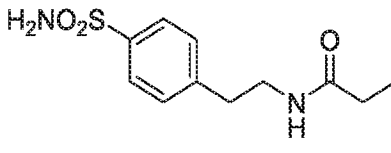
[00931] In some embodiments, it was observed that in some instances certain oligonucleotides that did not induce appreciable TLR9 activation, or induced very low level of TLR9 activation above mock against human or mouse TLR9.

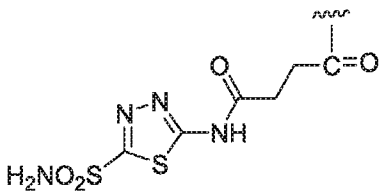
Example Oligonucleotides Comprising Additional Moieties

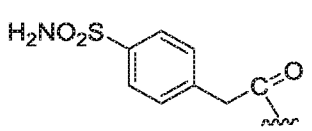
[00932] In some embodiments, the present disclosure provides oligonucleotides comprising one or more additional moieties, e.g., targeting moieties, carbohydrate moieties, etc. In some embodiments, the present disclosure provides oligonucleotides comprising one or more sulfonamide moieties. In some embodiments, a provided oligonucleotide comprise one or two or more sulfonamide moieties. In some embodiments, the present disclosure provides oligonucleotides that can modulate splicing, e.g., DMD oligonucleotides that can modulate exon skipping, wherein the oligonucleotides comprise one or more sulfonamide moieties. In some embodiments, the present disclosure provides oligonucleotides that mediate skipping of DMD exon 23, 45, 51 or 53, or multiple DMD exons, wherein the oligonucleotides comprise one or more sulfonamide moieties.

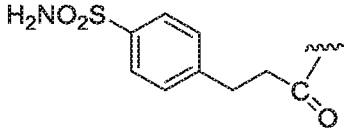
[00933] In some embodiments, a sulfonamide moiety has or comprises the structure of $-L-SO_2N(R^1)_2$. In some embodiments, a sulfonamide moiety has or comprises the structure of $-SO_2N(R^1)_2$. In some embodiments, a sulfonamide moiety has or comprises the structure of $-Cy-SO_2N(R^1)_2$. In some embodiments, –Cy– is aromatic. In some embodiments, –Cy– is an optionally substituted phenyl ring. In some embodiments, –Cy– is . In some embodiments, –Cy– is an optionally substituted heteroaryl ring. In some embodiments, –Cy– is an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms. In some embodiments, –Cy– is  . In some embodiments, each R^1 is –H.

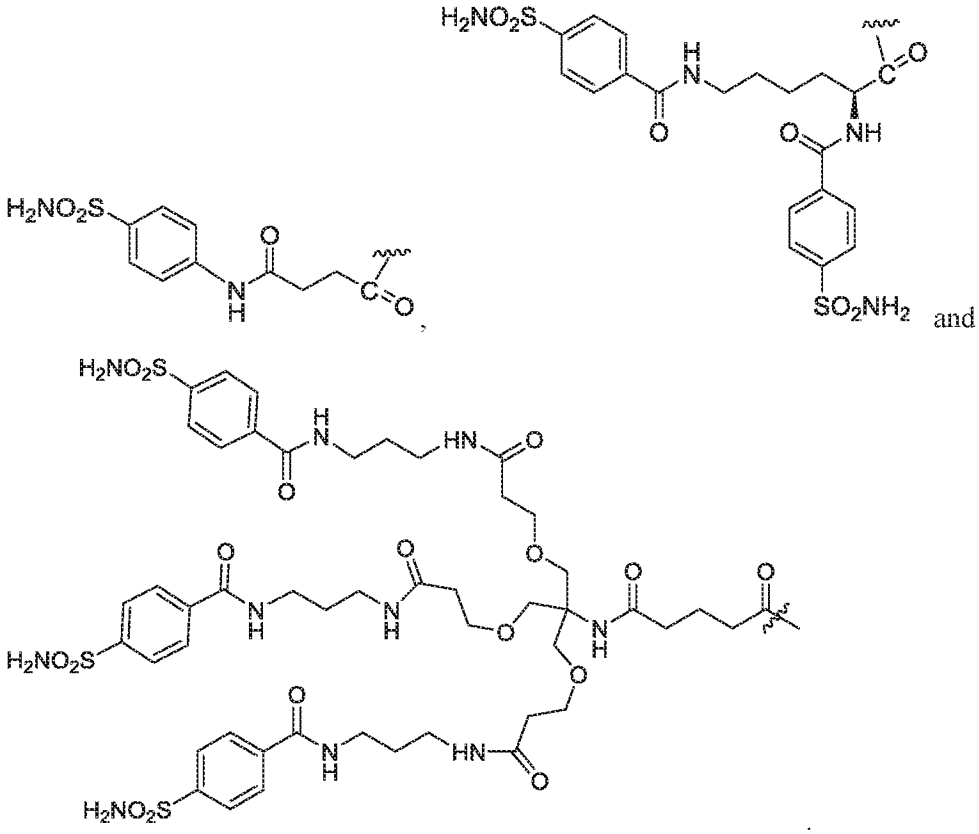
[00934] A sulfonamide moiety can be connected to an oligonucleotide chain via various suitable linkers in accordance with the present disclosure, such as those described herein and/or in WO/2017/062862, linkers of which is incorporated herein by reference. Example sulfonamides moieties, including mono-, bi-, and tri-sulfonamide moieties, are described below:











and

[00935] In some embodiments, an oligonucleotide comprise a modified internucleotidic linkage and a sulfonamide moiety optionally through a linker. In some embodiments, an oligonucleotide comprising a modified internucleotidic linkage and a sulfonamide moiety is a siRNA, double-straned siRNA, single-stranded siRNA, gapmer, skipmer, blockmer, antisense oligonucleotide, antagomir, microRNA, pre-microRNs, antimir, supermir, ribozyme, Ul adaptor, RNA activator, RNAi agent, decoy oligonucleotide, triplex forming oligonucleotide, aptamer or adjuvant. In some embodiments, the present disclosure provides an oligonucleotide which comprises a modified internucleotidic linkage which comprises a sulfonamide. In some embodiments, an oligonucleotide comprises a sulfonamide and a chirally controlled internucleotidic linkage. In some embodiments, an oligonucleotide comprises a sulfonamide and a chirally controlled internucleotidic linkage which is a phosphorothioate internucleotidic linkage.

[00936] In some embodiments, the present disclosure pertains to an oligonucleotide which comprises a sulfonamide moiety or a derivative or variant thereof. In some embodiments, the present disclosure pertains to an oligonucleotide composition, wherein the oligonucleotide comprises a sulfonamide moiety or a derivative or variant thereof and the oligonucleotide comprises at least one chirally controlled internucleotidic linkage.

[00937] In some embodiments, the present disclosure pertains to an oligonucleotide which

comprises a sulfonamide moiety or a derivative or variant thereof, wherein the oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a target gene or gene product thereof.

[00938] In some embodiments, the present disclosure pertains to an oligonucleotide which comprises a sulfonamide moiety or a derivative or variant thereof, wherein the oligonucleotide is capable of mediating modulation of exon skipping of a target gene. In some embodiments, the present disclosure pertains to an oligonucleotide which comprises a sulfonamide moiety or a derivative or variant thereof, wherein the oligonucleotide is capable of increasing skipping of an exon of a target gene.

[00939] Example oligonucleotides that can be utilized for splicing modulation, e.g., exon skipping, that comprise a sulfonamide moiety include WV-3548, WV-3366, etc. Other oligonucleotides comprising a sulfonamide moiety were designed, constructed and/or tested for various activities. For example, oligonucleotides comprising a "mono-sulfonamide" moiety, such as WV-2836, WV-7419, WV-7421, WV-7422, WV-7408, WV-7409, WV-7427, WV-7863, and WV-7864; oligonucleotide comprising a "bi-sulfonamide", WV-7423; and oligonucleotide comprising a "tri-sulfonamide", WV-7417.

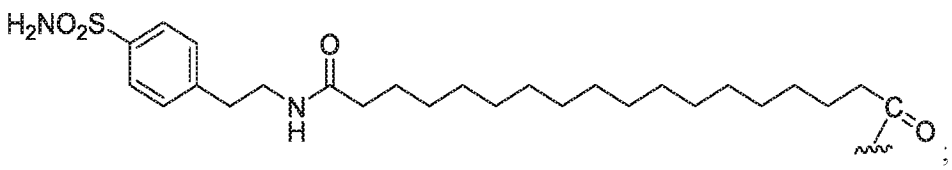
Table 26A. Certain Malat1 oligonucleotides.

Oligo-nucleotide	Description	Naked Sequence	Linkage / Stereochemistry
WV-2735	Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTG CCAATGCTAG	XXXXXXXXXXX XXXXXXXX
WV-2835	Mod027L001 * Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTGC CAATGCTAG	XXXXXXXXXXX XXXXXXXXX
WV-2836	Mod028L001 * Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTGC C AATGCTAG	XXXXXXXXXXX XXXXXXXXX
WV-3174	mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTGG T TATGACUC	XXXXXXXXXXX XXXXXXXX
WV-7301	Teo * Geo * m5Ceo * m5Ceo * Aeo * G * G * C * T * G * G * T * T * A * T * Geo * Aeo * m5Ceo * Teo * m5Ceo	TGCCAGGCTGG T TATGACTC	XXXXXXXXXXX XXXXXXXX
WV-7408	Mod027L001Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTGC CA ATGCTAG	OXXXXXXXXXX X XXXXXXXX
WV-7409	Mod028L001Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTGC C AATGCTAG	OXXXXXXXXXX X XXXXXXXX
WV-7417	Mod029L001 * Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A	GGGTCAGCTGC CAATGCTAG	XXXXXXXXXXX XXXXXXXXX

	* A * T * Geo * m5Ceo * Teo * Aeo * Geo		
WV-7419	Mod045L001 * Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTGC CAATGCTAG	XXXXXXXXXXX XXXXXXXXX
WV-7421	Mod047L001 * Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTGC CAATGCTAG	XXXXXXXXXXX XXXXXXXXX
WV-7422	Mod048L001 * Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTG CCAATGCTAG	XXXXXXXXXXX XXXXXXXXX
WV-7423	Mod049L001 * Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTG CCAATGCTAG	XXXXXXXXXXX XXXXXXXXX
WV-7427	Mod045L001Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTG CCAATGCTAG	OXXXXXXXXXX X XXXXXXXX
WV-7863	Mod046L001Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTG CCAATGCTAG	OXXXXXXXXXX X XXXXXXXX
WV-7864	Mod054L001Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTG CCAATGCTAG	OXXXXXXXXXX X XXXXXXXX
WV-9430	Mod029L001mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTG GTTATGACUC	OXXXXXXXXX XXXXXXXXXX
WV-7420	Mod046L001 * Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTG CCAATGCTAG	XXXXXXXXX XXXXXXXXXXX

For this Table, descriptions match those of Table A1, and

Mod045:



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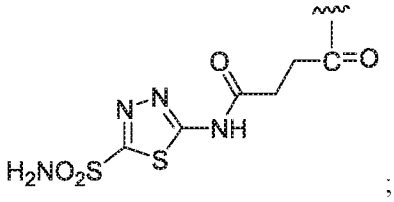
Mod046:



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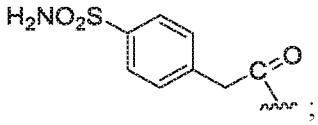
Mod047:



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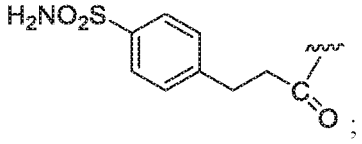
Mod048:



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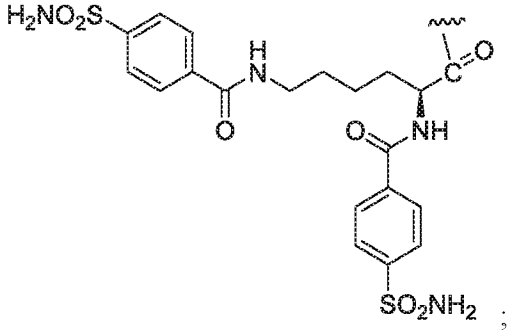
Mod049:



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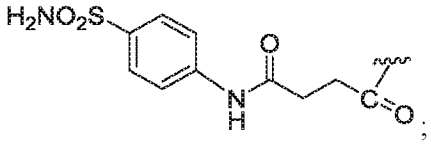
Mod054:



;

In these Mods, −C(O)− connects to −NH− of a linker (e.g., L001).

[00940] Oligonucleotides comprising a sulfonamide moiety were tested for their ability to knockdown Malat1. Tested oligonucleotides were gymnotically delivered to Δ48-50 patient derived myotubes, which were dosed at 3,1, 0.3 and 0.1 μM concentrations. Cells were allowed to differentiate for 4 days (e.g., this experiment was 4 days post-differentiation). qPCR was used to evaluate knockdown of Malat-1. The results are shown in Table 26B.

Table 26B. Example data of Malat1 oligonucleotides.

Numbers represent relative Malat-1 mRNA level.

	WV-3174	WV-8927	WV-8929	WV-8930	WV-8931	WV-8934	WV-9385	WV-9390	Mock

3 μM	10		11	10	11	9	8	33	95
1 μM	18		28	24	22	19	20	49	100
0.3 μM	39	56	50	67	46	42	43	67	95
0.1 μM	63	73	68	81	68	69	56	81	100

Various Malat1 oligonucleotides, many comprising a sulfonamide moiety, were tested for their ability to knockdown Malat1 in pre-differentiated myotubes. Certain data are shown in Table 26C. Δ48-50 patient derived myoblasts were differentiated for 4 days prior to dosing with at 1 and 0.1 μM concentrations. RNA was harvested 48 hours post-treatment for measurement.

Table 26C. Example data of Malat1 oligonucleotides.

Numbers represent relative Malat-1 mRNA level. Numbers are approximate.

	WV-3174	WV-8927	WV-8929	WV-8930	WV-8931	WV-8934	WV-9385	WV-9390
1 μM	22	31	25	25	36	24	18	45
0.1 μM	62	70	79	72	78	55	59	66

	WV-8448	WV-7558	WV-7559	WV-7560	MOCK
1 μM	33	34	22	23	98
0.1 μM	68	72	69	82	98

[00941] In some experiments, animals were dosed with oligonucleotides, including some which comprise a sulfonamide moiety, and the animals were later sacrificed and their tissues tested for the level of the ligonucleotides.

[00942] In some experiments, the following protocol was used: Animals: 32 male Mdx mice and 32 male C57BL/6 mice (all 8-10 week-old). Test animals were acclimated to the facility for at least 3 days upon arrival. Dosing: S.C. (subcutaneous) dosing on days 1, 3 and 5 (5 mL/kg). Necropsy: animals were euthanized 72 hours after the last SC injection. All animals were perfused with PBS. The following tissues were collected: brain, sciatic nerves, spinal cord, eyes, liver, kidney, spleen, heart, diaphragm, gastrocnemius, quadriceps and triceps, white fat, brown fat. Fresh tissues will be rinsed briefly with PBS, gently blotted dry, weighed and snap frozen in Liquid Nitrogen in 2-mL tubes and stored at -80C (on dry ice). Histology: Quadricep and Kidney postfixed in 10% Formalin and processed to slides (paraffin embedded sections). In some experiments, suitable variants of this protocol were used.

[00943] Certain results are shown in Tables 27, 28 and 29.

Table 27. Knock-down and oligonucleotide presence in various tissues.

Numbers indicate Malat1 mRNA levels relative to mHprt (mHPRT or mHPRT1), and presence of oligonucleotide (ug/g). Experimental procedure: Study Species: 5-6 wks MDX mice; Route: Subcutaneous; # Doses: QD for 3 days; Time Point Post Last Dose: 2 days; Daily Dose Level (ug): 12.5

mg/kg.

Malat1 Sequence	Quadriceps pD Mean± SD	Triceps pD Mean± SD	Gastro pD Mean± SD	Diaphragm pD Mean± SD	Heart pD Mean± SD	Heart pK Mean± SD (ug/g)
PBS	1.000 ± 0.142	1.000 ± 0.265	1.000 ± 0.042	1.000 ± 0.276	1.000 ± 0.074	0.000 ± 0.000
WV-2735	0.776 ± 0.122	0.699 ± 0.150	0.731 ± 0.107	0.879 ± 0.158	0.707 ± 0.173	1.631 ± 0.692
WV-2835	0.639 ± 0.119	0.588 ± 0.036	0.417 ± 0.065	0.895 ± 0.116	0.510 ± 0.066	1.987 ± 0.203
WV-2836	0.621 ± 0.124	0.834 ± 0.206	0.616 ± 0.169	0.769 ± 0.229	0.619 ± 0.389	7.001 ± 1.331

Table 28. Knock-down and oligonucleotide presence in various tissues.

Numbers indicate Malat1 mRNA levels relative to mHprt, and presence of oligonucleotide (ug/g). Experimental procedure: Study Species: 10-12 wks MDX mice; Route: Subcutaneous; # Doses: QD for 3 days; Time Point Post Last Dose: 3 days; and Daily Dose Level (ug): 12 mg/kg.

Oligo-nucleotide	Quadriceps pD Mean± SD	Triceps pD Mean± SD	Gastro pD Mean± SD	Diaphragm pD Mean± SD	Heart pD Mean± SD
PBS	1.000 ± 0.266	1.000 ± 0.207	1.000 ± 0.138	1.000 ± 0.191	1.000 ± 0.221
WV-2735	0.952 ± 0.232	0.876 ± 0.180	0.998 ± 0.072	0.651 ± 0.046	1.032 ± 0.541
WV-2835	0.593 ± 0.167	0.877 ± 0.180	0.645 ± 0.124	0.563 ± 0.091	1.032 ± 0.240
WV-2836	0.556 ± 0.172	0.739 ± 0.047	0.695 ± 0.102	0.614 ± 0.120	0.544 ± 0.109
WV-3174	0.610 ± 0.109	1.009 ± 0.047	0.809 ± 0.137	0.698 ± 0.069	0.588 ± 0.258
WV-7301	0.624 ± 0.074	0.846 ± 0.172	0.837 ± 0.141	0.453 ± 0.031	0.887 ± 0.142

Oligonucleotide	Quadriceps pK Mean± SD (ug/g)	Diaphragm pK Mean± SD (ug/g)	Heart pK Mean± SD (ug/g)
PBS	0.000 ± 0.000	0.096 ± 0.015	0.000 ± 0.000
WV-2735	5.616 ± 2.724	3.207 ± 1.465	0.342 ± 0.169
WV-2835	8.421 ± 3.374	5.734 ± 1.465	0.777 ± 0.203
WV-2836	11.221 ± 7.877	6.142 ± 1.006	0.664 ± 0.441
WV-3174	9.792 ± 8.339	4.609 ± 1.006	0.619 ± 0.122
WV-7301	6.659 ± 3.858	5.728 ± 2.092	0.707 ± 0.191

Table 29. Knock-down and oligonucleotide presence in various tissues.

Numbers indicate Malat1 mRNA levels relative to mHprt, and presence of oligonucleotide (ug/g). Experimental procedure: Study Species: 10-12 wks wt mice; Route: Subcutaneous; # Doses: QD for 3 days; Time Point Post Last Dose: 3 days; and Daily Dose Level (ug): 12 mg/kg.

Oligo-nucleotide	Quadriceps pD Mean± SD	Triceps pD Mean± SD	Gastro pD Mean± SD	Diaphragm pD Mean± SD	Heart pD Mean± SD
PBS	1.000 ± 0.266	1.000 ± 0.191	1.000 ± 0.249	1.000 ± 0.191	1.000 ± 0.147
WV-2735	0.753 ± 0.230	0.667 ± 0.132	0.756 ± 0.136	0.651 ± 0.046	0.596 ± 0.140
WV-2835	0.611 ± 0.165	0.549 ± 0.077	0.656 ± 0.101	0.563 ± 0.091	0.546 ± 0.092

WV-2836	0.640 ± 0.186	0.596 ± 0.114	0.812 ± 0.216	0.614 ± 0.120	0.774 ± 0.168
WV-3174	0.796 ± 0.142	0.610 ± 0.111	0.870 ± 0.081	0.698 ± 0.069	0.703 ± 0.099
WV-7301	0.456 ± 0.116	0.498 ± 0.097	0.753 ± 0.113	0.453 ± 0.031	0.368 ± 0.031

Oligonucleotide	Quadriceps pK Mean± SD (ug/g)	Diaphragm pK Mean± SD (ug/g)	Heart pK Mean± SD (ug/g)
PBS	0.000 ± 0.000	0.108 ± 0.016	0.000 ± 0.000
WV-2735	2.787 ± 0.734	9.219 ± 3.234	0.428 ± 0.084
WV-2835	2.700 ± 0.891	9.895 ± 2.466	0.726 ± 0.207
WV-2836	2.273 ± 0.621	9.751 ± 6.912	0.670 ± 0.242
WV-3174	2.142 ± 0.778	7.568 ± 1.807	0.612 ± 0.172
WV-7301	2.868 ± 0.334	6.174 ± 2.456	0.975 ± 0.216

Table 30. Knock-down and oligonucleotide presence in various tissues.

Numbers indicate Malat1 mRNA levels relative to mHprt, and presence of oligonucleotide (ug/g).

Experimental procedure: Study Species: 5-6 wks wt mice; Route: Subcutaneous; # Doses: QD for 1 days; Time Point Post Last Dose: 3 days; and Daily Dose Level (ug): 200 mg/kg.

Malat1 Sequence	Quadriceps pD Mean± SD	Gastro pD Mean± SD	Diaphragm pD Mean± SD	Heart pD Mean± SD
PBS	1.000 ± 0.256	1.000 ± 0.309	1.000 ± 0.345	1.000 ± 0.432
WV-3174	0.752 ± 0.118	0.833 ± 0.160	0.647 ± 0.058	0.599 ± 0.120
WV-3174	0.603 ± 0.118	0.678 ± 0.145	0.421 ± 0.092	0.582 ± 0.185
WV-3174	0.454 ± 0.112	0.523 ± 0.104	0.380 ± 0.081	0.415 ± 0.062
WV-3174	0.342 ± 0.033	0.505 ± 0.119	0.322 ± 0.077	0.340 ± 0.055

Malat1 Sequence	Quadriceps pK Mean± SD (ug/g)	Gastro pK Mean± SD (ug/g)	Diaphragm pK Mean± SD (ug/g)	Heart pK Mean± SD (ug/g)
PBS	0.011 ± 0.025	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
WV-3174	1.388 ± 0.677	1.704± 0.524	2.502 ± 0.919	1.781 ± 0.668
WV-3174	6.651 ± 5.930	4.563 ± 1.705	7.366 ± 3.939	2.532 ± 0.487
WV-3174	12.374 ± 4.081	14.574 ± 8.235	12.075 ± 3.739	4.611 ± 1.050
WV-3174	15.227 ± 4.925	14.124 ± 2.285	22.734 ± 4.484	12.660 ± 2.437

Example Methods for Preparing Oligonucleotides and Compositions

[00944] Among other things, the present disclosure provides technologies (methods, reagents, conditions, purification processes, etc.) for prepaing oligonucleotides and oligonucleotide compositions, including chirally controlled oligonucleotides and chirally controlled oligonucleotide nucleotides. Various technologies (methods, reagents, conditions, purification processes, etc.), as described herein, can be utilized to prepare provided oligonucleotides and compositions thereof in accordance with the present disclosure, including but not limited to those described in US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, WO 2017/210647, WO 2018/223056, WO 2018/237194, and/or WO 2019/055951, the preparation technologies of each of which are incorporated

herein by reference.

[00945] In some embodiments, the present disclosure provides chirally controlled oligonucleotides. In some embodiments, a provided chirally controlled oligonucleotide is over 50% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 55% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 60% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 65% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 70% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 75% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 80% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 85% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 90% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 91% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 92% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 93% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 94% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 95% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 96% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 97% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 98% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 99% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 99.5% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 99.6% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 99.7% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 99.8% pure. In some embodiments, a provided chirally controlled oligonucleotide is over about 99.9% pure. In some embodiments, a provided chirally controlled oligonucleotide is over at least about 99% pure.

[00946] In some embodiments, a chirally controlled oligonucleotide composition is a composition designed to comprise a single oligonucleotide type. In certain embodiments, such compositions are about 50% diastereomerically pure. In some embodiments, such compositions are about 50% diastereomerically pure. In some embodiments, such compositions are about 50% diastereomerically pure. In some embodiments, such compositions are about 55% diastereomerically pure. In some embodiments, such compositions are about 60% diastereomerically pure. In some embodiments, such compositions are about 65% diastereomerically pure. In some embodiments, such compositions are about 70% diastereomerically pure. In some embodiments, such compositions are about 75%

diastereomerically pure. In some embodiments, such compositions are about 80% diastereomerically pure. In some embodiments, such compositions are about 85% diastereomerically pure. In some embodiments, such compositions are about 90% diastereomerically pure. In some embodiments, such compositions are about 91% diastereomerically pure. In some embodiments, such compositions are about 92% diastereomerically pure. In some embodiments, such compositions are about 93% diastereomerically pure. In some embodiments, such compositions are about 94% diastereomerically pure. In some embodiments, such compositions are about 95% diastereomerically pure. In some embodiments, such compositions are about 96% diastereomerically pure. In some embodiments, such compositions are about 97% diastereomerically pure. In some embodiments, such compositions are about 98% diastereomerically pure. In some embodiments, such compositions are about 99% diastereomerically pure. In some embodiments, such compositions are about 99.5% diastereomerically pure. In some embodiments, such compositions are about 99.6% diastereomerically pure. In some embodiments, such compositions are about 99.7% diastereomerically pure. In some embodiments, such compositions are about 99.8% diastereomerically pure. In some embodiments, such compositions are about 99.9% diastereomerically pure. In some embodiments, such compositions are at least about 99% diastereomerically pure.

[00947] Among other things, the present disclosure recognizes the challenge of stereoselective (rather than stereorandom or racemic) preparation of oligonucleotides. Among other things, the present disclosure provides methods and reagents for stereoselective preparation of oligonucleotides comprising multiple (*e.g.*, more than 5, 6, 7, 8, 9, or 10) internucleotidic linkages, and particularly for oligonucleotides comprising multiple (*e.g.*, more than 5, 6, 7, 8, 9, or 10) chiral internucleotidic linkages. In some embodiments, in a stereorandom or racemic preparation of oligonucleotides, at least one chiral internucleotidic linkage is formed with less than 90:10, 95:5, 96:4, 97:3, or 98:2 diastereoselectivity. In some embodiments, for a stereoselective or chirally controlled preparation of oligonucleotides, each chiral internucleotidic linkage is formed with greater than 90:10, 95:5, 96:4, 97:3, or 98:2 diastereoselectivity. In some embodiments, for a stereoselective or chirally controlled preparation of oligonucleotides, each chiral internucleotidic linkage is formed with greater than 95:5 diastereoselectivity. In some embodiments, for a stereoselective or chirally controlled preparation of oligonucleotides, each chiral internucleotidic linkage is formed with greater than 96:4 diastereoselectivity. In some embodiments, for a stereoselective or chirally controlled preparation of oligonucleotides, each chiral internucleotidic linkage is formed with greater than 97:3 diastereoselectivity. In some embodiments, for a stereoselective or chirally controlled preparation of oligonucleotides, each chiral internucleotidic linkage is formed with greater than 98:2 diastereoselectivity. In some embodiments, for a stereoselective or chirally controlled preparation of oligonucleotides, each chiral internucleotidic linkage is formed with greater than 99:1

diastereoselectivity. In some embodiments, diastereoselectivity of a chiral internucleotidic linkage in an oligonucleotide may be measured through a model reaction, *e.g.* formation of a dimer under essentially the same or comparable conditions wherein the dimer has the same internucleotidic linkage as the chiral internucleotidic linkage, the 5'-nucleoside of the dimer is the same as the nucleoside to the 5'-end of the chiral internucleotidic linkage, and the 3'-nucleoside of the dimer is the same as the nucleoside to the 3'-end of the chiral internucleotidic linkage.

[00948] In some embodiments, a chirally controlled oligonucleotide composition is a composition designed to comprise multiple oligonucleotide types. In some embodiments, methods of the present disclosure allow for the generation of a library of chirally controlled oligonucleotides such that a pre-selected amount of any one or more chirally controlled oligonucleotide types can be mixed with any one or more other chirally controlled oligonucleotide types to create a chirally controlled oligonucleotide composition. In some embodiments, the pre-selected amount of an oligonucleotide type is a composition having any one of the above-described diastereomeric purities.

[00949] In some embodiments, the present disclosure provides methods for making a chirally controlled oligonucleotide comprising steps of:

(1) coupling;

(2) capping;

(3) optionally modifying;

(4) deblocking; and

(5) repeating steps (1) – (4) until a desired length is achieved.

[0001] In some embodiments, the present disclosure provides a method, *e.g.*, for preparing an oligonucleotide, comprising one or more cycles, each of which independently comprises:

(1) a coupling step;

(2) optionally a pre-modification capping step;

(3) a modification step;

(4) optionally a post-modification capping step; and

(5) optionally a de-blocking step.

[00950] In some embodiments, a cycle comprises one or more pre-modification capping steps. In some embodiments, a cycle comprises one or more post-modification capping steps. In some embodiments, a cycle comprises one or more pre- and post-modification capping steps. In some embodiments, a cycle comprises one or more de-blocking steps. In some embodiments, a cycle comprises a coupling step, a pre-modification capping step, a modification step, a post-modification capping step, and a de-blocking step. In some embodiments, a cycle comprises a coupling step, a pre-modification capping step, a modification step, and a de-blocking step. In some embodiments, a cycle comprises a

coupling step, a modification step, a post-modification capping step and a de-blocking step. In some embodiments, comprise a coupling step, a pre-modification capping step, a modification step, a post-modification capping step, and a de-blocking step. In some embodiments, one or more cycles comprise a coupling step, a pre-modification capping step, a modification step, and a de-blocking step. In some embodiments, one or more cycles comprise a coupling step, a modification step, a post-modification capping step and a de-blocking step.

[00951] When describing the provided methods, the word "cycle" has its ordinary meaning as understood by a person of ordinary skill in the art. In some embodiments, one round of steps (1)-(4) is referred to as a cycle. In some embodiments, some cycles comprise modifying. In some embodiments, some cycles do not comprise modifying. In some embodiments, some cycles comprise and some cycles do not comprise modifying. In some embodiments, each cycle independently comprises a modifying step. In some embodiments, each cycle does not comprise a cycling step.

[00952] In some embodiments, to form a chirally controlled internucleotidic linkage, a chirally pure phosphoramidite comprising a chiral auxiliary is utilized to stereoselectively form the chirally controlled internucleotidic linkage. Various phosphoramidite and chiral auxiliaries, e.g., those described in US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, WO 2017/210647, WO 2018/223056, WO 2018/237194, and/or WO 2019/055951, the phosphoramidite and chiral auxiliaries of each of which are incorporated herein by reference, may be utilized in accordance with the present disclosure.

[00953] In some embodiments, a coupling step provides an oligonucleotide comprises an internucleotidic linkage of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., or a salt form thereof, wherein P^L is P. In some embodiments, such an internucleotidic linkage is a chirally controlled internucleotidic linkage. In some embodiments, such an internucleotidic linkage comprises a chiral auxiliary moiety.

[00954] In some embodiments, a modifying step provides an oligonucleotide comprises an internucleotidic linkage of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, **III**, etc., or a salt form thereof, wherein P^L is P=W. In some embodiments, a modifying step provides an oligonucleotide comprises an internucleotidic linkage of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., or a salt form thereof, wherein P^L is P=W. In some embodiments, W is S. In some embodiments, W is O. In some embodiments, such an internucleotidic linkage is a chirally controlled internucleotidic linkage. In some embodiments, such an internucleotidic linkage comprises a chiral auxiliary moiety. In some embodiments, a modifying step provides a non-negatively charged

internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., or a salt form thereof. In some embodiments, such an internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, such an internucleotidic linkage is a chirally controlled internucleotidic linkage. In some embodiments, such an internucleotidic linkage comprises a chiral auxiliary moiety. In some embodiments, such an internucleotidic linkage comprises no chiral auxiliary moiety. In some embodiments, a chiral auxiliary moiety falls off during modification.

[00955] Provided technologies provide various advantages. Among other things, as demonstrated herein, provided technologies can greatly improve oligonucleotide synthesis crude purity and yield, particularly for modified and/or chirally pure oligonucleotides that provide a number of properties and activities that are critical for therapeutic purposes. With the capability to provide unexpectedly high crude purity and yield for therapeutically important oligonucleotides, provided technologies can significantly reduce manufacturing costs (through, *e.g.*, simplified purification, greatly improved overall yields, etc.). In some embodiments, provided technologies can be readily scaled up to produce oligonucleotides in sufficient quantities and qualities for clinical purposes. In some embodiments, provided technologies comprising chiral auxiliaries that comprise electron-withdrawing groups in G^2 (*e.g.*, PSM chiral auxiliaries) are particularly useful for preparing chirally controlled internucleotidic linkages comprising P-N bonds (*e.g.*, non-negatively charged internucleotidic linkages such as n001, n002, n003, n004, n005, n006, n007, n008, n009, n010, *etc.*) and can significantly simplify manufacture operations, reduce cost, and/or facilitate downstream formation.

[00956] In some embodiments, provided technologies provides improved reagents compatibility. For example, as demonstrated in the present disclosure, provided technologies provide flexibility to use different reagent systems for oxidation, sulfurization and/or azide reactions, particularly for chirally controlled oligonucleotide synthesis.

[00957] Among other things, the present disclosure provides oligonucleotide compositions of high crude purity. In some embodiments, the present disclosure provides chirally controlled oligonucleotide composition of high crude purity. In some embodiments, the present disclosure provides chirally controlled oligonucleotide of high crude purity. In some embodiments, the present disclosure provides oligonucleotide of high crude purity and/or high stereopurity.

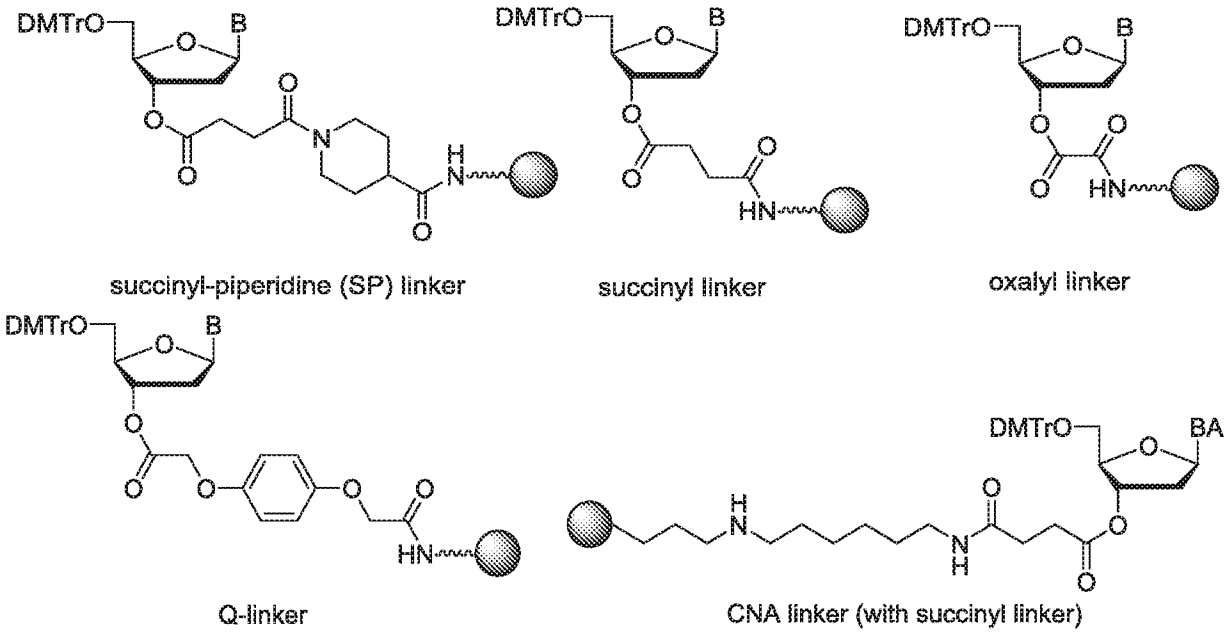
Support and Linkers

[00958] In some embodiments, oligonucleotides can be prepared in solution. In some embodiments, oligonucleotides can be prepared using a support. In some embodiments, oligonucleotides are prepared using a solid support. Suitable support that can be utilized in accordance with the present disclosure include, e.g., solid support described in US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, WO 2017/210647, WO 2018/223056, WO 2018/237194, and/or WO 2019/055951, the solid support of each of which is incorporated herein by reference.

[00959] In some embodiments, a linker moiety is utilized to connect an oligonucleotide chain to a support during synthesis. Suitable linkers are widely utilized in the art, and include those described in US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, WO 2017/210647, WO 2018/223056, WO 2018/237194, and/or WO 2019/055951, the linker of each of which is incorporated herein by reference

[00960] In some embodiments, the linking moiety is a succinamic acid linker, or a succinate linker (-CO-CH_2-CH_2-CO-), or an oxalyl linker (-CO-CO-). In some embodiments, the linking moiety and the nucleoside are bonded together through an ester bond. In some embodiments, a linking moiety and a nucleoside are bonded together through an amide bond. In some embodiments, a linking moiety connects a nucleoside to another nucleotide or nucleic acid. Suitable linkers are disclosed in, for example, Oligonucleotides And Analogues A Practical Approach, Ekstein, F. Ed., IRL Press, N.Y., 1991, Chapter 1 and Solid-Phase Supports for Oligonucleotide Synthesis, Pon, R. T., Curr. Prot. Nucleic Acid Chem., 2000, 3.1.1-3.1.28. In some embodiments, a universal linker (UnyLinker) is used to attached the oligonucleotide to the solid support (Ravikumar et al., Org. Process Res. Dev., 2008, 12 (3), 399–410). In some embodiments, other universal linkers are used (Pon, R. T., Curr. Prot. Nucleic Acid Chem., 2000, 3.1.1-3.1.28). In some embodiments, various orthogonal linkers (such as disulfide linkers) are used (Pon, R. T., Curr. Prot. Nucleic Acid Chem., 2000, 3.1.1-3.1.28).

[00961] Among other things, the present disclosure recognizes that a linker can be chosen or designed to be compatible with a set of reaction conditions employed in oligonucleotide synthesis. In some embodiments, to avoid degradation of oligonucleotides and to avoid desulfurization, auxiliary groups are selectively removed before de-protection. In some embodiments, DPSE group can selectively be removed by F^- ions. In some embodiments, the present disclosure provides linkers that are stable under a DPSE de-protection condition, *e.g.*, 0.1M TBAF in MeCN, 0.5M HF-Et_3N in THF or MeCN, *etc.* In some embodiments, a provided linker is a linker as exemplified below:



Solvents

[00962] Syntheses of provided oligonucleotides are generally performed in aprotic organic solvents. In some embodiments, a solvent is a nitrile solvent such as, *e.g.*, acetonitrile. In some embodiments, a solvent is a basic amine solvent such as, *e.g.*, pyridine. In some embodiments, a solvent is an ethereal solvent such as, *e.g.*, tetrahydrofuran. In some embodiments, a solvent is a halogenated hydrocarbon such as, *e.g.*, dichloromethane. In some embodiments, a mixture of solvents is used. In certain embodiments a solvent is a mixture of any one or more of the above-described classes of solvents.

[00963] In some embodiments, when an aprotic organic solvent is not basic, a base is present in the reacting step. In some embodiments where a base is present, the base is an amine base such as, *e.g.*, pyridine, quinoline, or *N,N*-dimethylaniline. Example other amine bases include pyrrolidine, piperidine, *N*-methyl pyrrolidine, pyridine, quinoline, *N,N*-dimethylaminopyridine (DMAP), or *N,N*-dimethylaniline.

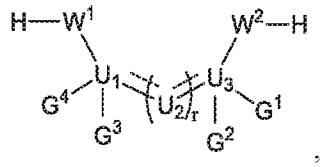
[00964] In some embodiments, a base is other than an amine base.

[00965] In some embodiments, an aprotic organic solvent is anhydrous. In some embodiments, an anhydrous aprotic organic solvent is freshly distilled. In some embodiments, a freshly distilled anhydrous aprotic organic solvent is a basic amine solvent such as, *e.g.*, pyridine. In some embodiments, a freshly distilled anhydrous aprotic organic solvent is an ethereal solvent such as, *e.g.*, tetrahydrofuran. In some embodiments, a freshly distilled anhydrous aprotic organic solvent is a nitrile solvent such as, *e.g.*, acetonitrile.

Chiral reagents/Chiral auxiliaries

[00966] In some embodiments, chiral reagents (may also be referred to as chiral auxiliaries) are used to confer stereoselectivity in the production of chirally controlled oligonucleotides. Many chiral reagents, also referred to by those of skill in the art and herein as chiral auxiliaries, may be used in accordance with methods of the present disclosure. Examples of such chiral reagents are described herein and in US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/223056, WO 2018/237194, and/or WO 2019/055951, the chiral auxiliaries of each of which is incorporated by reference.

[00967] In some embodiments, a chiral reagent for use in accordance with the methods of the present disclosure is of Formula **3-I**, below:



Formula 3-I

wherein:

W^1 and W^2 are any of $-O-$, $-S-$, $-NG^5-$, or $-NG^5-O-$;

U_1 and U_3 are carbon atoms which are bonded to U_2 if present, or to each other if r is 0, via a single, double or triple bond;

U_2 is $-C-$, $-CG^8-$, $-CG^8G^8-$, $-NG^8-$, $-N-$, $-O-$, or $-S-$ where r is an integer of 0 to 5; and

each of G^1, G^2, G^3, G^4, G^5, and G^8 is independently R^1 as described in the present disclosure.

[00968] In some embodiments, W^1 and W^2 are any of $-O-$, $-S-$, or $-NG^5-$, U_1 and U_3 are carbon atoms which are bonded to U_2 if present, or to each other if r is 0, via a single, double or triple bond. U_2 is $-C-$, $-CG^8-$, $-CG^8G^8-$, $-NG^8-$, $-N-$, $-O-$, or $-S-$ where r is an integer of 0 to 5 and no more than two heteroatoms are adjacent. When any one of U_2 is C, a triple bond must be formed between a second instance of U_2, which is C, or to one of U_1 or U_3. Similarly, when any one of U_2 is CG^8, a double bond is formed between a second instance of U_2 which is $-CG^8-$ or $-N-$, or to one of U_1 or U_3.

[00969] In some embodiments, $-U_1G^3G^4-(U_2)_r-U_3G^1G^2-$ is $-CG^3G^4-CG^1G^2-$. In some embodiments, $-U_1-(U_2)_r-U_3-$ is $-CG^3=CG^1-$. In some embodiments, $-U_1-(U_2)_r-U_3-$ is $-C\equiv C-$. In some embodiments, $-U_1-(U_2)_r-U_3-$ is $-CG^3=CG^8-CG^1G^2-$. In some embodiments, $-U_1-(U_2)_r-U_3-$ is $-CG^3G^4-O-CG^1G^2-$. In some embodiments, $-U_1-(U_2)_r-U_3-$ is $-CG^3G^4-NG^8-CG^1G^2-$. In some embodiments, $-U_1-(U_2)_r-U_3-$ is $-CG^3G^4-N-CG^2-$. In some embodiments, $-U_1-(U_2)_r-U_3-$ is $-CG^3G^4-N=CG^8-CG^1G^2-$.

[00970] In some embodiments, G^1, G^2, G^3, G^4, G^5, and G^8 are independently R^1 as described in the

present disclosure. In some embodiments, G^1, G^2, G^3, G^4, G^5, and G^8 are independently R as described in the present disclosure. In some embodiments, G^1, G^2, G^3, G^4, G^5, and G^8 are independently hydrogen, or an optionally substituted group selected from aliphatic, alkyl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaliphatic, heterocyclyl, heteroaryl, and aryl; or two of G^1, G^2, G^3, G^4, and G^5 are G^6 (taken together to form an optionally substituted, saturated, partially unsaturated or unsaturated carbocyclic or heteroatom-containing ring of up to about 20 ring atoms which is monocyclic or polycyclic, and is fused or unfused). In some embodiments, a ring so formed is substituted by oxo, thioxo, alkyl, alkenyl, alkynyl, heteroaryl, or aryl moieties. In some embodiments, when a ring formed by taking two G^6 together is substituted, it is substituted by a moiety which is bulky enough to confer stereoselectivity during the reaction.

[00971] In some embodiments, a ring formed by taking two of G^6 together is optionally substituted cyclopentyl, pyrrolyl, cyclopropyl, cyclohexenyl, cyclopentenyl, tetrahydropyranyl, or piperazinyl. In some embodiments, a ring formed by taking two of G^6 together is optionally substituted cyclopentyl, pyrrolyl, cyclopropyl, cyclohexenyl, cyclopentenyl, tetrahydropyranyl, pyrrolidinyl, or piperazinyl.

[00972] In some embodiments, G^1 is optionally substituted phenyl. In some embodiments, G^1 is phenyl. In some embodiments, G^2 is methyl or hydrogen. In some embodiments, G^2 is hydrogen. In some embodiments, G^1 is optionally substituted phenyl and G^2 is methyl. In some embodiments, G^1 is phenyl and G^2 is methyl. In some embodiments, G^1 is $-CH_2Si(R)_3$, wherein one R is optionally substituted C_{1-6} aliphatic, and the other two R are each independently an optionally substituted 3-20 membered, monocyclic or polycyclic, saturated, partially unsaturated or aromatic ring having 0-5 heteroatoms. In some embodiments, the other two R are each independently optionally substituted phenyl. In some embodiments, G^1 is $-CH_2SiMePh_2$.

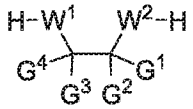
[00973] In some embodiments, r is 0.

[00974] In some embodiments, W^1 is $-NG^5-O-$. In some embodiments, W^1 is $-NG^5-O-$, wherein the $-O-$ is bonded to $-H$. In some embodiments, W^1 is $-NG^5-$. In some embodiments, one of G^3 and G^4 is taken together with G^5 to form an optionally substituted 3-10 membered ring. In some embodiments, one of G^3 and G^4 is taken together with G^5 to form an optionally substituted pyrrolidinyl ring. In some embodiments, one of G^3 and G^4 is taken together with G^5 to form a pyrrolidinyl ring. In some embodiments, G^5 is optionally substituted C_{1-6} aliphatic. In some embodiments, G^5 is methyl. In some embodiments, one of G^1 and G^2 and one of G^3 and G^4 are taken together with their intervening atoms to form an optionally substituted 3-10 membered ring having 0-3 heteroatoms. In some embodiments, a formed ring 3-membered. In some embodiments, a formed ring 4-membered. In some embodiments, a formed ring 5-membered. In some embodiments, a formed ring 6-membered. In some

embodiments, a formed ring 7-membered. In some embodiments, a formed ring is substituted. In some embodiments, a formed ring is unsubstituted. In some embodiments, a formed ring has no heteroatom. In some embodiments, a formed ring is saturated. For example compounds, see WV-CA-293 and WV-CA-294.

[00975] In some embodiments, W^2 is –O–.

[00976] In some embodiments, a chiral reagent is a compound of Formula 3-AA:

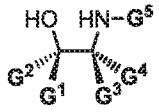
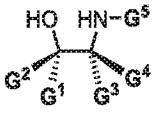
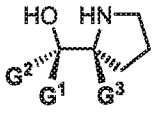
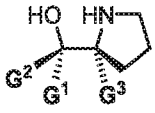
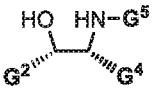
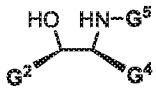
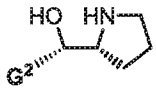
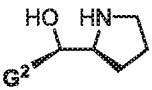


Formula 3-AA

wherein each variable is independently as defined above and described herein.

[00977] In some embodiments of Formula 3AA, W^1 and W^2 are independently -NG^5-, -O-, or -S-; G^1, G^2, G^3, G^4, and G^5 are independently hydrogen, or an optionally substituted group selected from alkyl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaliphatic, heterocyclyl, heteroaryl, or aryl; or two of G^1, G^2, G^3, G^4, and G^5 are G^6 (taken together to form an optionally substituted saturated, partially unsaturated or unsaturated carbocyclic or heteroatom-containing ring of up to about 20 ring atoms which is monocyclic or polycyclic, fused or unfused), and no more than four of G^1, G^2, G^3, G^4, and G^5 are G^6. Similarly to the compounds of Formula 3-I, any of G^1, G^2, G^3, G^4, or G^5 are optionally substituted by oxo, thioxo, alkyl, alkenyl, alkynyl, heteroaryl, or aryl moieties. In some embodiments, such substitution induces stereoselectivity in chirally controlled oligonucleotide production. In some embodiments, a heteroatom-containing moiety, e.g., heteroaliphatic, heterocyclyl, heteroaryl, etc., has 1-5 heteroatoms. In some embodiments, the heteroatoms are selected from nitrogen, oxygen, sulfure and silicon. In some embodiments, at least one heteroatom is nitrogen.

[00978] In some embodiments, W^1 is $-NG^5-O-$. In some embodiments, W^1 is $-NG^5-O-$, wherein the –O– is bonded to –H. In some embodiments, W^1 is $-NG^5-$. In some embodiments, G^5 and one of G^3 and G^4 are taken together to form an optionally substituted 3-10 membered ring having 0-3 heteroatoms in addition to the nitrogen atom of W^1. In some embodiments, G^5 and G^3 are taken together to form an optionally substituted 3-10 membered ring having 0-3 heteroatoms in addition to the nitrogen atom of W^1. In some embodiments, G^5 and G^4 are taken together to form an optionally substituted 3-10 membered ring having 0-3 heteroatoms in addition to the nitrogen atom of W^1. In some embodiments, a formed ring is an optionally substituted 4, 5, 6, 7, or 8 membered ring. In some embodiments, a formed ring is an optionally substituted 4-membered ring. In some embodiments, a formed ring is an optionally substituted 5-membered ring. In some embodiments, a formed ring is an optionally substituted 6-membered ring. In some embodiments, a formed ring is an optionally substituted 7-membered ring.

[00979] In some embodiments, a provided chiral reagent has the structure of  . In some embodiments, a provided chiral reagent has the structure of  . In some embodiments, a provided chiral reagent has the structure of  . In some embodiments, a provided chiral reagent has the structure of  . In some embodiments, a provided chiral reagent has the structure of  . In some embodiments, a provided chiral reagent has the structure of  . In some embodiments, a provided chiral reagent has the structure of  . In some embodiments, a provided chiral reagent has the structure of  .

[00980] In some embodiments, W^1 is $-NG^5$, W^2 is O, each of G^1 and G^3 is independently hydrogen or an optionally substituted group selected from C_{1-10} aliphatic, heterocyclyl, heteroaryl and aryl, G^2 is $-C(R)_2Si(R)_3$, and G^4 and G^5 are taken together to form an optionally substituted saturated, partially unsaturated or unsaturated heteroatom-containing ring of up to about 20 ring atoms which is monocyclic or polycyclic, fused or unfused. In some embodiments, each R is independently hydrogen, or an optionally substituted group selected from C_1–C_6 aliphatic, carbocyclyl, aryl, heteroaryl, and heterocyclyl. In some embodiments, G^2 is $-C(R)_2Si(R)_3$, wherein $-C(R)_2-$ is optionally substituted $-CH_2-$, and each R of $-Si(R)_3$ is independently an optionally substituted group selected from C_{1-10} aliphatic, heterocyclyl, heteroaryl and aryl. In some embodiments, at least one R of $-Si(R)_3$ is independently optionally substituted C_{1-10} alkyl. In some embodiments, at least one R of $-Si(R)_3$ is independently optionally substituted phenyl. In some embodiments, one R of $-Si(R)_3$ is independently optionally substituted phenyl, and each of the other two R is independently optionally substituted C_{1-10} alkyl. In some embodiments, one R of $-Si(R)_3$ is independently optionally substituted C_{1-10} alkyl, and each of the other two R is independently optionally substituted phenyl. In some embodiments, G^2 is optionally substituted $-CH_2Si(Ph)(Me)_2$. In some embodiments, G^2 is optionally substituted $-CH_2Si(Me)(Ph)_2$. In some embodiments, G^2 is $-CH_2Si(Me)(Ph)_2$. In some embodiments, G^4 and G^5 are

taken together to form an optionally substituted saturated 5-6 membered ring containing one nitrogen atom (to which G^5 is attached). In some embodiments, G^4 and G^5 are taken together to form an optionally substituted saturated 5-membered ring containing one nitrogen atom. In some embodiments, G^1 is hydrogen. In some embodiments, G^3 is hydrogen. In some embodiments, both G^1 and G^3 are hydrogen.

[00981] In some embodiments, W^1 is $-NG^5$, W^2 is O, each of G^1 and G^3 is independently R^1, G^2 is $-R^1$, and G^4 and G^5 are taken together to form an optionally substituted saturated, partially unsaturated or unsaturated heteroatom-containing ring of up to about 20 ring atoms which is monocyclic or polycyclic, fused or unfused. In some embodiments, each of G^1 and G^3 is independently R. In some embodiments, each of G^1 and G^3 is independently $-H$. In some embodiments, G^2 is connected to the rest of the molecule through a carbon atom, and the carbon atom is substituted with one or more electron-withdrawing groups. In some embodiments, G^2 is methyl substituted with one or more electron-withdrawing groups. In some embodiments, G^2 is methyl substituted with one and no more than one electron-withdrawing group. In some embodiments, G^2 is methyl substituted with two or more electron-withdrawing groups. Among other things, a chiral auxiliary having G^2 comprising an electron-withdrawing group can be readily removed by a base (base-labile, *e.g.*, under an anhydrous condition substantially free of water; in many instances, preferably before oligonucleotides comprising internucleotidic linkages comprising such chiral auxiliaries are exposed to conditions/reagent systems comprising a substantial amount of water, particular in the presence of a base(*e.g.*, cleavage conditions/reagent systems using NH_4OH)) and provides various advantages as described herein, *e.g.*, high crude purity, high yield, high stereoselectivity, more simplified operation, fewer steps, further reduced manufacture cost, and/or more simplified downstream formulation (*e.g.*, low amount of salt(s) after cleavage), *etc.* In some embodiments, as described in the Examples, such auxiliaries may provide alternative or additional chemical compatibility with other functional and/or protection groups. In some embodiments, as demonstrated in the Examples, base-labile chiral auxiliaries are particularly useful for construction of chirally controlled non-negatively charged internucleotidic linkages (*e.g.*, neutral internucleotidic linkages such as n001); in some instances, as demonstrated in the Examples, they can provide significantly improved yield and/or crude purity with high stereoselectivity, *e.g.*, when utilized with removal using a base under an anhydrous condition. In some embodiments, such a chiral auxiliary is bonded to a linkage phosphorus via an oxygen atom (*e.g.*, which corresponds to a $-OH$ group in a corresponding chiral auxiliary compound, *e.g.*, a compound of formula **I**), the carbon atom in the chiral auxiliary to which the oxygen is bonded

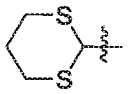
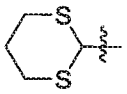
(the alpha carbon) also bonds to −H (in addition to other groups; in some embodiments, a secondary carbon), and the next carbon atom (the beta carbon) in the chiral auxiliary is boned to one or two electron-withdrawing groups. In some embodiments, $-W^2-H$ is −OH. In some embodiments, G^1 is −H. In some embodiments, G^2 comprises one or two electron-withdrawing groups or can otherwise facilitate remove of the chiral auxiliary by a base. In some embodiments, G^1 is −H, G^2 comprises one or two electron-withdrawing groups, $-W^2-H$ is −OH. In some embodiments, G^1 is −H, G^2 comprises one or two electron-withdrawing groups, $-W^2-H$ is −OH, $-W^1-H$ is $-NG^5-H$, and one of G^3 and G^4 is taken together with G^5 to form with their intervening atoms a ring as described herein (*e.g.*, an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having in addition to the nitrogen atom to which G^5 is on, 0-5 heteroatoms (*e.g.*, an optionally substituted 3, 4, 5, or 6-membered monocyclic saturated ring having in addition to the nitrogen atom to which G^5 is on no other heteroatoms)).

[00982] As appreciated by those skilled in the art, various electron-withdrawing groups are known in the art and can be utilized in accordance with the present disclosure. In some embodiments, an electronic-withdrawing group comprises and/or is connected to the carbon atom through, e.g., −S(O)−, $-S(O)_2-$, $-P(O)(R^1)-$, $-P(S)R^1-$, or −C(O)−. In some embodiments, an electron-withdrawing group is −CN, $-NO_2$, halogen, $-C(O)R^1$, −C(O)OR', $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$. In some embodiments, an electron-withdrawing group is aryl or heteroaryl, e.g., phenyl, substituted with one or more of −CN, $-NO_2$, halogen, $-C(O)R^1$, −C(O)OR', $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$.

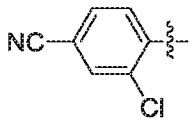
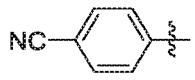
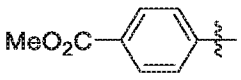
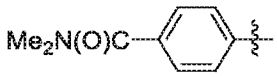
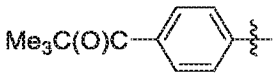
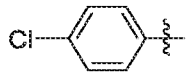
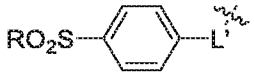
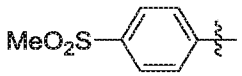
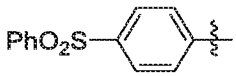
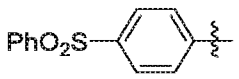
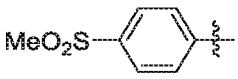
[00983] In some embodiments, G^2 is −L−R'. In some embodiments, G^2 is −L'−L"−R', wherein L' is $-C(R)_2-$ or optionally substituted $-CH_2-$, and L" is −P(O)(R')−, −P(O)(R')O−, −P(O)(OR')−, −P(O)(OR')O−, −P(O)[N(R')]−, −P(O)[N(R')]O−, −P(O)[N(R')][N(R')]−, −P(S)(R')−, $-S(O)_2-$, $-S(O)_2-$, $-S(O)_2O-$, −S(O)−, −C(O)−, −C(O)N(R')−, or −S−. In some embodiments, L' is $-C(R)_2-$. In some embodiments, L' is optionally substituted $-CH_2-$.

[00984] In some embodiments, L' is $-C(R)_2-$. In some embodiments, each R is independently hydrogen, or an optionally substituted group selected from C_1-C_6 aliphatic, carbocyclyl, aryl, heteroaryl, and heterocyclyl. In some embodiments, L' is $-CH_2-$. In some embodiments, L" is −P(O)(R')−, −P(S)(R')−, $-S(O)_2-$. In some embodiments, G^2 is −L'−C(O)N(R')$_2$. In some embodiments, G^2 is $-L'-P(O)(R')_2$. In some embodiments, G^2 is $-L'-P(S)(R')_2$. In some embodiments, each R' is independently optionally substituted aliphatic, heteroaliphatic, aryl, or heteroaryl as described in the present disclosure (e.g., those embodiments described for R). In some embodiments, each R' is independently optionally substituted phenyl. In some embodiments, each R' is independently optionally

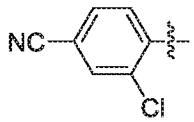
substituted phenyl wherein one or more substituents are independently selected from –CN, –OMe, –Cl, –Br, and –F. In some embodiments, each R' is independently substituted phenyl wherein one or more substituents are independently selected from –CN, –OMe, –Cl, –Br, and –F. In some embodiments, each R' is independently substituted phenyl wherein the substituents are independently selected from –CN, –OMe, –Cl, –Br, and –F. In some embodiments, each R' is independently mono-substituted phenyl, wherein the substituent is independently selected from –CN, –OMe, –Cl, –Br, and –F. In some embodiments, two R' are the same. In some embodiments, two R' are different. In some embodiments, G^2 is –L'–S(O)R'. In some embodiments, G^2 is –L'–C(O)N(R')$_2$. In some embodiments, G^2 is –L'–S(O)$_2$R'. In some embodiments, R' is optionally substituted aliphatic, heteroaliphatic, aryl, or heteroaryl as described in the present disclosure (e.g., those embodiments described for R). In some embodiments, R' is optionally substituted phenyl. In some embodiments, R' is optionally substituted phenyl wherein one or more substituents are independently selected from –CN, –OMe, –Cl, –Br, and –F. In some embodiments, R' is substituted phenyl wherein one or more substituents are independently selected from –CN, –OMe, –Cl, –Br, and –F. In some embodiments, R' is substituted phenyl wherein each substituent is independently selected from –CN, –OMe, –Cl, –Br, and –F. In some embodiments, R' is mono-substituted phenyl. In some embodiments, R' is mono-substituted phenyl, wherein the substituent is independently selected from –CN, –OMe, –Cl, –Br, and –F. In some embodiments, a substituent is an electron-withdrawing group. In some embodiments, an electron-withdrawing group is –CN, –NO$_2$, halogen, –C(O)R^1, –C(O)OR', –C(O)N(R')$_2$, –S(O)R^1, –S(O)$_2$R^1, –P(W)(R^1)$_2$, –P(O)(R^1)$_2$, –P(O)(OR')$_2$, or –P(S)(R^1)$_2$.

[00985] In some embodiments, G^2 is optionally substituted –CH$_2$–L"–R, wherein each of L" and R is independently as described in the present disclosure. In some embodiments, G^2 is optionally substituted –CH(–L"–R)$_2$, wherein each of L" and R is independently as described in the present disclosure. In some embodiments, G^2 is optionally substituted –CH(–S–R)$_2$. In some embodiments, G^2 is optionally substituted –CH$_2$–S–R. In some embodiments, the two R groups are taken together with their intervening atoms to form a ring. In some embodiments, a formed ring is an optionally substituted 5, 6, 7-membered ring having 0-2 heteroatoms in addition to the intervening heteroatoms. In some embodiments, G^2 is optionally substituted  . In some embodiments, G^2 is  . In some embodiments, –S– may be converted to –S(O)– or –S(O)$_2$–, e.g., by oxidation, e.g., to facilitate removal by a base.

[00986] In some embodiments, G^2 is –L'–R', wherein each variable is as described in the present disclosure. In some embodiments, G^2 is –CH$_2$–R'. In some embodiments, G^2 is –CH(R')$_2$. In some embodiments, G^2 is –C(R')$_3$. In some embodiments, R' is optionally substituted aryl or heteroaryl. In

some embodiments, R' is substituted aryl or heteroaryl wherein one or more substituents are independently an electron-withdrawing group. In some embodiments, –L'– is optionally substituted $-CH_2-$, and R' is R, wherein R is optionally substituted aryl or heteroaryl. In some embodiments, R is substituted aryl or heteroaryl wherein one or more substituents are independently an electron-withdrawing group. In some embodiments, R is substituted aryl or heteroaryl wherein each substituent is independently an electron-withdrawing group. In some embodiments, R is aryl or heteroaryl substituted with two or more substituents, wherein each substituent is independently an electron-withdrawing group. In some embodiments, an electron-withdrawing group is –CN, $-NO_2$, halogen, $-C(O)R^1$, –C(O)OR', $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$. In some embodiments, R' is  . In some embodiments, R' is *p*-NO_2Ph–. In some embodiments, R' is  . In some embodiments, R' is  . In some embodiments, R' is  . In some embodiments, R' is  . In some embodiments, R' is  . In some embodiments, R' is  . In some embodiments, R' is  . In some embodiments, R' is  . In some embodiments, R' is 2,4,6-trichlorophenyl. In some embodiments, R' is 2,4,6-trifluorophenyl. In some embodiments, G^2 is $-CH(4\text{-chlorophenyl})_2$. In some embodiments, G^2 is $-CH(R')_2$, wherein each R' is  . In some embodiments, G^2 is $-CH(R')_2$, wherein each R' is  . In some embodiments, R' is –C(O)R. In some embodiments, R' is $CH_3C(O)$–.

[00987] In some embodiments, G^2 is $-L'-S(O)_2R'$, wherein each variable is as described in the present disclosure. In some embodiments, G^2 is $-CH_2-S(O)_2R'$. In some embodiments, G^2 is –L'–S(O)R', wherein each variable is as described in the present disclosure. In some embodiments, G^2 is $-CH_2-S(O)R'$. In some embodiments, G^2 is $-L'-C(O)_2R'$, wherein each variable is as described in the present disclosure. In some embodiments, G^2 is $-CH_2-C(O)_2R'$. In some embodiments, G^2 is –L'–C(O)R', wherein each variable is as described in the present disclosure. In some embodiments, G^2 is $-CH_2-C(O)R'$. In some embodiments, –L'– is optionally substituted $-CH_2-$, and R' is R. In some embodiments, R is optionally substituted aryl or heteroaryl. In some embodiments, R is optionally

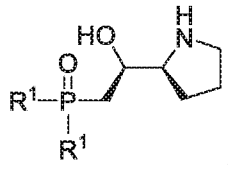
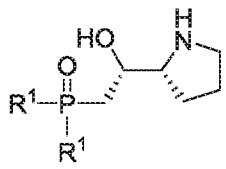
substituted aliphatic. In some embodiments, R is optionally substituted heteroaliphatic. In some embodiments, R is optionally substituted heteroaryl. In some embodiments, R is optionally substituted aryl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is not phenyl, or mono-, di- or tri-substituted phenyl, wherein each substituent is selected from $-NO_2$, halogen, $-CN$, $-C_{1-3}$ alkyl, and C_{1-3} alkyloxy. In some embodiments, R is substituted aryl or heteroaryl wherein one or more substituents are independently an electron-withdrawing group. In some embodiments, R is substituted aryl or heteroaryl wherein each substituent is independently an electron-withdrawing group. In some embodiments, R is aryl or heteroaryl substituted with two or more substituents, wherein each substituent is independently an electron-withdrawing group. In some embodiments, an electron-withdrawing group is $-CN$, $-NO_2$, halogen, $-C(O)R^1$, $-C(O)OR'$, $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$. In some embodiments, R' is phenyl. In some embodiments, R' is substituted phenyl. In some embodiments, R' is  . In some embodiments, R' is . In some embodiments, R' is . In some embodiments, R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R' is t-butyl. In some embodiments, R' is isopropyl. In some embodiments, R' is methyl. In some embodiments, G^2 is $-CH_2C(O)OMe$. In some embodiments, G^2 is $-CH_2C(O)Ph$. In some embodiments, G^2 is $-CH_2C(O)$-tBu.

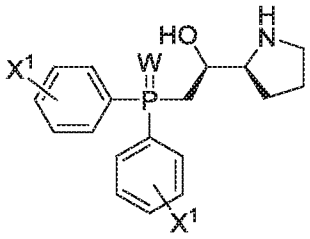
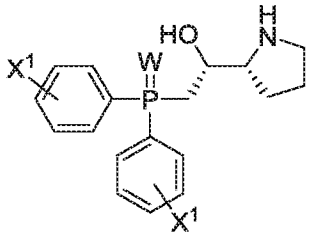
[00988] In some embodiments, G^2 is $-L'-NO_2$. In some embodiments, G^2 is $-CH_2-NO_2$. In some embodiments, G^2 is $-L'-S(O)_2N(R')_2$. In some embodiments, G^2 is $-CH_2-S(O)_2N(R')_2$. In some embodiments, G^2 is $-L'-S(O)_2NHR'$. In some embodiments, G^2 is $-CH_2-S(O)_2NHR'$. In some embodiments, R' is methyl. In some embodiments, G^2 is $-CH_2-S(O)_2NH(CH_3)$. In some embodiments, R' is $-CH_2Ph$. In some embodiments, G^2 is $-CH_2-S(O)_2NH(CH_2Ph)$. In some embodiments, G^2 is $-CH_2-S(O)_2N(CH_2Ph)_2$. In some embodiments, R' is phenyl. In some embodiments, G^2 is $-CH_2-S(O)_2NHPh$. In some embodiments, G^2 is $-CH_2-S(O)_2N(CH_3)Ph$. In some embodiments, G^2 is $-CH_2-S(O)_2N(CH_3)_2$. In some embodiments, G^2 is $-CH_2-S(O)_2NH(CH_2Ph)$. In some embodiments, G^2 is $-CH_2-S(O)_2NHPh$. In some embodiments, G^2 is $-CH_2-S(O)_2NH(CH_2Ph)$. In some embodiments, G^2 is $-CH_2-S(O)_2N(CH_3)_2$. In some embodiments, G^2 is $-CH_2-S(O)_2N(CH_3)Ph$. In some embodiments, G^2 is $-L'-S(O)_2N(R')(OR')$. In some embodiments, G^2 is $-CH_2-S(O)_2N(R')(OR')$. In some embodiments, each R' is methyl. In some embodiments, G^2 is $-CH_2-S(O)_2N(CH_3)(OCH_3)$. In some embodiments, G^2 is $-CH_2-S(O)_2N(Ph)(OCH_3)$. In some embodiments, G^2 is $-CH_2-S(O)_2N(CH_2Ph)(OCH_3)$. In some embodiments, G^2 is $-CH_2-S(O)_2N(CH_2Ph)(OCH_3)$. In some embodiments, G^2 is $-L'-S(O)_2OR'$. In

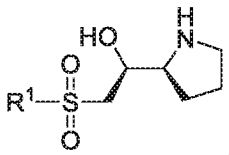
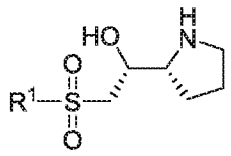
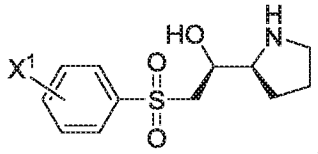
some embodiments, G^2 is $-CH_2-S(O)_2OR'$. In some embodiments, G^2 is $-CH_2-S(O)_2OPh$. In some embodiments, G^2 is $-CH_2-S(O)_2OCH_3$. In some embodiments, G^2 is $-CH_2-S(O)_2OCH_2Ph$.

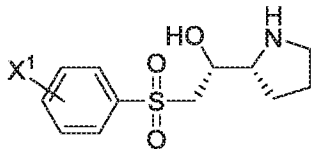
[00989] In some embodiments, G^2 is $-L'-P(O)(R')_2$. In some embodiments, G^2 is $-CH_2-P(O)(R')_2$. In some embodiments, G^2 is $-L'-P(O)[N(R')_2]_2$. In some embodiments, G^2 is $-CH_2-P(O)[N(R')_2]_2$. In some embodiments, G^2 is $-L'-P(O)[O(R')_2]_2$. In some embodiments, G^2 is $-CH_2-P(O)[O(R')_2]_2$. In some embodiments, G^2 is $-L'-P(O)(R')[N(R')_2]_2$. In some embodiments, G^2 is $-CH_2-P(O)(R')[N(R')_2]$. In some embodiments, G^2 is $-L'-P(O)(R')[O(R')]$. In some embodiments, G^2 is $-CH_2-P(O)(R')[O(R')]$. In some embodiments, G^2 is $-L'-P(O)(OR')[N(R')_2]$. In some embodiments, G^2 is $-CH_2-P(O)(OR')[N(R')_2]$. In some embodiments, G^2 is $-L'-C(O)N(R')_2$, wherein each variable is as described in the present disclosure. In some embodiments, G^2 is $-CH_2-C(O)N(R')_2$. In some embodiments, each R' is independently R. In some embodiments, one R' is optionally substituted aliphatic, and one R is optionally substituted aryl. In some embodiments, one R' is optionally substituted C_{1-6} aliphatic, and one R is optionally substituted phenyl. In some embodiments, each R' is independently optionally substituted C_{1-6} aliphatic. In some embodiments, G^2 is $-CH_2-P(O)(CH_3)Ph$. In some embodiments, G^2 is $-CH_2-P(O)(CH_3)_2$. In some embodiments, G^2 is $-CH_2-P(O)(Ph)_2$. In some embodiments, G^2 is $-CH_2-P(O)(OCH_3)_2$. In some embodiments, G^2 is $-CH_2-P(O)(CH_2Ph)_2$. In some embodiments, G^2 is $-CH_2-P(O)[N(CH_3)Ph]_2$. In some embodiments, G^2 is $-CH_2-P(O)[N(CH_3)_2]_2$. In some embodiments, G^2 is $-CH_2-P(O)[N(CH_2Ph)_2]_2$. In some embodiments, G^2 is $-CH_2-P(O)(OCH_3)_2$. In some embodiments, G^2 is $-CH_2-P(O)(OPh)_2$.

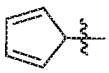
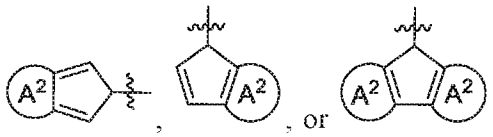
[00990] In some embodiments, G^2 is $-L'-SR'$. In some embodiments, G^2 is $-CH_2-SR'$. In some embodiments, R' is optionally substituted phenyl. In some embodiments, R' is phenyl.

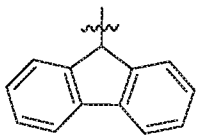
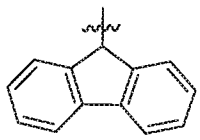
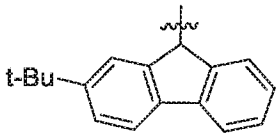
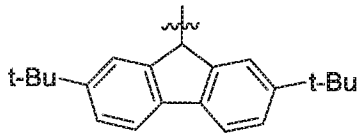
[00991] In some embodiments, a provided chiral reagent has the structure of  , wherein each R^1 is independently as described in the present disclosure. In some embodiments, a provided chiral reagent has the structure of  , wherein each R^1 is independently as described in the present disclosure. In some embodiments, each R^1 is independently R as described in the present disclosure. In some embodiments, each R^1 is independently R, wherein R is optionally substituted aliphatic, aryl, heteroaliphatic, or heteroaryl as described in the present disclosure. In some embodiments, each R^1 is phenyl. In some embodiments, R^1 is $-L-R'$. In some embodiments, R^1 is $-L-R'$, wherein L is

–O–, –S–, or –N(R')–. In some embodiments, a provided chiral reagent has the structure of  , wherein each X^1 is independently –H, an electron-withdrawing group, $–NO_2$, –CN, –OR, –Cl, –Br, or –F, and W is O or S. In some embodiments, a provided chiral reagent has the structure of  , wherein each X^1 is independently –H, an electron-withdrawing group, $–NO_2$, –CN, –OR, –Cl, –Br, or –F, and W is O or S. In some embodiments, each X^1 is independently –CN, –OR, –Cl, –Br, or –F, wherein R is not –H. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is $–CH_3$. In some embodiments, one or more X^1 are independently electron-withdrawing groups (e.g., –CN, $–NO_2$, halogen, $–C(O)R^1$, $–C(O)OR'$, $–C(O)N(R')_2$, $–S(O)R^1$, $–S(O)_2R^1$, $–P(W)(R^1)_2$, $–P(O)(R^1)_2$, $–P(O)(OR')_2$, $–P(S)(R^1)_2$, etc.).

[00992] In some embodiments, a provided chiral reagent has the structure of  , wherein R^1 is as described in the present disclosure. In some embodiments, a provided chiral reagent has the structure of  , wherein R^1 is as described in the present disclosure. In some embodiments, R^1 is R as described in the present disclosure. In some embodiments, R^1 is R, wherein R is optionally substituted aliphatic, aryl, heteroaliphatic, or heteroaryl as described in the present disclosure. In some embodiments, R^1 is –L–R'. In some embodiments, R^1 is –L–R', wherein L is –O–, –S–, or –N(R')–. In some embodiments, a provided chiral reagent has the structure of  , wherein X^1 is –H, an electron-withdrawing group, $–NO_2$, –CN, –OR, –Cl, –Br, or –F, and W is O or S.

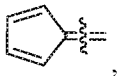
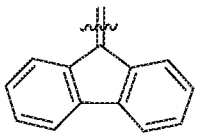
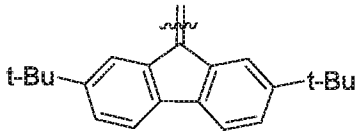
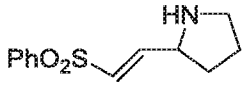
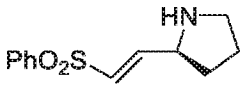
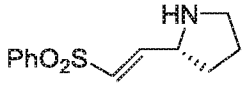
In some embodiments, a provided chiral reagent has the structure of  , wherein X^1 is −H, an electron-withdrawing group, $-NO_2$, −CN, −OR, −Cl, −Br, or −F, and W is O or S. In some embodiments, X^1 is −CN, −OR, −Cl, −Br, or −F, wherein R is not −H. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is $-CH_3$. In some embodiments, X^1 is an electron-withdrawing group (e.g., −CN, $-NO_2$, halogen, $-C(O)R^1$, $-C(O)OR'$, $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$,$-P(S)(R^1)_2$, etc.). In some embodiments, X^1 is an electron-withdrawing group that is not −CN, $-NO_2$, or halogen. In some embodiments, X^1 is not −H, −CN, $-NO_2$, halogen, or C_{1-3} alkyloxy.

[00993] In some embodiments, G^2 is $-CH(R^{21})-CH(R^{22})=C(R^{23})(R^{24})$, wherein each of R^{21}, R^{22}, R^{23}, and R^{24} is independently R. In some embodiments, R^{22} and R^{23} are both R, and the two R groups are taken together with their intervening atoms to form an optionally substituted aryl or heteroaryl ring as described herein. In some embodiments, one or more substituents are independently electron-withdrawing groups. In some embodiments, R^{21} and R^{24} are both R, and the two R groups are taken together with their intervening atoms to form an optionally substituted ring as described herein. In some embodiments, R^{21} and R^{24} are both R, and the two R groups are taken together with their intervening atoms to form an optionally substituted saturated or partially saturated ring as described herein. In some embodiments, R^{22} and R^{23} are both R, and the two R groups are taken together with their intervening atoms to form an optionally substituted aryl or heteroaryl ring as described herein, and R^{21} and R^{24} are both R, and the two R groups are taken together with their intervening atoms to form an optionally substituted partially saturated ring as described herein. In some embodiments, R^{21} is −H. In some embodiments, R^{24} is −H. In some embodiments, G^2 is optionally substituted  . In some embodiments, G^2 is optionally substituted  , wherein each Ring A^2 is independently a 3-15 membered monocyclic, bicyclic or polycyclic ring as described herein. In some embodiments, Ring A^2 is an optionally substituted 5-10 membered monocyclic aryl or heteroaryl ring having 1-5 heteroatoms as described herein. In some embodiments, Ring A^2 is an optionally substituted phenyl ring as described herein. In some embodiments, In some embodiments, G^2 is

optionally substituted  . In some embodiments, G^2 is  . In some embodiments, G^2 is  . In some embodiments, G^2 is  .

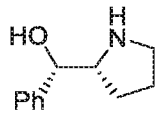
[00994] Certain useful example compounds for chiral auxiliaries are presented in, *e.g.*, Tables CA-1 to CA-13. In some embodiments, a useful compound is an enantiomer of a compound in, *e.g.*, Tables CA-1 to CA-13. In some embodiments, a useful compound is a diastereomer of a compound in, *e.g.*, Tables CA-1 to CA-13. In some embodiments, a compound useful for chiral auxiliaries for removal under basic conditions (*e.g.*, by a base under an anhydrous condition) is a compound of Tables CA-1 to CA-13, or an enantiomer or a diastereomer thereof. In some embodiments, such a compound is a compound of Table CA-1 or an enantiomer or a diastereomer thereof. In some embodiments, such a compound is a compound of Table CA-2 or an enantiomer or a diastereomer thereof. In some embodiments, such a compound is a compound of Table CA-3 or an enantiomer or a diastereomer thereof. In some embodiments, such a compound is a compound of Table CA-4 or an enantiomer or a diastereomer thereof. In some embodiments, such a compound is a compound of Table CA-5 or an enantiomer or a diastereomer thereof. In some embodiments, such a compound is a compound of Table CA-6 or an enantiomer or a diastereomer thereof. In some embodiments, such a compound is a compound of Table CA-7 or an enantiomer or a diastereomer thereof. In some embodiments, such a compound is a compound of Table CA-8 or an enantiomer or a diastereomer thereof. In some embodiments, such a compound is a compound of Table CA-9 or an enantiomer or a diastereomer thereof. In some embodiments, such a compound is a compound of Table CA-10 or an enantiomer or a diastereomer thereof. In some embodiments, such a compound is a compound of Table CA-11 or an enantiomer or a diastereomer thereof. In some embodiments, such a compound is a compound of Table CA-12 or an enantiomer or a diastereomer thereof. In some embodiments, such a compound is a compound of Table CA-13 or an enantiomer or a diastereomer thereof.

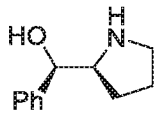
[00995] In some embodiments, when contacted with a base, a chiral auxiliary moiety, *e.g.*, of an internucleotidic linkage, whose corresponding compound is a compound of Formula 3-I or 3-AA may be released as an alkene, which has the same structure as a product formed by elimination of a water molecule from the corresponding compound (elimination of $-W^2-H$ = $-OH$ and an alpha-H of G^2). In some embodiments, such an alkene has the structure of (electron-withdrawing group)$_2$=C(R^1)–L–N(R^5)(R^6), (electron-withdrawing group)H=C(R^1)–L–N(R^5)(R^6), CH(–L"–R')=C(R^1)–L–N(R^5)(R^6) wherein the CH group is optionally substituted, or

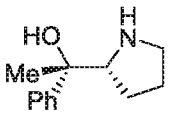
C^x=C(R^1)–L–N(R^5)(R^6), wherein C^x is optionally substituted  , and may be optionally fused with one or more optionally substituted rings, and each other variable is independently as described herein. In some embodiments, C^x is optionally substituted  . In some embodiments, C^x is  . In some embodiments, such an alkene is  . In some embodiments, such an alkene is  . In some embodiments, such an alkene is  .

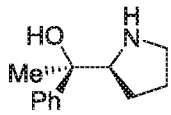
[00996] In some embodiments, a chiral reagent is an aminoalcohol. In some embodiments, a chiral reagent is an aminothiol. In some embodiments, a chiral reagent is an aminophenol. In some embodiments, a chiral reagent is (*S*)- and (*R*)-2-methylamino-1-phenylethanol, (1*R*, 2*S*)-ephedrine, or (1*R*, 2*S*)-2-methylamino-1,2-diphenylethanol.

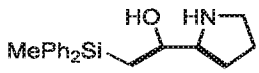
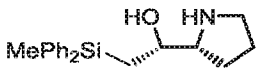
[00997] In some embodiments of the disclosure, a chiral reagent is a compound of one of the following formulae:


Formula O


Formula P

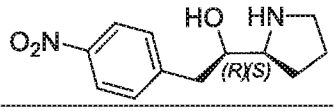
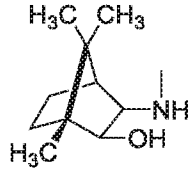
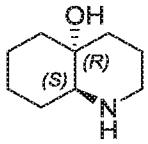
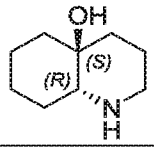
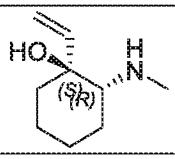
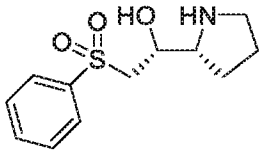
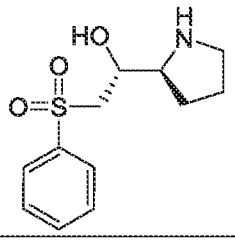
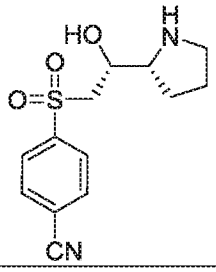
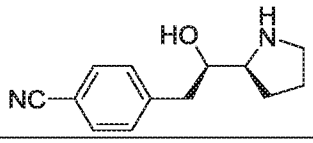
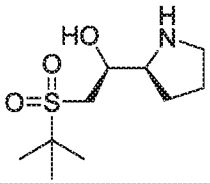

Formula Q

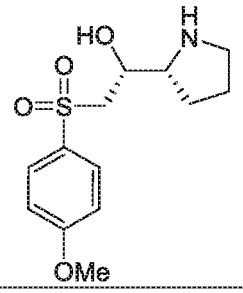
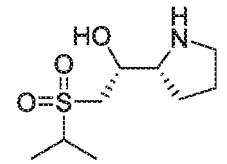
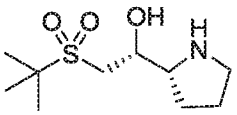
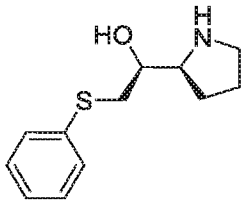
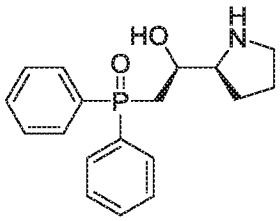
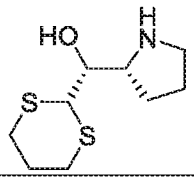
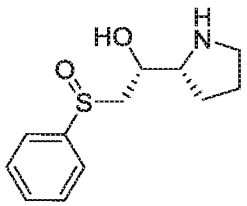
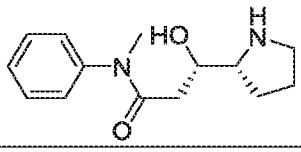

Formula R

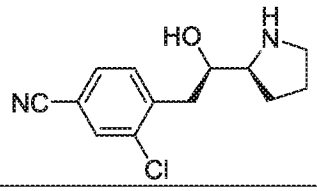
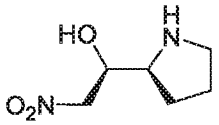
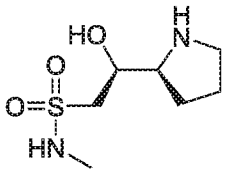
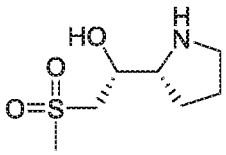
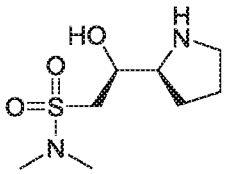
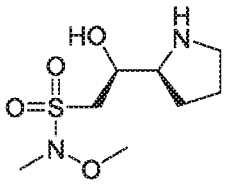
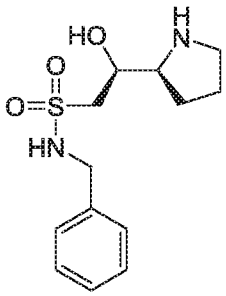
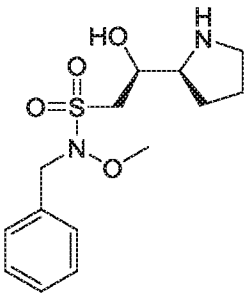


DPSE.

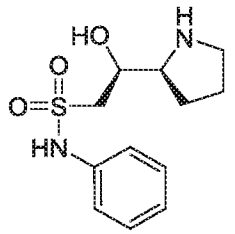
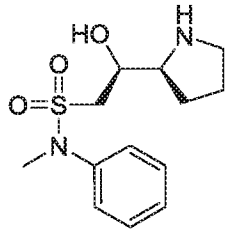
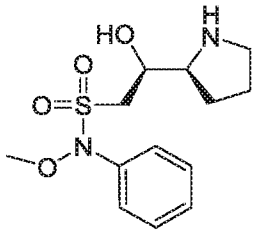
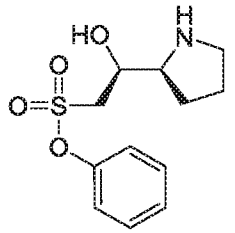
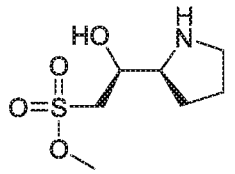
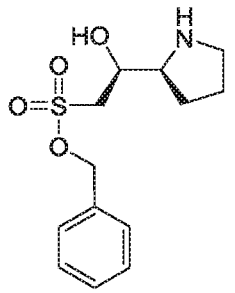
[00998] In some embodiments, a useful chiral reagent is a compound selected from the compounds below, or its related stereoisomer, particularly enantiomer (e.g., WV-CA-237 is a related stereoisomer of WV-CA-236 (a related diastereomer, having the same constitution, the same configuration at one chiral center but not the other); WV-CA-108 is a related enantiomer of WV-CA-236 (mirror image of each other)):

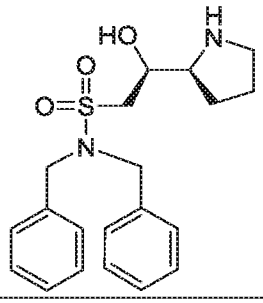
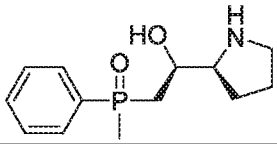
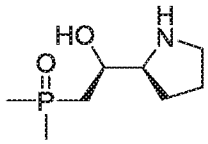
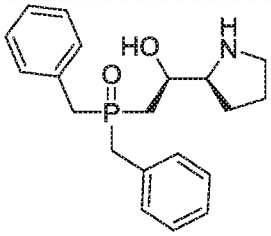
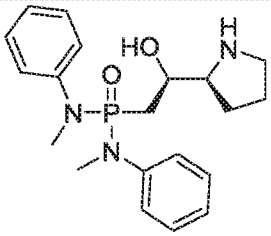
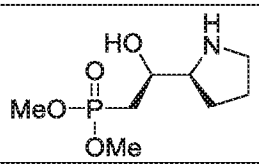
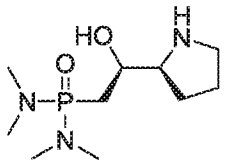
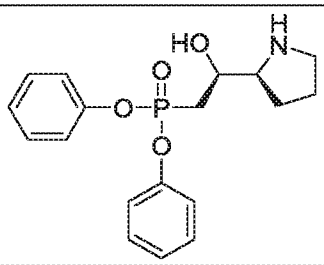
Table CA-1. Example chiral auxiliaries.

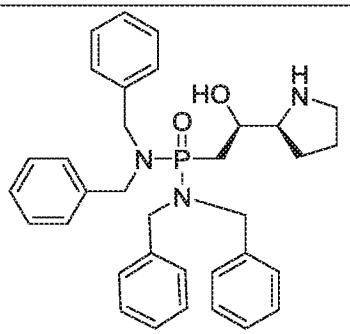
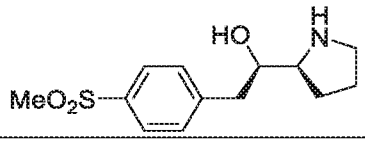
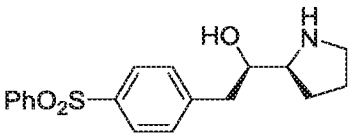
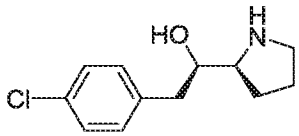
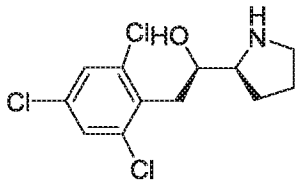
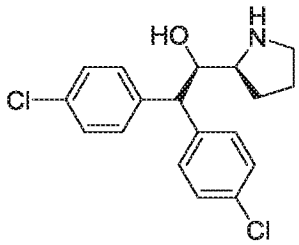
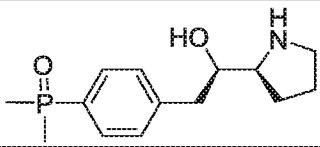
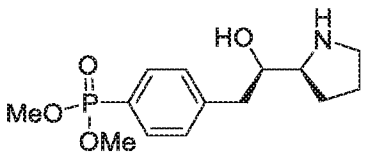
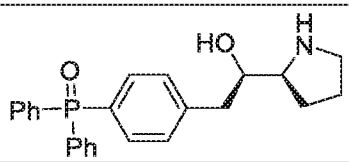
WV-CA-231	
WV-CA-232	
WV-CA-233	
WV-CA-234	
WV-CA-235	
WV-CA-236	
WV-CA-237	
WV-CA-238	
WV-CA-239	
WV-CA-240	

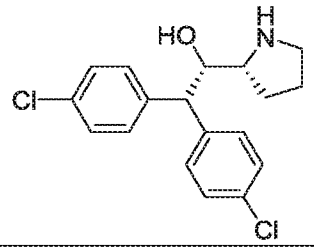
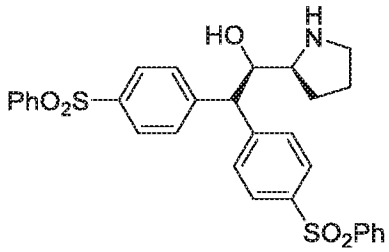
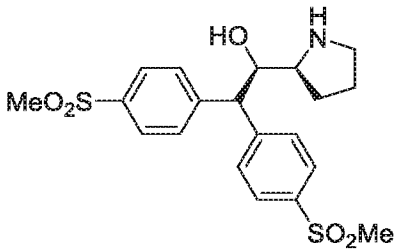
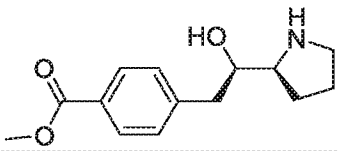
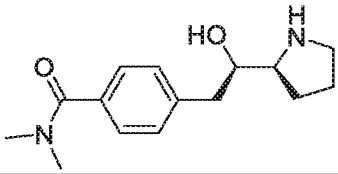
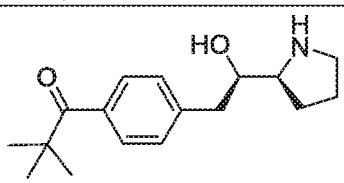
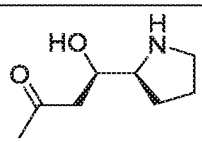
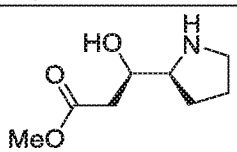
WV-CA-241	
WV-CA-242	
WV-CA-243	
WV-CA-244	
WV-CA-245	
WV-CA-246	
WV-CA-247	
WV-CA-248	

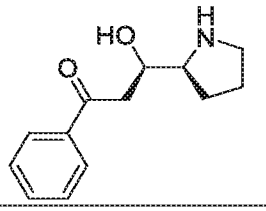
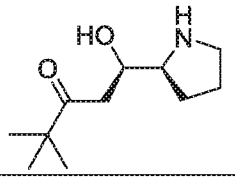
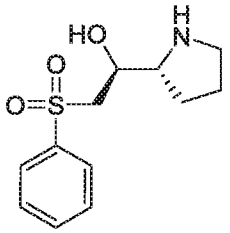
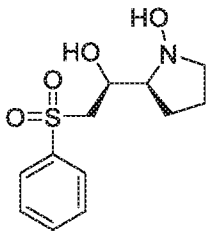
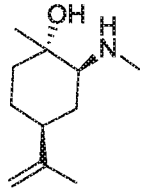
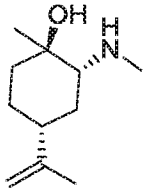
WV-CA-249	
WV-CA-250	
WV-CA-251	
WV-CA-252	
WV-CA-253	
WV-CA-254	
WV-CA-255	
WV-CA-256	

WV-CA-257	
WV-CA-258	
WV-CA-259	
WV-CA-260	
WV-CA-261	
WV-CA-262	

WV-CA-263	
WV-CA-264	
WV-CA-265	
WV-CA-266	
WV-CA-267	
WV-CA-268	
WV-CA-269	
WV-CA-270	

WV-CA-271	
WV-CA-272	
WV-CA-273	
WV-CA-274	
WV-CA-275	
WV-CA-276	
WV-CA-277	
WV-CA-278	
WV-CA-279	

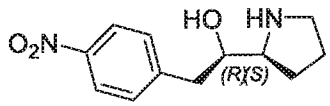
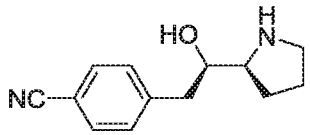
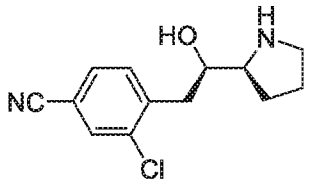
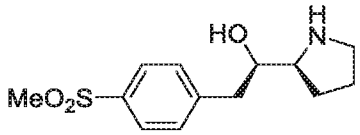
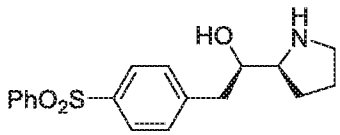
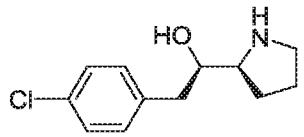
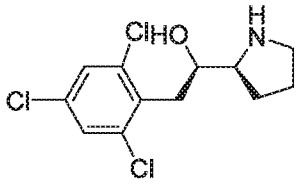
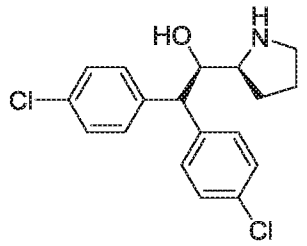
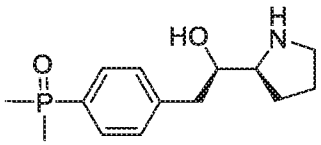
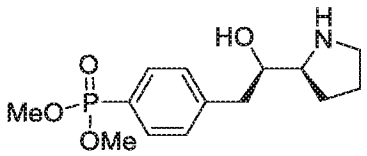
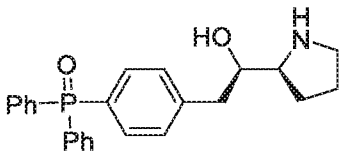
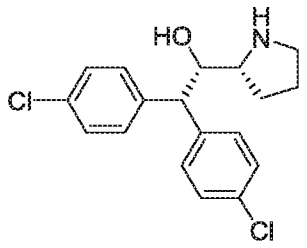
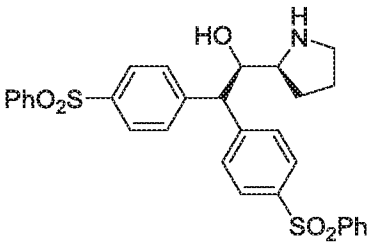
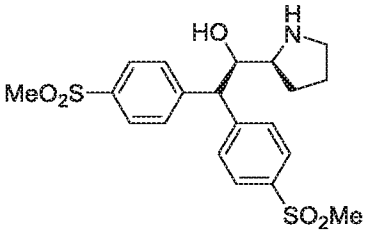
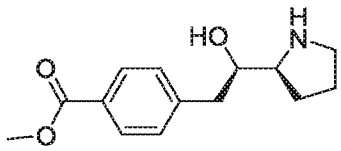
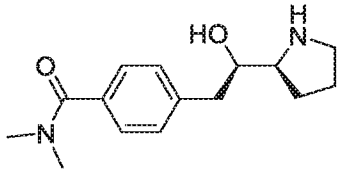
WV-CA-280	
WV-CA-281	
WV-CA-282	
WV-CA-283	
WV-CA-284	
WV-CA-285	
WV-CA-286	
WV-CA-287	

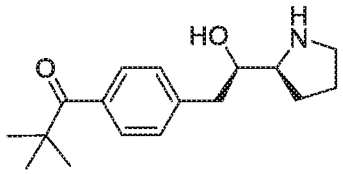
WV-CA-288	
WV-CA-289	
WV-CA-290	
WV-CA-291	
WV-CA-293	
WV-CA-294	

[00999] In some embodiments, a provided compound is an enantiomer of a compound selected from Table CA-1 or a salt thereof. In some embodiments, a provided compound is a diastereomer of a compound selected from Table CA-1 or a salt thereof.

[001000] In some embodiments, a useful chiral reagent is a compound selected from the compounds below, or its related stereoisomer, particularly enantiomer:

Table CA-2. Example chiral auxiliaries.

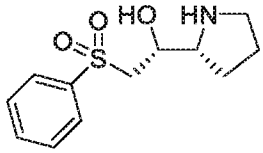
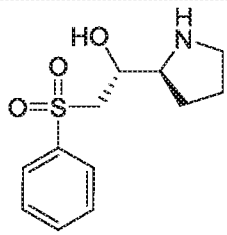
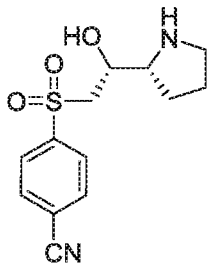
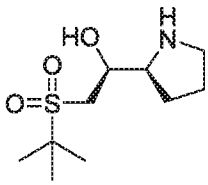
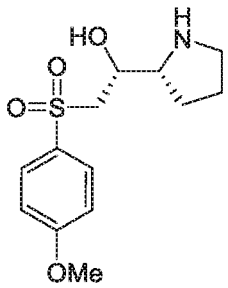
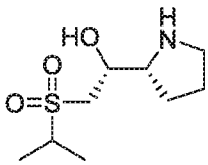
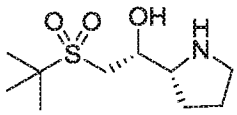
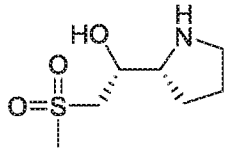
WV-CA-231		WV-CA-239	
WV-CA-249		WV-CA-272	
WV-CA-273		WV-CA-274	
WV-CA-275		WV-CA-276	
WV-CA-277		WV-CA-278	
WV-CA-279		WV-CA-280	
WV-CA-281		WV-CA-282	
WV-CA-283		WV-CA-284	

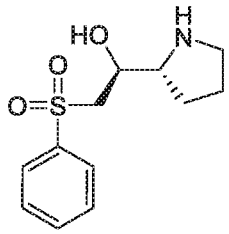
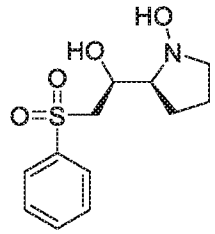
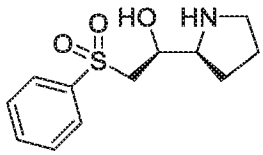
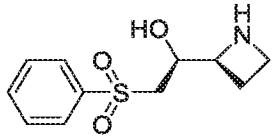
WV-CA-285			

[001001] In some embodiments, a provided compound is an enantiomer of a compound selected from Table CA-2 or a salt thereof. In some embodiments, a provided compound is a diastereomer of a compound selected from Table CA-2 or a salt thereof.

[001002] In some embodiments, a useful chiral reagent is a compound selected from the compounds below, or its related stereoisomer, particularly enantiomer:

Table CA-3. Example chiral auxiliaries.

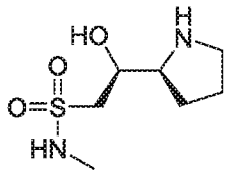
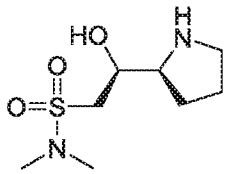
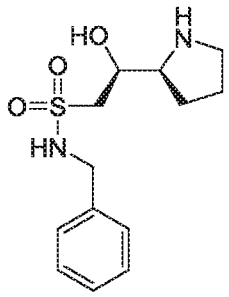
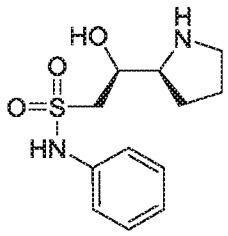
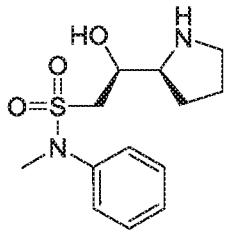
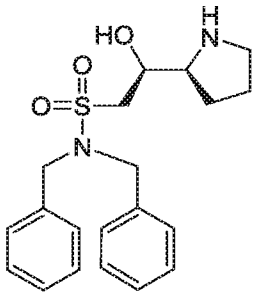
WV-CA-236		WV-CA-237	
WV-CA-238		WV-CA-240	
WV-CA-241		WV-CA-242	
WV-CA-243		WV-CA-252	

WV-CA-290		WV-CA-291	
WV-CA-108		WV-CA-183	

[001003] In some embodiments, a provided compound is an enantiomer of a compound selected from Table CA-3 or a salt thereof. In some embodiments, a provided compound is a diastereomer of a compound selected from Table CA-3 or a salt thereof.

[001004] In some embodiments, a useful chiral reagent is a compound selected from the compounds below, or its related stereoisomer, particularly enantiomer:

Table CA-4. Example chiral auxiliaries.

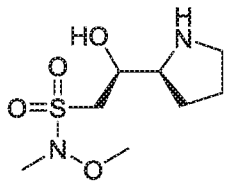
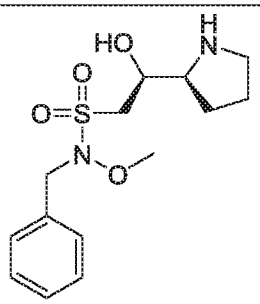
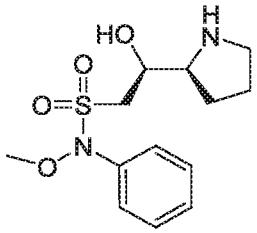
WV-CA-251		WV-CA-253	
WV-CA-255		WV-CA-257	
WV-CA-258		WV-CA-263	

[001005] In some embodiments, a provided compound is an enantiomer of a compound selected from Table CA-4 or a salt thereof. In some embodiments, a provided compound is a diastereomer of a

compound selected from Table CA-4 or a salt thereof.

[001006] In some embodiments, a useful chiral reagent is a compound selected from the compounds below, or its related stereoisomer, particularly enantiomer:

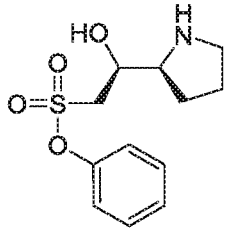
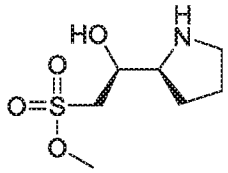
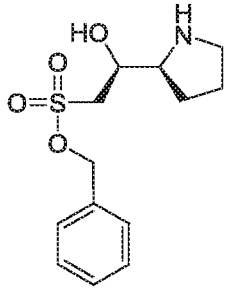
Table CA-5. Example chiral auxiliaries.

WV-CA-254		WV-CA-256	
WV-CA-259			

[001007] In some embodiments, a provided compound is an enantiomer of a compound selected from Table CA-5 or a salt thereof. In some embodiments, a provided compound is a diastereomer of a compound selected from Table CA-5 or a salt thereof.

[001008] In some embodiments, a useful chiral reagent is a compound selected from the compounds below, or its related stereoisomer, particularly enantiomer:

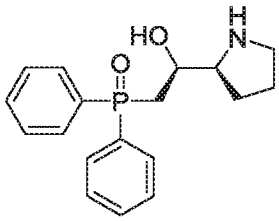
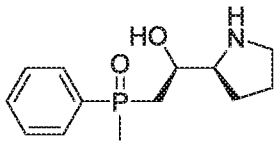
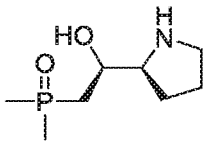
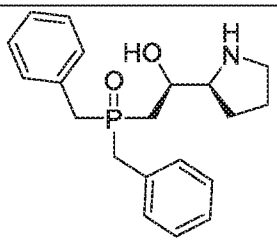
Table CA-6. Example chiral auxiliaries.

WV-CA-260		WV-CA-261	
WV-CA-262			

[001009] In some embodiments, a provided compound is an enantiomer of a compound selected from Table CA-6 or a salt thereof. In some embodiments, a provided compound is a diastereomer of a compound selected from Table CA-6 or a salt thereof.

[001010] In some embodiments, a useful chiral reagent is a compound selected from the compounds below, or its related stereoisomer, particularly enantiomer:

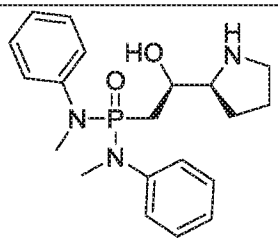
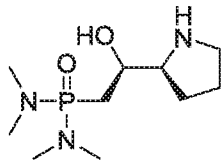
Table CA-7. Example chiral auxiliaries.

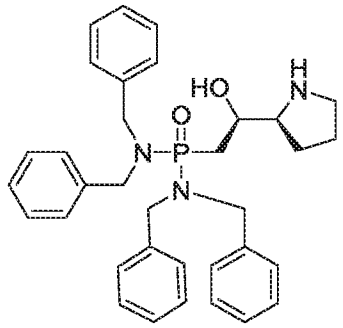
WV-CA-245		WV-CA-264	
WV-CA-265		WV-CA-266	

[001011] In some embodiments, a provided compound is an enantiomer of a compound selected from Table CA-7 or a salt thereof. In some embodiments, a provided compound is a diastereomer of a compound selected from Table CA-7 or a salt thereof.

[001012] In some embodiments, a useful chiral reagent is a compound selected from the compounds below, or its related stereoisomer, particularly enantiomer:

Table CA-8. Example chiral auxiliaries.

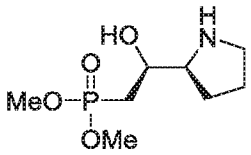
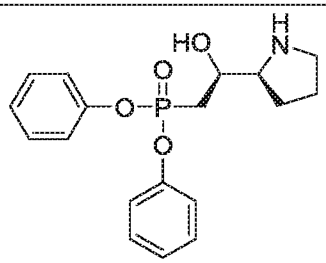
WV-CA-267		WV-CA-269	

WV-CA-271			

[001013] In some embodiments, a provided compound is an enantiomer of a compound selected from Table CA-8 or a salt thereof. In some embodiments, a provided compound is a diastereomer of a compound selected from Table CA-8 or a salt thereof.

[001014] In some embodiments, a useful chiral reagent is a compound selected from the compounds below, or its related stereoisomer, particularly enantiomer:

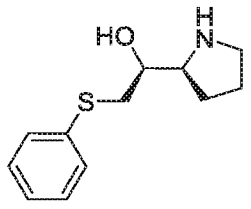
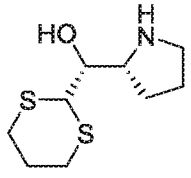
Table CA-9. Example chiral auxiliaries.

WV-CA-268		WV-CA-270	

[001015] In some embodiments, a provided compound is an enantiomer of a compound selected from Table CA-9 or a salt thereof. In some embodiments, a provided compound is a diastereomer of a compound selected from Table CA-9 or a salt thereof.

[001016] In some embodiments, a useful chiral reagent is a compound selected from the compounds below, or its related stereoisomer, particularly enantiomer:

Table CA-10. Example chiral auxiliaries.

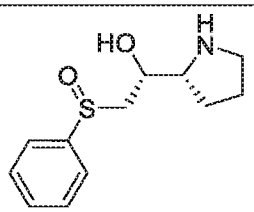
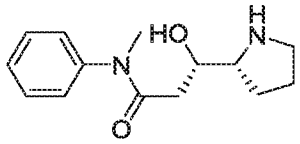
WV-CA-244		WV-CA-246	

[001017] In some embodiments, a provided compound is an enantiomer of a compound selected from Table CA-10 or a salt thereof. In some embodiments, a provided compound is a diastereomer of a

compound selected from Table CA-10 or a salt thereof.

[001018] In some embodiments, a useful chiral reagent is a compound selected from the compounds below, or its related stereoisomer, particularly enantiomer:

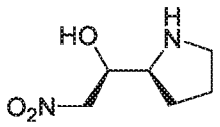
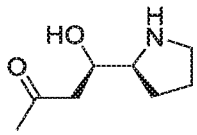
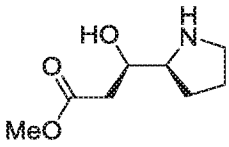
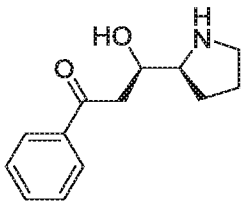
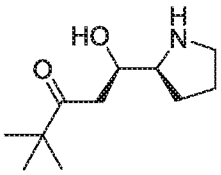
Table CA-11. Example chiral auxiliaries.

WV-CA-247		WV-CA-248	

[001019] In some embodiments, a provided compound is an enantiomer of a compound selected from Table CA-11 or a salt thereof. In some embodiments, a provided compound is a diastereomer of a compound selected from Table CA-11 or a salt thereof.

[001020] In some embodiments, a useful chiral reagent is a compound selected from the compounds below, or its related stereoisomer, particularly enantiomer:

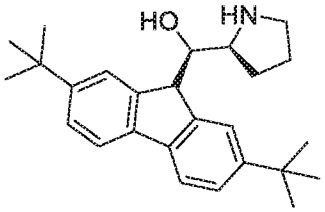
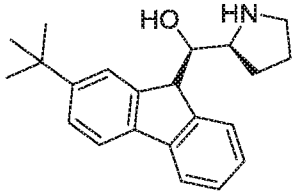
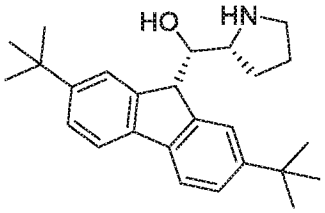
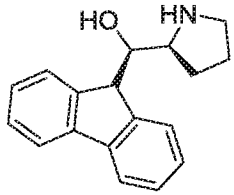
Table CA-12. Example chiral auxiliaries.

WV-CA-250		WV-CA-286	
WV-CA-287		WV-CA-288	
WV-CA-289			

[001021] In some embodiments, a provided compound is an enantiomer of a compound selected from Table CA-12 or a salt thereof. In some embodiments, a provided compound is a diastereomer of a compound selected from Table CA-12 or a salt thereof.

[001022] In some embodiments, a useful chiral reagent is a compound selected from the compounds below, or its related stereoisomer, particularly enantiomer:

Table CA-13. Example chiral auxiliaries.

WV-CA-110		WV-CA-315	
WV-CA-110b		WV-CA-324	

[001023] In some embodiments, a provided compound is an enantiomer of a compound selected from Table CA-13 or a salt thereof. In some embodiments, a provided compound is a diastereomer of a compound selected from Table CA-13 or a salt thereof.

[001024] As appreciated by those skilled in the art, chiral reagents are typically stereopure or substantially stereopure, and are typically utilized as a single stereoisomer substantially free of other stereoisomers. In some embodiments, compounds of the present disclosure are stereopure or substantially stereopure.

[001025] As demonstrated herein, when used for preparing a chiral internucleotidic linkage, to obtain stereoselectivity generally stereochemically pure chiral reagents are utilized. Among other things, the present disclosure provides stereochemically pure chiral reagents, including those having structures described.

[001026] The choice of chiral reagent, for example, the isomer represented by Formula Q or its stereoisomer, Formula R, permits specific control of chirality at a linkage phosphorus. Thus, either an *R*p or *S*p configuration can be selected in each synthetic cycle, permitting control of the overall three dimensional structure of a chirally controlled oligonucleotide. In some embodiments, a chirally controlled oligonucleotide has all *R*p stereocenters. In some embodiments of the disclosure, a chirally controlled oligonucleotide has all *S*p stereocenters. In some embodiments of the disclosure, each linkage phosphorus in the chirally controlled oligonucleotide is independently *R*p or *S*p. In some embodiments of the disclosure, each linkage phosphorus in the chirally controlled oligonucleotide is independently *R*p or *S*p, and at least one is *R*p and at least one is *S*p. In some embodiments, the selection of *R*p and *S*p centers is made to confer a specific three dimensional superstructure to a chirally controlled oligonucleotide. Examples of such selections are described in further detail herein.

[001027] In some embodiments, a provided oligonucleotide comprise a chiral auxiliary moiety,

e.g., in an internucleotidic linkage. In some embodiments, a chiral auxiliary is connected to a linkage phosphorus. In some embodiments, a chiral auxiliary is connected to a linkage phosphorus through W^2. In some embodiments, a chiral auxiliary is connected to a linkage phosphorus through W^2, wherein W^2 is O. Optionally, W^1, e.g., when W^1 is $-NG^5-$, is capped during oligonucleotide synthesis. In some embodiments, W^1 in a chiral auxiliary in an oligonucleotide is capped, e.g., by a capping reagent during oligonucleotide synthesis. In some embodiments, W^1 may be purposeful capped to modulate oligonucleotide property. In some embodiments, W^1 is capped with $-R^1$. In some embodiments, R^1 is $-C(O)R'$. In some embodiments, R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R' is methyl.

[001028] In some embodiments, a chiral reagent for use in accordance with the present disclosure is selected for its ability to be removed at a particular step in the above-depicted cycle. For example, in some embodiments it is desirable to remove a chiral reagent during the step of modifying the linkage phosphorus. In some embodiments, it is desirable to remove a chiral reagent before the step of modifying the linkage phosphorus. In some embodiments, it is desirable to remove a chiral reagent after the step of modifying the linkage phosphorus. In some embodiments, it is desirable to remove a chiral reagent after a first coupling step has occurred but before a second coupling step has occurred, such that a chiral reagent is not present on the growing oligonucleotide during the second coupling (and likewise for additional subsequent coupling steps). In some embodiments, a chiral reagent is removed during the "deblock" reaction that occurs after modification of the linkage phosphorus but before a subsequent cycle begins. Example methods and reagents for removal are described herein.

[001029] In some embodiments, removal of chiral auxiliary is achieved when performing the modification and/or deblocking step, as illustrated in Scheme I. It can be beneficial to combine chiral auxiliary removal together with other transformations, such as modification and deblocking. A person of ordinary skill in the art would appreciate that the saved steps/transformation could improve the overall efficiency of synthesis, for instance, with respect to yield and product purity, especially for longer oligonucleotides. One example wherein the chiral auxiliary is removed during modification and/or deblocking is illustrated in Scheme I.

[001030] In some embodiments, a chiral reagent for use in accordance with methods of the present disclosure is characterized in that it is removable under certain conditions. For instance, in some embodiments, a chiral reagent is selected for its ability to be removed under acidic conditions. In certain embodiments, a chiral reagent is selected for its ability to be removed under mildly acidic conditions. In certain embodiments, a chiral reagent is selected for its ability to be removed by way of an E1 elimination reaction (*e.g.*, removal occurs due to the formation of a cation intermediate on the chiral reagent under acidic conditions, causing the chiral reagent to cleave from the oligonucleotide). In some embodiments, a

chiral reagent is characterized in that it has a structure recognized as being able to accommodate or facilitate an E1 elimination reaction. One of skill in the relevant arts will appreciate which structures would be envisaged as being prone toward undergoing such elimination reactions.

[001031] In some embodiments, a chiral reagent is selected for its ability to be removed with a nucleophile. In some embodiments, a chiral reagent is selected for its ability to be removed with an amine nucleophile. In some embodiments, a chiral reagent is selected for its ability to be removed with a nucleophile other than an amine.

[001032] In some embodiments, a chiral reagent is selected for its ability to be removed with a base. In some embodiments, a chiral reagent is selected for its ability to be removed with an amine. In some embodiments, a chiral reagent is selected for its ability to be removed with a base other than an amine.

[001033] In some embodiments, chirally pure phosphoramidites comprising chiral auxiliaries may be isolated before use. In some embodiments, chirally pure phosphoramidites comprising chiral auxiliaries may be used without isolation - in some embodiments, they may be used directly after formation.

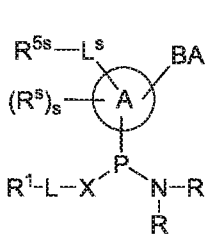
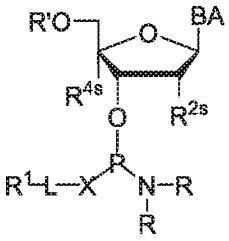
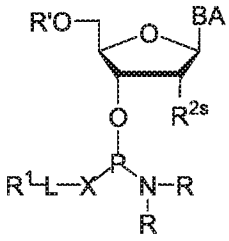
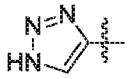
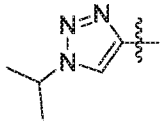
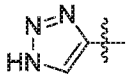
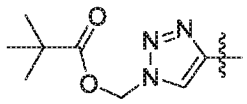
Activation

[001034] As appreciated by those skilled in the art, oligonucleotide preparation may use various conditions, reagents, etc. to active a reaction component, e.g., during phosphoramidite preparation, during one or more steps during in the cycles, during post-cycle cleavage/deprotection, etc. Various technologies for activation can be utilized in accordance with the present disclosure, including but not limited to those described in US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, WO 2017/210647, WO 2018/223056, WO 2018/237194, and/or WO 2019/055951, the activation technologies of each of which are incorporated by reference. Certain activation technologies, e.g., reagents, conditions, methods, etc. are illustrated in the Examples.

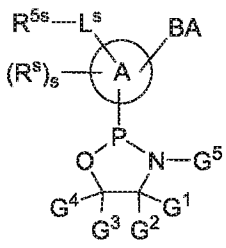
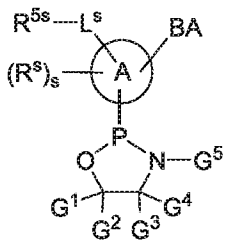
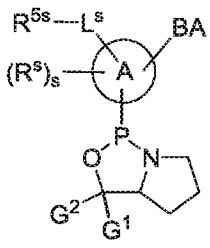
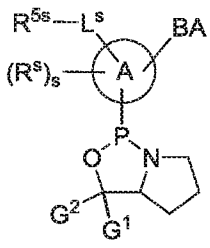
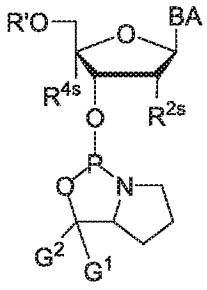
Coupling

[001035] In some embodiments, cycles of the present disclosure comprise stereoselective condensation/coupling steps to form chirally controlled internucleotidic linkages. For condensation, often an activating reagent is used, such as 4,5-dicyanoimidazole (DCI), 4,5-dichloroimidazole, 1-phenylimidazolium triflate (PhIMT), benzimidazolium triflate (BIT), benztriazole, 3-nitro-1,2,4-triazole (NT), tetrazole, 5-ethylthiotetrazole (ETT), 5-benzylthiotetrazole (BTT), 5-(4-nitrophenyl)tetrazole, *N*-cyanomethylpyrrolidinium triflate (CMPT), *N*-cyanomethylpiperidinium triflate, *N*-

cyanomethyldimethylammonium triflate, etc. Suitable conditions and reagents, including chiral phosphoramidites, include those described in US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, WO 2017/210647, WO 2018/223056, WO 2018/237194, and/or WO 2019/055951, the condensation reagents, conditions and methods of each of which are incorporated by reference. Certain coupling technologies, e.g., reagents, conditions, methods, etc. are illustrated in the Examples.

[001036] In some embodiments, a phosphoramidite for coupling has the structure of  ,  , or  , wherein each variable is independently as described in the present disclosure. In some embodiments, each R is independently optionally substituted C_{1-6} aliphatic. A person skill in the art will appreciate that two R groups in any structure or formula can either be the same or different. In some embodiments, each R is independently optionally substituted C_{1-6} alkyl. In some embodiments, each R is independently optionally substituted C_{1-6} alkenyl. In some embodiments, each R is independently optionally substituted C_{1-6} alkynyl. In some embodiments, each R is indenpendtly isopropyl. In some embodiments, $-X-L-R^1$ comprises an optionally substituted triazole group. In some embodiments, X is a covalent bond. In some embodiments, L is a covalent bond. In some embodiments, $-X-L-R^1$ is R^1. In some embodiments, R^1 comprise an optionally substituted ring. In some embodiments, R^1 is R as described herein. In some embodiments, R^1 is optionally substituted  . In some embodiments, R^1 is  . In some embodiments, R^1 is  .In some embodiments, R^1 is  . In some embodiments, $-L-$ comprises C_{1-6} alkylene. In some embodiments, $-L-$ comprises C_{1-6} alkenylene. In some embodiments, $-L-$ comprises . In some embodiments, R^1 is R as described herein. In some embodiments, $-L-$ is and R^1 is H. In some embodiments, $-L-R^1$ is . In some embodiments, $-X-L-R^1$ is . In some embodiments, $-X-L-R^1$ is $-OCH_2CH_2CN$.

[001037] In some embodiments, a chiral phosphoramidite for coupling has the structure of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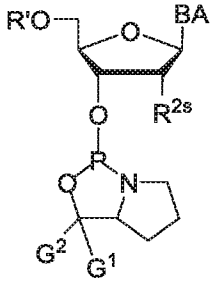
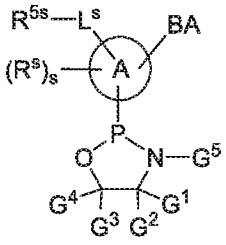

, wherein each variable is independently as described in the present disclosure. In some embodiments, a chiral phosphoramidite for coupling has the structure of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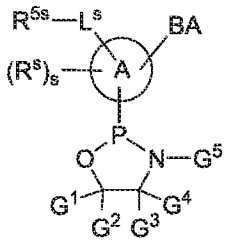
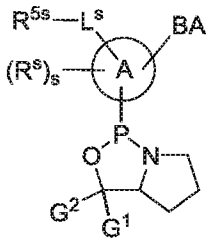
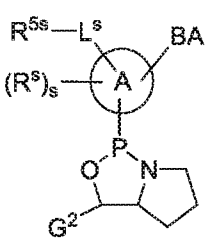
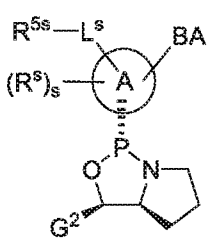
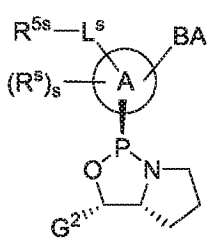
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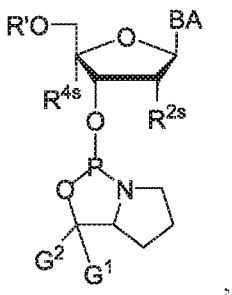
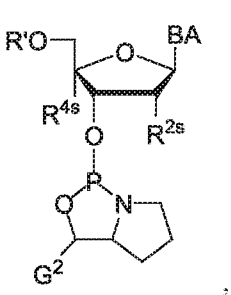
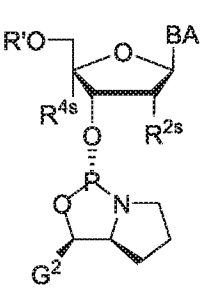
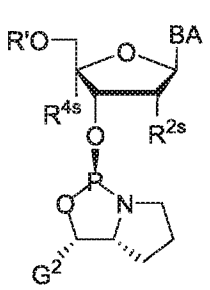
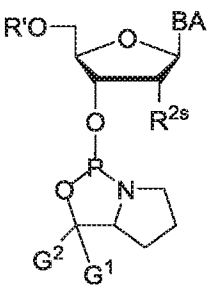
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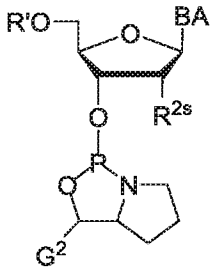
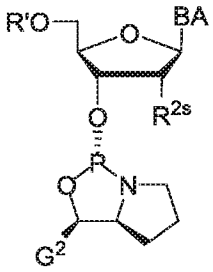
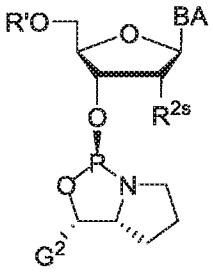
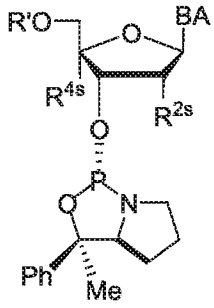
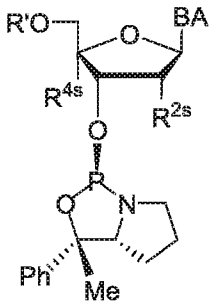




. In some embodiments, a chiral phosphoramidite for coupling has the structure of

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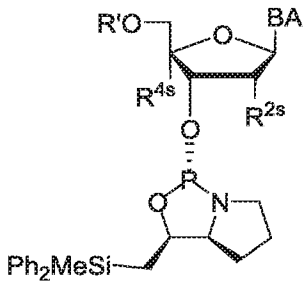
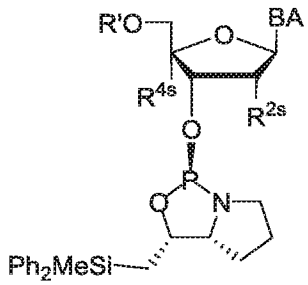
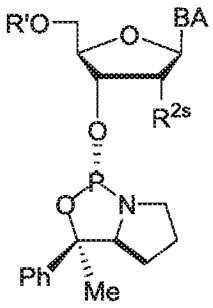
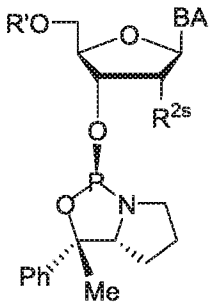

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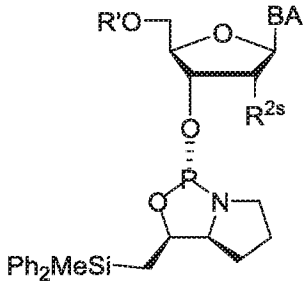
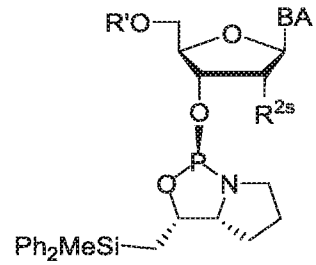
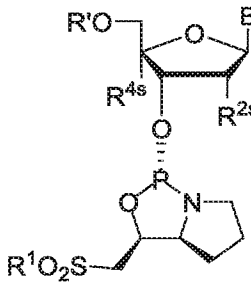
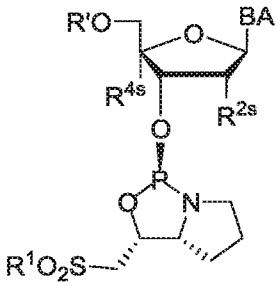
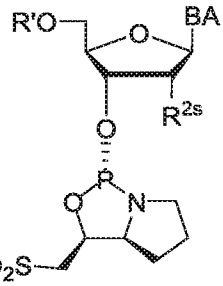



, wherein each variable is independently as described in the present disclosure. In some embodiments, G^1 or G^2 comprises an electron-withdrawing group as described in the present disclosure. In some embodiments, a chiral phosphoramidite for coupling has the structure of

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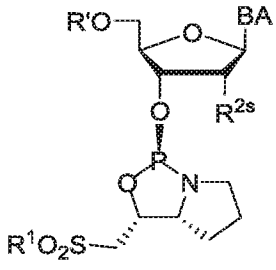
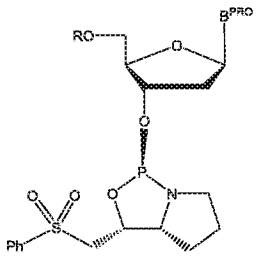
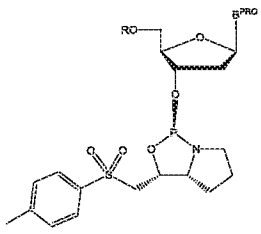
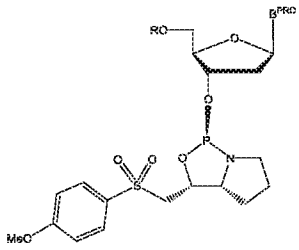
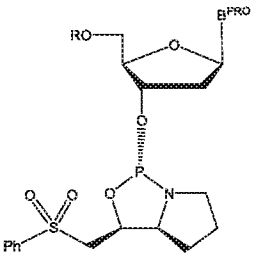
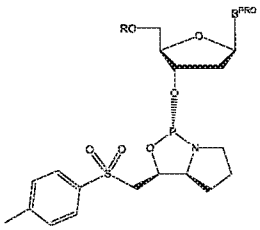
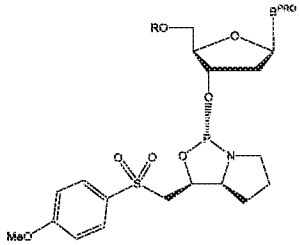
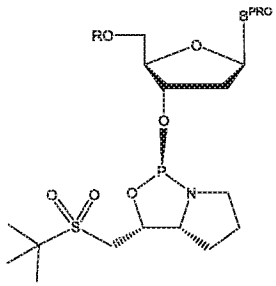
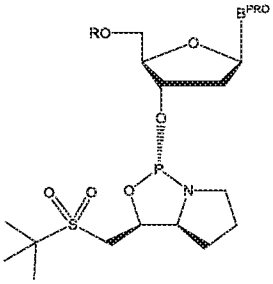
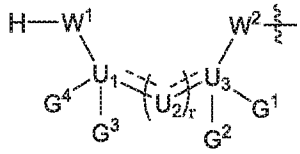
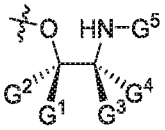
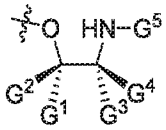
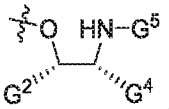
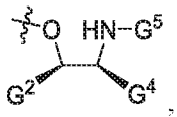
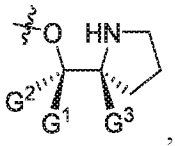
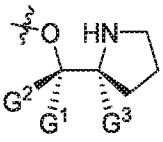
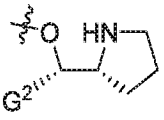
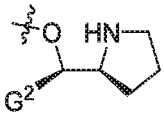










, wherein each variable is independently as described in the present disclosure. In some embodiments, R^1 is R' as described in the present disclosure. In some embodiments, R^1 is R as described in the present disclosure. In some embodiments, R is optionally substituted phenyl as described in the present disclosure. In some embodiments, R is phenyl. In some embodiments, R is 4-methyl phenyl. In some embodiments, R is 4-methoxy phenyl. In some embodiments, R is optionally substituted C_{1-6} aliphatic as described in the present disclosure. In some embodiments, R is optionally substituted C_{1-6} alkyl as described in the present disclosure. For example, in some embodiments, R is methyl; in some embodiments, R is isopropyl; in some embodiments, R is t-butyl; etc.

[001038] In some embodiments, R^{5s}–L^5– is R'O–. In some embodiments, R'O– is DMTrO–. In some embodiments, R^{4s} is –H. In some embodiments, R^{4s} and R^{2s} are taken together to form a bridge –L–O– as described in the present disclosure. In some embodiments, the –O– is connected to the carbon at the 2' position. In some embodiments, L is $-CH_2-$. In some embodiments, L is –CH(Me)–. In some embodiments, L is –(*R*)–CH(Me)–. In some embodiments, L is –(*S*)–CH(Me)–. In some embodiments, R^{2s} is –H. In some embodiments, R^{2s} is –F. In some embodiments, R^{2s} is –OR'. In some embodiments, R^{2s} is –OMe. In some embodiments, R^{2s} is –MOE. As appreciated by those skilled in the art, BA may be suitably protected during synthesis.

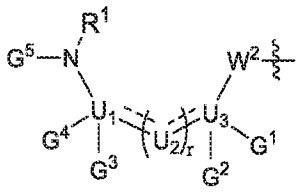
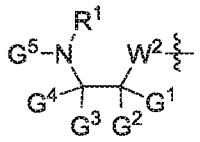
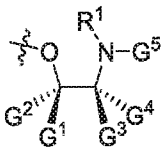
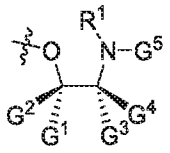
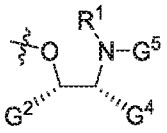
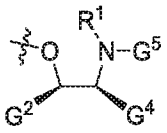
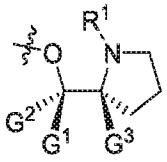
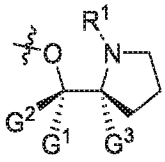
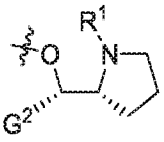
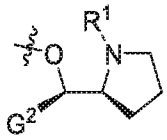
[001039] In some embodiments, an internucleotidic linkage formed in a coupling step has the

structure of formula I or a salt form thereof. In some embodiments, P^L is P. In some embodiments, $-X-L-R^1$ is  , ,  ,  ,  ,  ,  ,  ,  , or  , wherein each variable is independently in accordance with the present disclosure. In some embodiments, $-X-L-R^1$ is $-CH_2CH_2CN$.

[001040] In some embodiments, a coupling forms an internucleotidic linkage with a stereoselectivity of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more. In some embodiments, the stereoselectivity is 85% or more. In some embodiments, the stereoselectivity is 85% or more. In some embodiments, the stereoselectivity is 90% or more. In some embodiments, the stereoselectivity is 91% or more. In some embodiments, the stereoselectivity is 92% or more. In some embodiments, the stereoselectivity is 93% or more. In some embodiments, the stereoselectivity is 94% or more. In some embodiments, the stereoselectivity is 95% or more. In some embodiments, the stereoselectivity is 96% or more. In some embodiments, the stereoselectivity is 97% or more. In some embodiments, the stereoselectivity is 98% or more. In some embodiments, the stereoselectivity is 99% or more.

Capping

[001041] If the final nucleic acid is larger than a dimer, the unreacted -OH moiety is generally capped with a blocking/capping group. Chiral auxiliaries in oligonucleotides may also be capped with a blocking group to form a capped condensed intermediate. Suitable capping technologies (e.g., reagents, conditions, etc.) include those described in US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, WO 2017/210647, WO 2018/223056, WO 2018/237194, and/or WO 2019/055951, the capping technologies of each of which are incorporated by reference. In some embodiments, a capping reagent is a carboxylic acid or a derivate thereof. In some embodiments, a capping reagent is R'COOH. In some embodiments, a capping step introduces R'COO− to unreacted 5'-OH group and/or amino groups in chiral auxiliaries. In some embodiments, a cycle may comprise two or more capping steps. In some embodiments, a cycle comprises a first capping before modification of a coupling product (e.g., converting P(III) to P(V)), and another capping after modification of a coupling

product. In some embodiments, a first capping is performed under an amidation condition, e.g., which comprises an acylating reagent (e.g., an anhydride having the structure of $(RC(O))_2O$, (e.g., Ac_2O)) and a base (e.g., 2,6-lutidine). In some embodiments, a first capping caps an amino group, e.g., that of a chiral auxiliary in an internucleotidic linkage. In some embodiments, an internucleotidic linkage formed in a coupling step has the structure of formula I or a salt form thereof. In some embodiments, P^L is P. In some embodiments, $-X-L-R^1$ is  ,  ,  ,  ,  ,  ,  ,  ,  , or  , wherein each variable is independently in accordance with the present disclosure. In some embodiments, R^1 is $R-C(O)-$. In some embodiments, R is CH_3-. In some embodiments, each chirally controlled coupling (e.g., using a chiral auxiliary) is followed with a first capping. Typically, cycles for non-chirally controlled coupling using traditional phosphoramidite to construct natural phosphate linkages do not contain a first capping. In some embodiments, a second capping is performed, e.g., under an esterification condition (e.g., capping conditions of traditional phosphoramidite oligonucleotide synthesis) wherein free 5'−OH are capped.

[001042] Certain capping technologies, e.g., reagents, conditions, methods, etc. are illustrated in the Examples.

Modifying

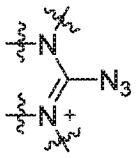
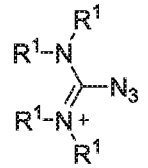
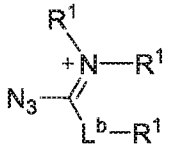
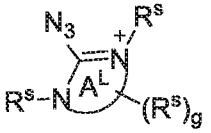
[001043] In some embodiments, an internucleotidic linkage wherein its linkage phosphorus exists as P(III) is modified to form another modified internucleotidic linkage (e.g., one of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, **III**, or a salt form thereof) or a natural phosphate linkage. In many embodiments, P(III) is modified by reaction with an electrophile. Various types of reactions suitable for P(III) may be utilized in accordance with the present disclosure. Suitable modifying technologies (e.g., reagents (e.g., sulfurization reagent, oxidation reagent, etc.), conditions, etc.) include those described in US 9695211, US 9605019, US 9598458, US

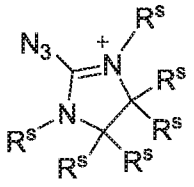
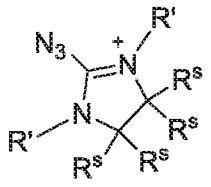
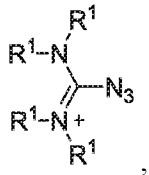
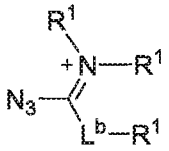
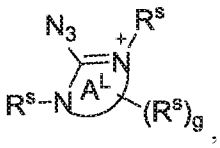
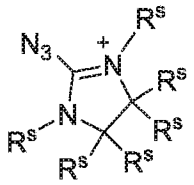
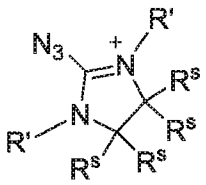
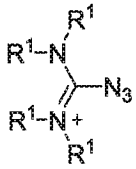
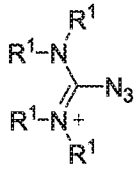
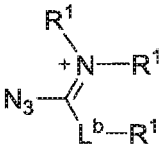
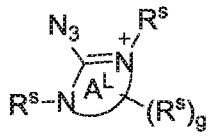
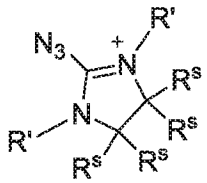
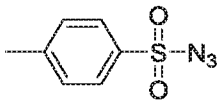
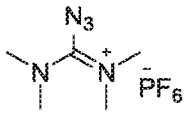
2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, WO 2017/210647, WO 2018/223056, WO 2018/237194, and/or WO 2019/055951, the modifying technologies of each of which are incorporated by reference.

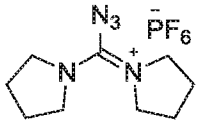
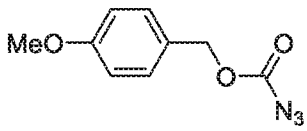
[001044] In some embodiments, as illustrated in the Examples, the present disclosure provides modifying reagents for introducing non-negatively charged internucleotidic linkages including neutral internucleotidic linkages.

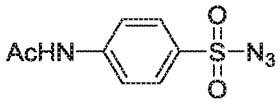
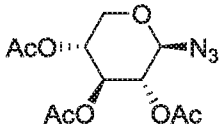
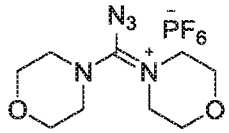
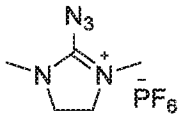
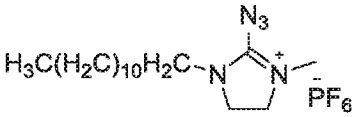
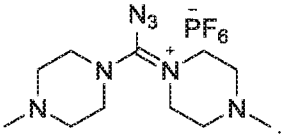
[001045] In some embodiments, modifying is within a cycle. In some embodiments, modifying can be outside of a cycle. For example, in some embodiments, one or more modifying steps can be performed after the oligonucleotide chain has been reached to introduce modifications simultaneously at one or more internucleotidic linkages and/or other locations.

[001046] In some embodiments, modifying comprises use of click chemistry, e.g., wherein an alkyne group of an oligonucleotide, e.g., of an internucleotidic linkage, is reacted with an azide. Various reagents and conditions for click chemistry can be utilized in accordance with the present disclosure. In some embodiments, an azide has the structure of R^1–N_3, wherein R^1 is as described in the present disclosure. In some embodiments, R^1 is optionally substituted C_{1-6} alkyl. In some embodiments, R^1 is isopropyl.

[001047] In some embodiments, as demonstrated in the examples, a P(III) linkage can be converted into a non-negatively charged internucleotidic linkage by reacting the P(III) linkage with an azide or an azido imidazolinium salt (e.g., a compound comprising  ; in some embodiments, referred to as an azide reaction) under suitable conditions. In some embodiments, an azido imidazolinium salt is a salt of PF_6^-. In some embodiments, an azido imidazolinium salt is a salt of  . In some embodiments, a useful reagent, e.g., an azido imidazolinium salt, is a salt of  . In some embodiments, a useful reagent is a salt of  . In some embodiments, a useful reagent is a

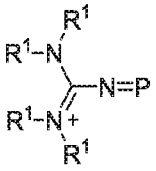
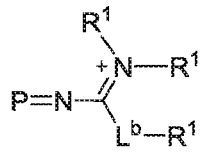
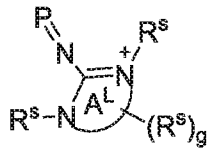
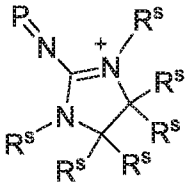
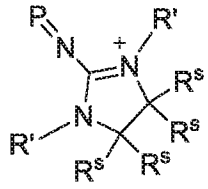
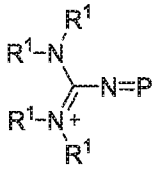
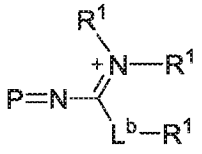
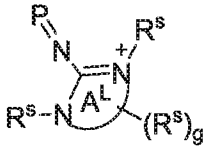
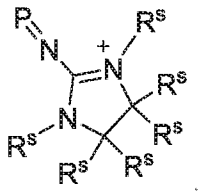
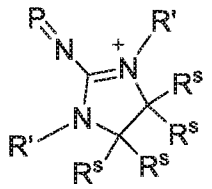
salt of  . In some embodiments, a useful reagent is a salt of  . Such reagents comprising nitrogen cations also contain counter anions (e.g., Q^- as described in the present disclosure), which are widely known in the art and are contained in various chemical reagents. In some embodiments, a useful reagent is Q^+Q^-, wherein Q^+ is  ,  ,  ,  , or  , and Q^- is a counter anion. In some embodiments, Q^+ is  . In some embodiments, Q^+ is  . In some embodiments, Q^+ is  . In some embodiments, Q^+ is  . In some embodiments, Q^+ is  . As appreciated by those skilled in the art, in a compound having the structure of Q^+Q^-, typically the number of positive charges in Q^+ equals the number of negative charges in Q^-. In some embodiments, Q^+ is a monovalent cation and Q^- is a monovalent anion. In some embodiments, Q^- is F^-, Cl^-, Br^-, BF_4^-, PF_6^-, TfO^-, Tf_2N^-, AsF_6^-, ClO_4^-, or SbF_6^-. In some embodiments, Q^- is PF_6^-. Those skilled in the art readily appreciate that many other types of counter anions are available and can be utilized in accordance with the present disclosure. In some embodiments, an azido imidazolinium salt is 2-azido-1,3-dimethylimidazolinium hexafluorophosphate. In some embodiments, an azide is  . In some embodiments, an azido imidazolinium salt is  . In some embodiments, an azido

imidazolinium salt is  . In some embodiments, an azide is  .

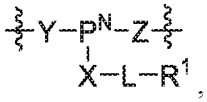
In some embodiments, an azide is  . In some embodiments, an azide is  . In some embodiments, an azido imidazolinium salt is  . In some embodiments, an azido imidazolinium salt is  . In some embodiments, an azido imidazolinium salt is  . In some embodiments, an azido imidazolinium salt is  .

[001048] In some embodiments, a P(III) linkage is reacted with an electrophile having the structure of $R-G^Z$, wherein R is as described in the present disclosure, and G^Z is a leaving group, e.g., –Cl, –Br, –I, –OTf, –Oms, –OTosyl, etc. In some embodiments, R is $-CH_3$. In some embodiments, R is $-CH_2CH_3$. In some embodiments, R is $-CH_2CH_2CH_3$. In some embodiments, R is $-CH_2OCH_3$. In some embodiments, R is $CH_3CH_2OCH_2-$. In some embodiments, R is $PhCH_2OCH_2-$. In some embodiments, R is $HC\equiv C-CH_2-$. In some embodiments, R is $H_3C-C\equiv C-CH_2-$. In some embodiments, R is $CH_2=CHCH_2-$. In some embodiments, R is CH_3SCH_2-. In some embodiments, R is $-CH_2COOCH_3$. In some embodiments, R is $-CH_2COOCH_2CH_3$. In some embodiments, R is $-CH_2CONHCH_3$.

[001049] In some embodiments, after a modifying step, a P(III) linkage phosphorus is converted into a P(V) internucleotidic linkage. In some embodiments, a P(III) linkage phosphorus is converted into a P(V) internucleotidic linkage, and all groups bounded to the linkage phosphorus remain unchanged. In some embodiments, a linkage phosphorus is converted from P into P(=O). In some embodiments, a linkage phosphorus is converted from P into P(=S). In some embodiments, a linkage phosphorus is converted from P into $P(=N-L-R^5)$. In some embodiments, a linkage phosphorus is converted from P

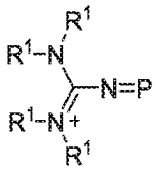
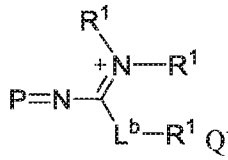
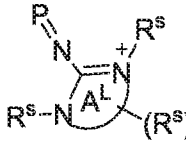
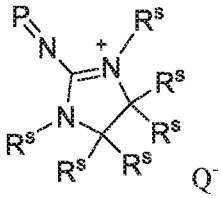
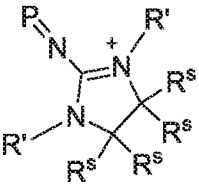
into  ,  ,  ,  , or  , wherein each variable is independently as described in the present disclosure. In some embodiments, P is converted into  . In some embodiments, P is converted into  . In some embodiments, P is converted into  . In some embodiments, P is converted into  . In some embodiments, P is converted into  . As appreciated by those skilled in the art, for each cation there typically exists a counter anion so that the total number of positive charges equals the total number of negative charges in a system (e.g., compound, composition, etc.). In some embodiments, a counter anion is Q^- as described in the present disclosure (e.g., F^-, Cl^-, Br^-, BF_4^-, PF_6^-, TfO^-, Tf_2N^-, AsF_6^-, ClO_4^-, SbF_6^-, etc.). In some embodiments, an internucleotidic linkage having the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof, wherein P^L is P, is converted into an internucleotidic linkage having the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, **III**, or a salt form thereof, wherein P^L is P(=W) or P→B(R')$_3$ or P^N. In some embodiments, an internucleotidic linkage having the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof, wherein P^L is P, is converted into an internucleotidic linkage having the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof, wherein P^L is P(=W) or P→B(R')$_3$. In some embodiments, a linkage phosphorus P, which is P^L in an internucleotidic linkage having the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof is converted into P^L which is P(=W) or P→B(R')$_3$. In some embodiments, a linkage phosphorus P, which is P^L in an internucleotidic linkage having the structure of formula **I** or a salt form thereof is converted into P^L which is P(=W) or

P→B(R')$_3$. In some embodiments, W is O (e.g., for an oxidation reaction). In some embodiments, W is S (e.g., for a sulfurization reaction). In some embodiments, W is =N–L–R^5 (e.g., for an azide reaction). In some embodiments, an internucleotidic linkage having the structure of formula I or a salt form thereof (e.g., wherein P^L is P) is converted into an internucleotidic linkage having the structure of formula III or a salt form thereof:



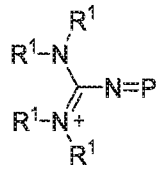
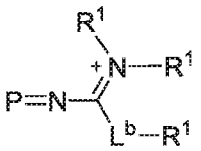
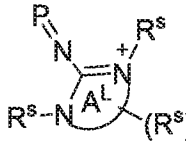
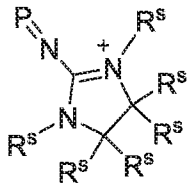
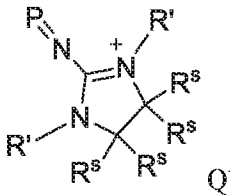
III

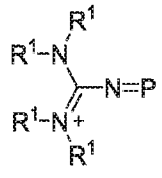
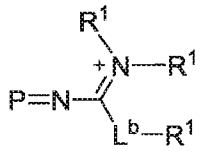
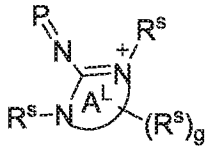
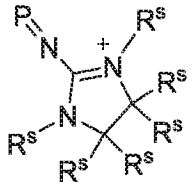
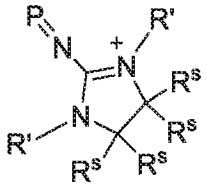
wherein:

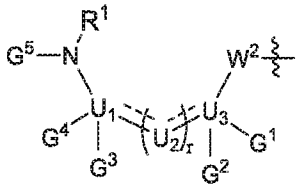
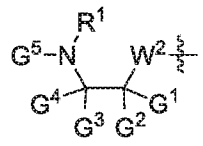
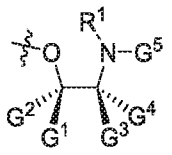
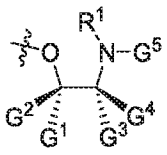
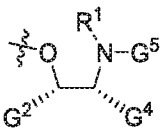
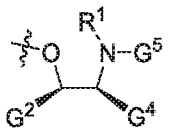
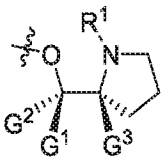
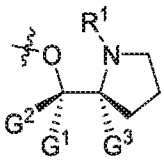
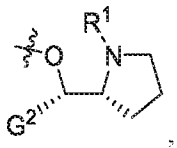
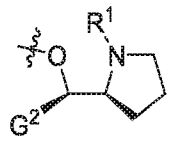
P^N is P(=N–L–R^5),  Q$^-$,  Q$^-$,  Q$^-$,  Q$^-$,  Q$^-$,

Q$^-$ is an anion, and

each other variables is independently as described in the present disclosure.

[001050] In some embodiments, P^N is P(=N–L–R^5). In some embodiments, P^N is  Q$^-$. In some embodiments, P^N is  Q$^-$. In some embodiments, P^N is  Q$^-$. In some embodiments, P^N is  Q$^-$. In some embodiments, P^N is  Q$^-$. In some embodiments, internucleotidic linkages of the present disclosure may exist in a salt form. In some embodiments, internucleotidic linkages of formula III may exist in a salt form. In some embodiments, in

a salt form of an internucleotidic linkage of formula **III** P^N is  ,  ,  ,  , or  . In some embodiments, P^N is $P{=}W^N$, wherein W^N is as described herein.

[001051] In some embodiments, Y, Z, and $-X-L-R^1$ remains the same during the conversion. In some embodiments, each of X, Y and Z is independently –O–. In some embodiments, as described herein, $-X-L-R^1$ is of such a structure that $H-X-L-R^1$ is a chiral reagent described herein, or a capped chiral reagent described herein wherein an amino group of the chiral reagent (typically of $-W^1-H$ or $-W^2-H$, which comprises an amino group $-NHG^5-$) is capped, e.g., with –C(O)R' (replacing a –H, e.g., $-N[-C(O)R']G^5-$). In some embodiments, $-X-L-R^1$ is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , wherein each variable is independently in accordance with the present disclosure. In some embodiments, wherein R^1 is –C(O)R. In some embodiments, R^1 is $CH_3C(O)-$. In some embodiments, as described herein, G^2 comprises an electron-withdrawing group. In some embodiments, G^2 is $-CH_2SO_2Ph$.

[001052] In some embodiments, an internucleotidic linkage (e.g., a modified internucleotidic linkage, a chiral internucleotidic linkage, a chirally controlled internucleotidic linkage, a non-negatively charged internucleotidic linkage, a neutral internucleotidic linkage, etc.) has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof, wherein P^L is $P(=N-L-R^5)$, or of formula **III** or a salt form thereof. In some

embodiments, such an internucleotidic linkage is chirally controlled. In some embodiments, all such internucleotidic linkages are chirally controlled. In some embodiments, linkage phosphorus of at least one of such internucleotidic linkages is *Rp*. In some embodiments, linkage phosphorus of at least one of such internucleotidic linkages is *Sp*. In some embodiments, linkage phosphorus of at least one of such internucleotidic linkages is *Rp*, and linkage phosphorus of at least one of such internucleotidic linkages is *Sp*. In some embodiments, oligonucleotides of the present disclosure comprises one or more (e.g., 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 1-40, 1-50, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, etc.) such internucleotidic linkages. In some embodiments, such oligonucleotide further comprise one or more other types of internucleotidic linkages, e.g., one or more natural phosphate linkages, and/or one or more phosphorothioate internucleotidic linkages (e.g., in some embodiments, one or more of which are independently chirally controlled; in some embodiments, each of which is independently chirally controlled; in some embodiments, at least one is *Rp*; in some embodiments, at least one is *Sp*; in some embodiments, at least one is *Rp* and at least one is *Sp*; etc.) In some embodiments, such oligonucleotides are stereopure (substantially free of other stereoisomers). In some embodiments, the present disclosure provides chirally controlled oligonucleotide compositions of such oligonucleotides. In some embodiments, the present disclosure provides chirally pure oligonucleotide compositions of such oligonucleotides.

[001053] In some embodiments, modifying proceeds with a stereoselectivity of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more. In some embodiments, the stereoselectivity is 85% or more. In some embodiments, the stereoselectivity is 85% or more. In some embodiments, the stereoselectivity is 85% or more. In some embodiments, the stereoselectivity is 90% or more. In some embodiments, the stereoselectivity is 91% or more. In some embodiments, the stereoselectivity is 92% or more. In some embodiments, the stereoselectivity is 93% or more. In some embodiments, the stereoselectivity is 94% or more. In some embodiments, the stereoselectivity is 95% or more. In some embodiments, the stereoselectivity is 96% or more. In some embodiments, the stereoselectivity is 97% or more. In some embodiments, the stereoselectivity is 98% or more. In some embodiments, the stereoselectivity is 99% or more. In some embodiments, modifying is stereospecific.

Deblocking

[001054] In some embodiments, a cycle comprises a cycle step. In some embodiments, the 5' hydroxyl group of the growing oligonucleotide is blocked (i.e., protected) and must be deblocked in order to subsequently react with a nucleoside coupling partner.

[001055] In some embodiments, acidification is used to remove a blocking group. Suitable deblocking technologies (e.g., reagents, conditions, etc.) include those described in US 9695211, US

9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, WO 2017/210647, WO 2018/223056, WO 2018/237194, and/or WO 2019/055951, the deblocking technologies of each of which are incorporated by reference. Certain deblocking technologies, e.g., reagents, conditions, methods, etc. are illustrated in the Examples.

Cleavage and Deprotection

[001056] At certain stage, e.g., after the desired oligonucleotide lengths have been achieved, cleavage and/or deprotection are performed to deprotect blocked nucleobases etc. and cleave the oligonucleotide products from support. In some embodiments, cleavage and deprotection are performed separately. In some embodiments, cleavage and deprotection are performed in one step, or in two or more steps but without separation of products in between. In some embodiments, cleavage and/or deprotection utilizes basic conditions and elevated temperature. In some embodiments, for certain chiral auxiliaries, a fluoride condition is required (e.g., TBAF, HF-ET_3N, etc., optionally with additional base). Suitable cleavage and deprotection technologies (e.g., reagents, conditions, etc.) include those described in US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, WO 2017/210647, WO 2018/223056, WO 2018/237194, and/or WO 2019/055951, the cleavage and deprotection technologies of each of which are incorporated by reference. Certain cleavage and deprotection technologies, e.g., reagents, conditions, methods, etc. are illustrated in the Examples.

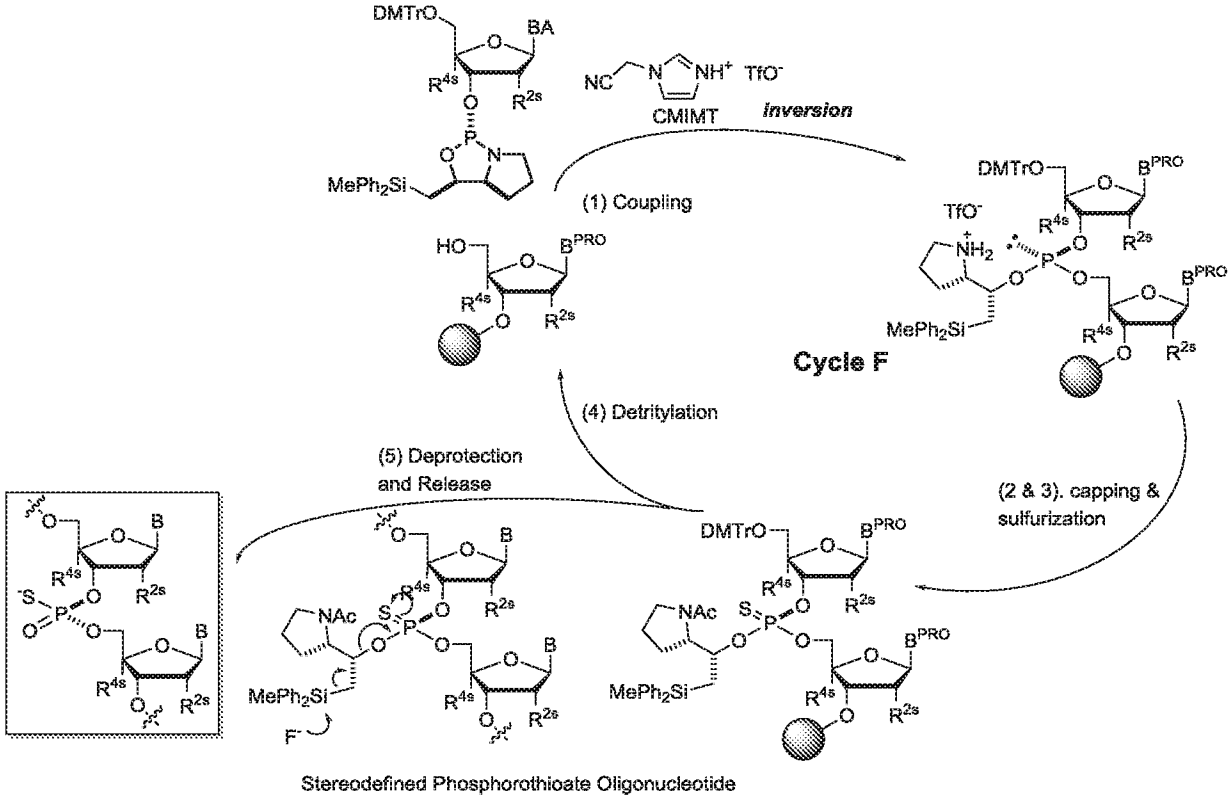
[001057] In some embodiments, certain chiral auxiliaries are removed under basic conditions. In some embodiments, oligonucleotides are contacted with a base, e.g., an amine having the structure of $N(R)_3$, to remove certain chiral auxiliaries (e.g., those comprising an electronic-withdrawing group in G^2 as described in the present disclosure). In some embodiments, a base is NHR_2. In some embodiments, each R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, each R is independently optionally substituted C_{1-6} alkyl. In some embodiments, an amine is DEA. In some embodiments, an amine is TEA. In some embodiments, an amine is provided as a solution, e.g., an acetonitrile solution. In some embodiments, such contact is performed under anhydrous conditions. In some embodiments, such a contact is performed immediately after desired oligonucleotide lengths are achieved (e.g., first step post synthesis cycles). In some embodiments, such a contact is performed before removal of chiral auxiliaries and/or protection groups and/or cleavage of oligonucleotides from a solid support. In some embodiments, contact with a base may remove cyanoethyl groups utilized in standard oligonucleotide synthesis, providing an natural phosphate linkage which may exist in a salt form (with the cation being, e.g., an ammonium salt). In some embodiments, contact with a base provides an

internucleotidic linkage of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, or **II-d-2**, or a salt form thereof. In some embodiments, contact with a base removes a chiral auxiliary from an internucleotidic linkage of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, or **II-d-2**, or a salt form thereof. In some embodiments, contact with a base removes a chiral auxiliary (e.g., $-X-L-R^1$) from an internucleotidic linkage of formula **I** or a salt form thereof (e.g., wherein P^L is $P(=N-L-R^5)$). In some embodiments, contact with a base removes a chiral auxiliary (e.g., $-X-L-R^1$) from an internucleotidic linkage of formula **III** or a salt form thereof. In some embodiments, In some embodiments, contact with a base converts an internucleotidic linkage of formula **I** or a salt form thereof (e.g., wherein P^L is $P(=N-L-R^5)$), or of formula **III** or a salt form thereof, into an internucleotidic linkage of formula **II-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, or **II-d-2**, or a salt form thereof.

Cycles

[001058] Suitable cycles for preparing oligonucleotides of the present disclosure include those described in US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, WO 2017/210647 (e.g., Schemes I, I-b, I-c, I-d, I-e, I-f, etc.), WO 2018/223056, WO 2018/237194, and/or WO 2019/055951, the cycles of each of which are incorporated by reference. For example, in some embodiments, an example cycle is Scheme I-f. Certain cycles are illustrated in the Examples (e.g., for preparation of natural phosphate linkages, utilizing other chiral auxiliaries, etc.).

Scheme I-e. Example cycle using DPSE chiral auxiliary.



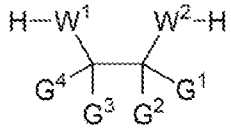
[001059] In some embodiments, R^{2s} is H or $-OR^1$, wherein R^1 is not hydrogen. In some embodiments, R^{2s} is H or $-OR^1$, wherein R^1 is optionally substituted C_{1-6} alkyl. In some embodiments, R^{2s} is H. In some embodiments, R^{2s} is $-OMe$. In some embodiments, R^{2s} is $-OCH_2CH_2OCH_3$. In some embodiments, R^{2s} is $-F$. In some embodiments, R^{4s} is $-H$. In some embodiments, R^{4s} and R^{2s} are taken together to form a bridge $-L-O-$ as described in the present disclosure. In some embodiments, the $-O-$ is connected to the carbon at the 2' position. In some embodiments, L is $-CH_2-$. In some embodiments, L is $-CH(Me)-$. In some embodiments, L is $-(R)-CH(Me)-$. In some embodiments, L is $-(S)-CH(Me)-$.

Purification and Characterization

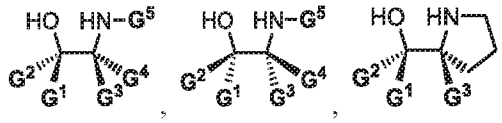
[001060] Various purification and/or characterization technologies (methods, instruments, protocols, etc.) can be utilized to purify and/or characterize oligonucleotides and oligonucleotide compositions in accordance with the present disclosure. In some embodiments, purification is performed using various types of HPLC/UPLC technologies. In some embodiments, characterization comprises MS, NMR, UV, etc. In some embodiments, purification and characterization may be performed together, e.g.,, HPLC-MS, UPLC-MS, etc. Example purification and characterization technologies include those described in US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO

2017/192679, WO 2017/210647, WO 2018/223056, WO 2018/237194, and/or WO 2019/055951, the purification and characterization technologies of each of which are incorporated by reference.

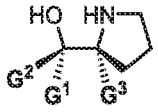
[001061] In some embodiments, the present disclosure provides methods for preparing provided oligonucleotide and oligonucleotide compositions. In some embodiments, a provided method comprises providing a provided chiral reagent having the structure of formula 3-I or 3-AA. In some embodiments, a provided method comprises providing a provided chiral reagent having the structure of



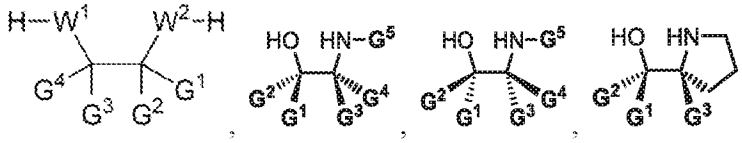
, wherein W^1 is $-NG^5$, W^2 is O, each of G^1 and G^3 is independently hydrogen or an optionally substituted group selected from C_{1-10} aliphatic, heterocyclyl, heteroaryl and aryl, G^2 is $-C(R)_2Si(R)_3$, and G^4 and G^5 are taken together to form an optionally substituted saturated, partially unsaturated or unsaturated heteroatom-containing ring of up to about 20 ring atoms which is monocyclic or polycyclic, fused or unfused, wherein each R is independently hydrogen, or an optionally substituted group selected from C_1–C_6 aliphatic, carbocyclyl, aryl, heteroaryl, and heterocyclyl. In some embodiments, a provided chiral reagent has the structure of



, or



, wherein each variable is independently as described in the present disclosure. In some embodiments, a provided methods comprises providing a phosphoramidite comprising a moiety from a chiral reagent having the structure of



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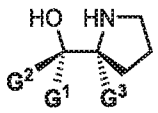
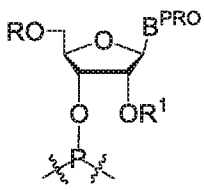


, wherein $-W^1H$ and $-W^2H$, or the hydroxyl and amino groups, form bonds with the phosphorus atom of the phosphoramidite. In some embodiments, $-W^1H$ and $-W^2H$, or the hydroxyl and amino groups, form bonds with the phosphorus atom of the phosphoramidite, *e.g.*, in



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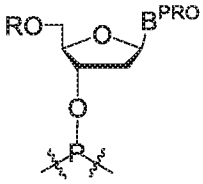
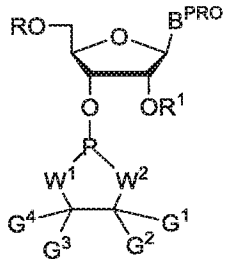
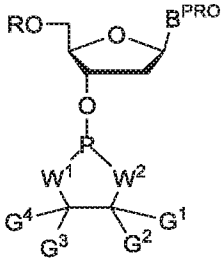
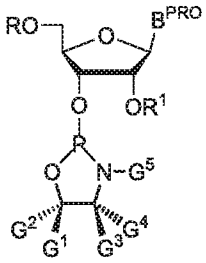
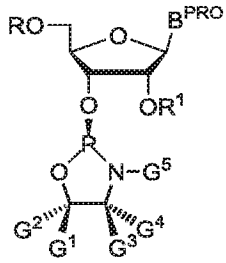
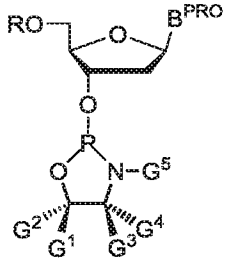
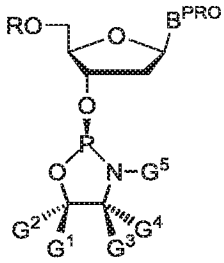
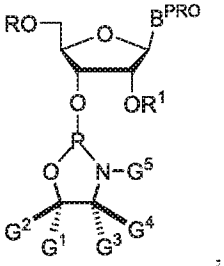
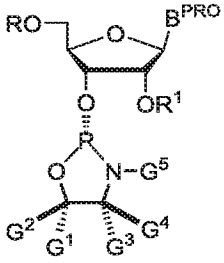
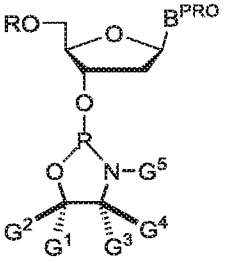
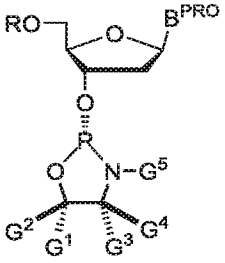
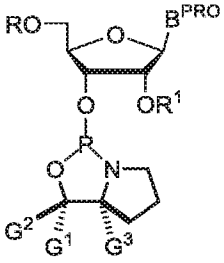
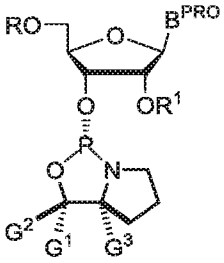
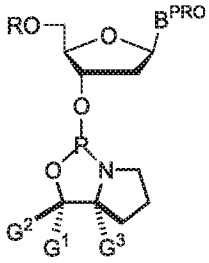
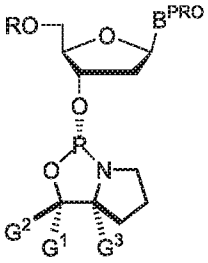
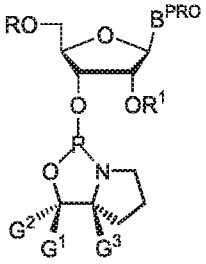
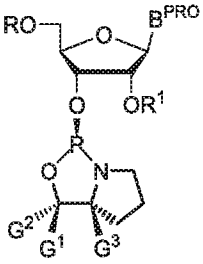
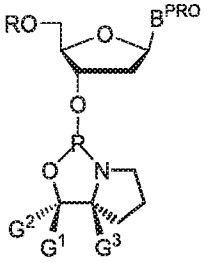
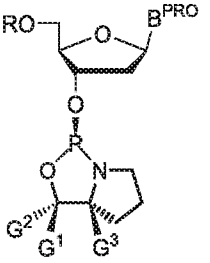
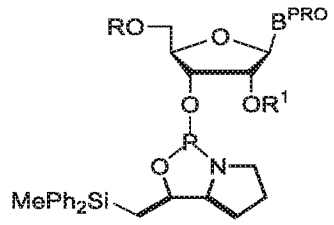
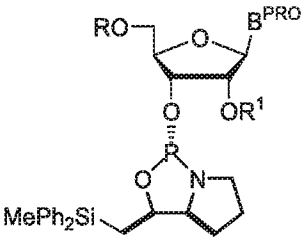
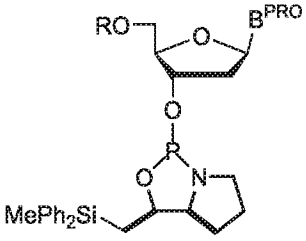
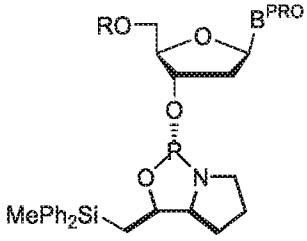
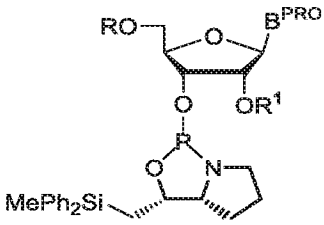
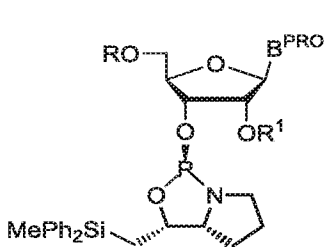
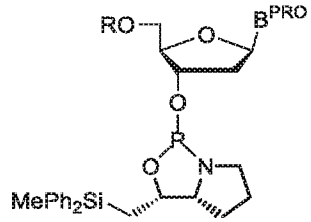
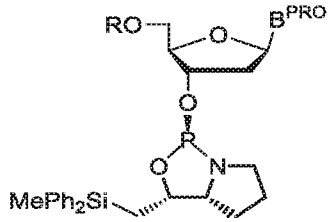
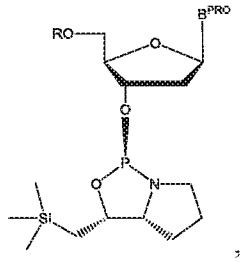
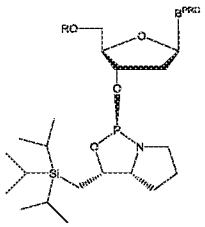
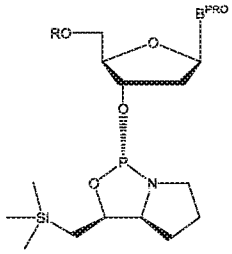
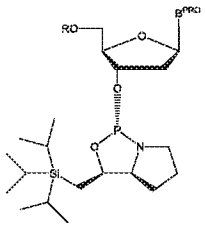



. In some embodiments, a phosphoramidite has the structure of ,

or wherein B^{PRO} is BA as described in the present disclosure, and each other variable is as described in the present disclosure. In some embodiments, B^{PRO} is a protected nucleobase. In some embodiments, B^{PRO} is protected A, T, G, C, U or a tautomers thereof. In some embodiments, R is a protection group. In some embodiments, R is DMTr.

[001062] In some embodiments, G^2 is $-C(R)_2Si(R)_3$, wherein $-C(R)_2-$ is optionally substituted $-CH_2-$, and each R of $-Si(R)_3$ is independently an optionally substituted group selected from C_{1-10} aliphatic, heterocyclyl, heteroaryl and aryl. In some embodiments, at least one R of $-Si(R)_3$ is independently optionally substituted C_{1-10} alkyl. In some embodiments, at least one R of $-Si(R)_3$ is independently optionally substituted phenyl. In some embodiments, one R of $-Si(R)_3$ is independently optionally substituted phenyl, and each of the other two R is independently optionally substituted C_{1-10} alkyl. In some embodiments, one R of $-Si(R)_3$ is independently optionally substituted C_{1-10} alkyl, and each of the other two R is independently optionally substituted phenyl. In some embodiments, G^2 is optionally substituted $-CH_2Si(Ph)(Me)_2$. In some embodiments, G^2 is optionally substituted $-CH_2Si(Me)(Ph)_2$. In some embodiments, G^2 is $-CH_2Si(Me)(Ph)_2$. In some embodiments, G^2 is $-CH_2SiMe_3$. In some embodiments, G^2 is $-CH_2Si(iPr)_3$. In some embodiments, G^4 and G^5 are taken together to form an optionally substituted saturated 5-6 membered ring containing one nitrogen atom (to which G^5 is attached). In some embodiments, G^4 and G^5 are taken together to form an optionally substituted saturated 5-membered ring containing one nitrogen atom. In some embodiments, G^1 is hydrogen. In some embodiments, G^3 is hydrogen. In some embodiments, both G^1 and G^3 are hydrogen. In some embodiments, both G^1 and G^3 are hydrogen, G^2 is $-C(R)_2Si(R)_3$, wherein $-C(R)_2-$ is optionally substituted $-CH_2-$, and each R of $-Si(R)_3$ is independently an optionally substituted group selected from C_{1-10} aliphatic, heterocyclyl, heteroaryl and aryl, and G^4 and G^5 are taken together to form an optionally substituted saturated 5-membered ring containing one nitrogen atom. In some embodiments, a provided method further comprises providing a fluoro-containing reagent. In some embodiments, a provided

fluoro-containing reagent removes a chiral reagent, or a product formed from a chiral reagent, from oligonucleotides after synthesis. Various known fluoro-containing reagents, including those F^- sources for removing $-SiR_3$ groups, can be utilized in accordance with the present disclosure, for example, TBAF, HF_3-Et_3N *etc*. In some embodiments, a fluoro-containing reagent provides better results, for example, shorter treatment time, lower temperature, less de-sulfurization, *etc*, compared to traditional methods, such as concentrated ammonia. In some embodiments, for certain fluoro-containing reagent, the present disclosure provides linkers for improved results, for example, less cleavage of oligonucleotides from support during removal of chiral reagent (or product formed therefrom during oligonucleotide synthesis). In some embodiments, a provided linker is an SP linker. In some embodiments, the present disclosure demonstrated that a HF-base complex can be utilized, such as HF-NR_3, to control cleavage during removal of chiral reagent (or product formed therefrom during oligonucleotide synthesis). In some embodiments, HF-NR_3 is HF-NEt_3. In some embodiments, HF-NR_3 enables use of traditional linkers, *e.g.*, succinyl linker.

[001063] In some embodiments, as described herein, G^2 comprises an electron-withdrawing group, e.g., at its α position. In some embodiments, G^2 is methyl substituted with one or more electron-withdrawing groups. In some embodiments, an electronic-withdrawing group comprises and/or is connected to the carbon atom through, e.g., $-S(O)-$, $-S(O)_2-$, $-P(O)(R^1)-$, $-P(S)R^1-$, or $-C(O)-$. In some embodiments, an electron-withdrawing group is $-CN$, $-NO_2$, halogen, $-C(O)R^1$, $-C(O)OR'$, $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$. In some embodiments, an electron-withdrawing group is aryl or heteroaryl, e.g., phenyl, substituted with one or more of $-CN$, $-NO_2$, halogen, $-C(O)R^1$, $-C(O)OR'$, $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$. In some embodiments, G^2 is $-CH_2S(O)R'$. In some embodiments, G^2 is $-CH_2S(O)_2R'$. In some embodiments, G^2 is $-CH_2P(O)(R')_2$. Additional example embodiments are described, e.g., as for chiral reagents/auxiliaries.

[001064] Confirmation that a stereocontrolled oligonucleotide (e.g., one prepared by a method described herein or in the art) comprises the intended stereocontrolled (chirally controlled) internucleotidic linkage can be performed using a variety of suitable technologies. A stereocontrolled (chirally controlled) oligonucleotide comprises at least one stereocontrolled internucleotidic linkage, which can be, e.g., a stereocontrolled internucleotidic linkage comprising a phosphorus, a stereocontrolled phosphorothioate internucleotidic linkage (PS) in the Rp configuration, a PS in the Sp configuration, etc. Useful technologies include, as non-limiting examples: NMR (e.g., 1D (one-dimensional) and/or 2D (two-dimensional) ^1H-^{31}P HETCOR (heteronuclear correlation spectroscopy)), HPLC, RP-HPLC, mass spectrometry, LC-MS, and/or stereospecific nucleases. In some embodiments, stereospecific nucleases include: benzonase, micrococcal nuclease, and svPDE (snake venome phosphodiesterase), which are

specific for internucleotidic linkages in the Rp configuration (e.g., a PS in the Rp configuration); and nuclease P1, mung bean nuclease, and nuclease S1, which are specific for internucleotidic linkages in the Sp configuration (e.g., a PS in the Sp configuration).

[001065] In some embodiments, the present disclosure pertains to a method of confirming or identifying the stereochemistry pattern of the backbone of an oligonucleotide and/or stereochemistry of particular internucleotidic linkages. In some embodiments, an oligonucleotide comprises a stereocontrolled internucleotidic linkage comprising a phosphorus, a stereocontrolled phosphorothioate (PS) in the Rp configuration, or a PS in the Sp configuration. In some embodiments, an oligonucleotide comprises at least one stereocontrolled internucleotidic linkage and at least one internucleotidic linkage which is not stereocontrolled. In some embodiments, a method comprises digestion of an oligonucleotide with a stereospecific nuclease. In some embodiments, a stereospecific nuclease is selected from: benzonase, micrococcal nuclease, and svPDE (snake venom phosphodiesterase), which are specific for internucleotidic linkages in the Rp configuration (e.g., a PS in the Rp configuration); and nuclease P1, mung bean nuclease, and nuclease S1, which are specific for internucleotidic linkages in the Sp configuration (e.g., a PS in the Sp configuration). In some embodiments, an oligonucleotide or fragments thereof produced by digestion with a stereospecific nuclease are analyzed. In some embodiments, an oligonucleotide or fragments thereof (e.g., produced by digestion with a stereospecific nuclease) are analyzed by NMR, 1D (one-dimensional) and/or 2D (two-dimensional) ^{1}H-^{31}P HETCOR (heteronuclear correlation spectroscopy), HPLC, RP-HPLC, mass spectrometry, LC-MS, UPLC, etc. In some embodiments, an oligonucleotide or fragments thereof are compared with chemically synthesized fragments of the oligonucleotide having a known pattern of stereochemistry.

[001066] Without wishing to be bound by any particular theory, the present disclosure notes that, in at least some cases, stereospecificity of a particular nuclease may be altered by a modification (e.g., 2'-modification) of a sugar, by a base sequence, or by a stereochemical context. For example, in some embodiments, benzonase and micrococcal nuclease, which are specific for Rp internucleotidic linkages, were both unable to cleave an isolated PS Rp internucleotidic linkage flanked by PS Sp internucleotidic linkages.

[001067] Various techniques and materials can be utilized. In some embodiments, the present disclosure provides useful combinations of technologies. For example, in some embodiments, stereochemistry of one or more particular internucleotidic linkages of an oligonucleotide can be confirmed by digestion of the oligonucleotide with a stereospecific nuclease and analysis of the resultant fragments (e.g., nuclease digestion products) by any of a variety of techniques (e.g., separation based on mass-to-charge ratio, NMR, HPLC, mass spectrometry, etc.). In some embodiments, stereochemistry of products of digesting an oligonucleotide with a stereospecific nuclease can be confirmed by comparison

(e.g., NMR, HPLC, mass spectrometry, etc.) with chemically synthesized fragments (e.g., dimers, trimers, tetramers, etc.) produced, e.g., via technologies that control stereochemistry.

[001068] In one example, an oligonucleotide was confirmed to have the designed and intended pattern of stereochemistry in the backbone. The tested oligonucleotide comprises a core comprising 2'-deoxy nucleosides, wherein all of the internucleotidic linkages were PS in the Sp configuration except for one PS in the Rp configuration; and two wings, each of which comprising 2'-OMe nucleosides, wherein all the internucleotidic linkages in each wing were phosphodiester (PO) except for one PS in the Sp configuration in each wing. The oligonucleotide was digested with a stereospecific nuclease (e.g., nuclease P1). The various fragments were analyzed (e.g., by LC-MS and by comparison with chemically synthesized fragments of known stereochemistry). It was confirmed that the oligonucleotide had the intended pattern of stereochemistry in its backbone.

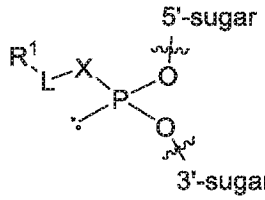
[001069] In another example, an oligonucleotide having a different sequence was confirmed to have the intended pattern of stereochemistry in its backbone, using digestion with a stereospecific nuclease and analysis of the resultant fragments. This oligonucleotide comprises a core comprising 2'-deoxy nucleotides, wherein all of the internucleotidic linkages were PS in the Sp configuration except for one PS in the Rp configuration; and two wings, each of which comprising 2'-OMe nucleotides, wherein all the internucleotidic linkages in each wing were phosphodiester (PO) except for one PS in the Sp configuration in each wing.

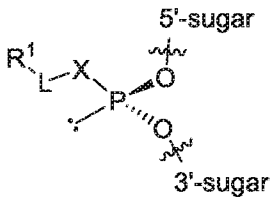
[001070] In yet another example, a different oligonucleotide was tested to confirm that the internucleotidic linkages were in the intended configurations. The oligonucleotide is capable of skipping exon 51 of DMD; the majority of the nucleotides in the oligonucleotide were 2'-F and the remainder were 2'-OMe; the majority of the internucleotidic linkages in the oligonucleotide were PS in the Sp configuration and the remainder were PO. This oligonucleotide was tested by digestion with stereospecific nucleases, and the resultant digestion fragments were analyzed (e.g., by LC-MS and by comparison with chemically synthesized fragments of known stereochemistry). The results confirmed that the oligonucleotide had the intended pattern of stereocontrolled internucleotidic linkages.

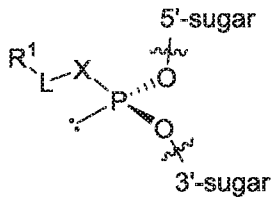
[001071] In some embodiments, NMR is useful for characterization and/or confirming stereochemistry. In a set of example experiments, a set of oligonucleotides comprising a stereocontrolled CpG motif were tested to confirm the intended stereochemistry of the CpG motif. Oligonucleotides of the set comprise a motif having the structure of pCpGp, wherein C is Cytosine, G is Guanine, and p is a phosphorothioate which is stereorandom or stereocontrolled (e.g., in the Rp or Sp configuration). For example, one oligonucleotide comprises a pCpGp structure, wherein the pattern of stereochemistry of the phosphorothioates (e.g., the ppp) was RRR; in another oligonucleotide, the pattern of stereochemistry of the ppp was RSS; in another oligonucleotide, the pattern of stereochemistry of the ppp was RSR; etc. In

the set, all possible patterns of stereochemistry of the ppp were represented. In the portion of the oligonucleotide outside the pCpGp structure, all the internucleotidic linkages were PO; all nucleosides in the oligonucleotides were 2'-deoxy. These various oligonucleotides were tested in NMR, without digestion with a stereospecific nuclease, and distinctive patterns of peaks were observed, indicating that each PS which was Rp or Sp produced a unique peak, and confirming that the oligonucleotides comprised stereocontrolled PS internucleotidic linkages of the intended stereochemistry.

[001072] Stereochemistry patterns of the internucleotidic linkages of various other stereocontrolled oligonucleotides were confirmed, wherein the oligonucleotides comprise a variety of chemical modifications and patterns of stereochemistry.

[001073] As those skilled in the art will appreciate, in some embodiments, a product oligonucleotide of a step, cycle or preparation is an oligonucleotide comprising O^{5P}, O^{P}, $*^{PD}$, $*^{PD}S$, $*^{PD}R$, $*^{N}$, $*^{N}S$ and/or $*^{N}R$ as described herein, which oligonucleotide is optionally linked to a support (*e.g.*, CPG) optionally via a linker (*e.g.*, a CAN linker). For example, in some embodiments, after coupling and/or pre-modification capping and before modification, O^{5P} is 

, 

, 

, or a salt form thereof. In some embodiments, after modification O^{5P} is L^{PO}, L^{PA}, L^{PB}, or a salt form thereof.

Metabolites

[001074] In some embodiments, a DMD oligonucleotide corresponds to a fragment of a different, longer DMD oligonucleotide. In some embodiments, a DMD oligonucleotide corresponds to a metabolite produced by cleavage (e.g., enzymatic cleavage by a nuclease) of a longer DMD oligonucleotide, which produces a fragment or portion of the longer DMD oligonucleotide. In some embodiments, the present disclosure pertains to an DMD oligonucleotide which corresponds to a metabolite produced by the cleavage of a DMD oligonucleotide described herein. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which corresponds to a portion, or fragment of a DMD oligonucleotide disclosed herein.

[001075] Several experiments were performed wherein a DMD oligonucleotide was incubated in

vitro in the presence of any of various substances comprising nucleases. In various experiments, such substances include brain homogenatem, cerebrospinal fluid or plasma from Sprague-Dawley rat or Cynomolgus monkey. Plasma was heparinized. Oligonucleotides were incubated for various time points (e.g., 0, 1, 2, 3, 4 or 5 days for brain tissue homogenate, with a pre-incubation period of 0, 1 or 2 days; 0, 1, 2, 4, 8, 16, 24 or 48 hrs for cerebrospinal fluid; or 0, 1, 2, 4, 8, 16 or 24 hrs for plasma). Pre-incubation indicates that the homogenate is incubated at 37 degrees °C for 0, 24 or 48 hrs to activate the enzymes before adding the oligonucleotide. Final concentration and volume of oligonucleotides was 20 μM in 200 μl. Products produced by cleavage of the oligonucleotides were analyzed by LC/MS.

[001076] For one DMD oligonucleotide, which is 20 bases long, tested in rat brain homogenate, the major metabolites represented the 3' end of the oligonucleotide, which were truncated by 4, 10, 11, 12, or 13 bases.

[001077] One test DMD oligonucleotide has a length of 20 bases and was tested in rat brain homogenate, yielding major metabolites which were truncated at the 5' end by 4, 10, 11, 12, or 13 bases, leaving metabolites representing the 3' end of the oligonucleotide and which were 16, 10, 9, 8 or 7 bases long, respectively. This oligonucleotide also produced a metabolite which was a 5' fragment which was 12 bases long (truncated at the 3' end by 8 bases).

[001078] A second test oligonucleotide has a length of 20 bases and was tested in rat brain homogenate, yielding major metabolites which were truncated at the 3' end by 4, 8, 9 or 10 bases, leaving metabolites representing the 5' end of the oligonucleotide and which were 16, 12, 11 or 10 bases long, respectively.

[001079] The two tested oligonucleotides comprise internucleotidic linkages which are phosphodiesters, phosphorothioate in the Rp configuration, and phosphorothioates in the Sp configuration. In some embodiments, phosphodiesters were more labile than the phosphorothioate in the Rp configuration or the phosphorothioate in the Sp configuration. In some cases, a metabolite of an oligonucleotide represents a product of a cleavage at a phosphodiester.

[001080] In some embodiments, the present disclosure pertains to a DMD oligonucleotide which corresponds to a metabolite of a DMD oligonucleotide disclosed herein. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,11, 12, 13, or more bases shorter than a DMD oligonucleotide disclosed herein. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which has a base sequence which is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,11, 12, 13, or more bases shorter than that of a DMD oligonucleotide disclosed herein.

[001081] In some embodiments, a metabolite is designated as 3'-N-#, or 5'-N-#, wherein the # indicates the number of bases removed, and the 3' or 5' indicates which end of the molecule from which the bases were deleted. For example, 3'-N-1 indicates a fragment or metabolite wherein 1 base was

removed from the 3' end.

[001082] In some embodiments, the present disclosure perhaps to an oligonucleotide which corresponds to a fragment or metabolite of a DMD oligonucleotide disclosed herein, wherein the fragment or metabolite can be described as corresponding to 3'-N-1, 3'-N-2, 3'-N-3, 3'-N-4, 3'-N-5, 3'-N-6, 3'-N-7, 3'-N-8, 3'-N-9, 3'-N-10, 3'-N-11, 3'-N-12, 5'-N-1, 5'-N-2, 5'-N-3, 5'-N-4, 5'-N-5, 5'-N-6, 5'-N-7, 5'-N-8, 5'-N-9, 5'-N-10, 5'-N-11, or 5'-N-12 of a DMD oligonucleotide described herein.

[001083] In some embodiments, the present disclosure pertains to a DMD oligonucleotide which is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,11, 12, 13, or more bases shorter on the 5' end than a DMD oligonucleotide disclosed herein. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which has a base sequence which is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,11, 12, 13, or more bases shorter on the 5' end than that of a DMD oligonucleotide disclosed herein. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,11, 12, 13, or more bases shorter on the 3' end than a DMD oligonucleotide disclosed herein. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which has a base sequence which is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,11, 12, 13, or more bases shorter on the 3' end than that of a DMD oligonucleotide disclosed herein.

[001084] In some embodiments, the present disclosure pertains to a DMD which corresponds to a metabolite of a DMD oligonucleotide, wherein the metabolite is truncated on the 5' and/or 3' end relative to the DMD oligonucleotide disclosed herein. In some embodiments, the present disclosure pertains to a DMD which corresponds to a metabolite of a DMD oligonucleotide, wherein the metabolite is truncated on both the 5' and 3' end relative to the DMD oligonucleotide disclosed herein. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,11, 12, 13, or more total bases shorter on the 5' and/or 3' end than a DMD oligonucleotide disclosed herein. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which has a base sequence which is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,11, 12, 13, or more bases total shorter on the 5' and/or 3' end than that of a DMD oligonucleotide disclosed herein.

[001085] In some embodiments, the present disclosure pertains to a DMD oligonucleotide which would be represented by a product of cleavage of a DMD oligonucleotide disclosed herein, which is cleaved at a phosphodiester linkage. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which would be represented by a product of cleavage of a DMD oligonucleotide disclosed herein, if such an oligonucleotide were cleaved at a phosphorothioate linkage in the Rp configuration. In some embodiments, the present disclosure pertains to a DMD oligonucleotide which would be represented by a product of cleavage of a DMD oligonucleotide disclosed herein, if such an oligonucleotide were cleaved at one or more phosphodiester linkages and/or phosphorothioate linkages in the Rp configuration.

Biological Applications, Example Use, and Dosing Regimens

[001086] As described herein, provided compositions and methods are useful for various purposes, e.g., those described in US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, and/or WO 2017/210647. Among other things, provided technologies can function and/or provide various benefits through a number of chemical and/or biological mechanisms, pathways, *etc.* (*e.g.*, RNase H, RNAi, splicing modulation (exon skipping(*e.g.*, for DMD in DMD subjects/samples), exon inclusion (*e.g.*, for SMN2 in SMA subjects/samples)), *etc.*). In some embodiments, provided technologies reduce levels, activities, expressions, *etc.* of a nucleic acid and/or a product thereof. For example, in some embodiments, provided technologies reduce levels and/or activities of target transcripts and/or products encoded thereby (without the intention to be limited by any particular theory, in some embodiments, via RNase H pathway). In some embodiments, provided technologies increase levels and/or activities of target transcripts and/or products encoded thereby (without the intention to be limited by any particular theory, in some embodiments, via exon skipping). A number of oligonucleotides comprising various types of modified internucleotidic linkages, including many comprising non-negatively charged internucleotidic linkages (e.g., n001), which have various base sequences and/or target various nucleic acids (e.g., transcripts of various genes) were prepared, and various useful properties, activities, and/or advantages were demonstrated. Certain such oligonucleotides, including many comprising non-negatively charged internucleotidic linkages, target transcripts of PNPLA3, C9orf72, SMN2, *etc.* and have demonstrated various activities and/or benefits. Example oligonucleotides comprising non-negatively charged internucleotidic linkages and targeting various genes, and compositions and uses thereof, include those described in WO 2018/223056, WO 2019/032607, PCT/US18/55653, and WO 2019/032612, each of which is independently incorporated herein by reference.

[001087] In some embodiments, the present disclosure provides methods for modulating level of a transcript or a product encoded thereby in a system, comprising administering an effective amount of a provided oligonucleotide or a composition thereof. In some embodiments, the present disclosure provides methods for modulating level of a transcript or a product encoded thereby in a system, comprising contacting the transcript a provided oligonucleotide or a composition thereof. In some embodiments, a system is an in vitro system. In some embodiments, a system is a cell. In some embodiments, a system is

a tissue. In some embodiments, a system is an organ. In some embodiments, a system is an organism. In some embodiments, a system is a subject. In some embodiments, a system is a human. In some embodiments, modulating level of a transcript decreases level of the transcript. In some embodiments, modulating level of a transcript increases level of the transcript.

[001088] In some embodiments, the present disclosure provides methods for preventing or treating a condition, disease, or disorder associated with a nucleic acid sequence or a product encoded thereby, comprising administering to a subject suffering therefrom or susceptible thereto an effective amount of a provided oligonucleotide or composition thereof, wherein the oligonucleotide or composition thereof modulate level of a transcript of the nucleic acid sequence. In some embodiments, a nucleic acid sequence is a gene. In some embodiments, modulating level of a transcript decreases level of the transcript. In some embodiments, modulating level of a transcript increases level of the transcript.

[001089] In some embodiments, change of the level of a modulated transcript, e.g., through knock-down, exon skipping, etc., is at least 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 200, 500, or 1000 fold.

[001090] In some embodiments, provided oligonucleotides and oligonucleotide compositions modulate splicing. In some embodiments, provided oligonucleotides and oligonucleotide compositions promote exon skipping, thereby produce a level of a transcript which has increased beneficial functions that the transcript prior to exon skipping. In some embodiments, a beneficial function is encoding a protein that has increased biological functions. In some embodiments, the present disclosure provides methods for modulating splicing, comprising administering to a splicing system a provided oligonucleotide or oligonucleotide composition, wherein splicing of at least one transcript is altered. In some embodiments, level of at least one splicing product is increased at least 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 200, 500, or 1000 fold. In some embodiments, the present disclosure provides methods for modulating DMD splicing, comprising administering to a splicing system a provided DMD oligonucleotide or composition thereof.

[001091] In some embodiments, the present disclosure provides methods for preventing or treating DMD, comprising administering to a subject susceptible thereto or suffering therefrom a pharmaceutical composition comprising an effective amount of a provided oligonucleotide or oligonucleotide composition.

[001092] In some embodiments, provided compositions and methods provide improved splicing patterns of transcripts compared to a reference pattern, which is a pattern from a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof. An improvement can be an improvement of any desired biological functions. In some embodiments, for example, in DMD, an improvement is production of an mRNA from which a

dystrophin protein with improved biological activities is produced.

[001093] In some embodiments, particularly useful and effective are chirally controlled oligonucleotides and chirally controlled oligonucleotide compositions, wherein the oligonucleotides (or oligonucleotides of a plurality in chirally controlled oligonucleotide compositions) optionally comprises one or more non-negatively charged internucleotidic linkages. Among other things, such oligonucleotides and oligonucleotide compositions can provide greatly improved effects, better delivery, lower toxicity, etc.

[001094] For Duchenne muscular dystrophy, example mutations and/or suitable DMD exons for skipping are widely known in the art, including but not limited to those described in US Patent No. 8,759,507, US Patent No. US 8,486,907, and reference cited therein.

[001095] In some embodiments, one or more skipped exons are selected from exon 2, 29, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59 and 60. In some embodiments, exon 2 of DMD is skipped. In some embodiments, exon 29 of DMD is skipped. In some embodiments, exon 40 of DMD is skipped. In some embodiments, exon 41 of DMD is skipped. In some embodiments, exon 42 of DMD is skipped. In some embodiments, exon 43 of DMD is skipped. In some embodiments, exon 44 of DMD is skipped. In some embodiments, exon 45 of DMD is skipped. In some embodiments, exon 46 of DMD is skipped. In some embodiments, exon 47 of DMD is skipped. In some embodiments, exon 48 of DMD is skipped. In some embodiments, exon 49 of DMD is skipped. In some embodiments, exon 50 of DMD is skipped. In some embodiments, exon 51 of DMD is skipped. In some embodiments, exon 52 of DMD is skipped. In some embodiments, exon 53 of DMD is skipped. In some embodiments, exon 54 of DMD is skipped. In some embodiments, exon 50 of DMD is skipped. In some embodiments, exon 55 of DMD is skipped. In some embodiments, a skipped exon is any exon whose inclusion decreases a desired function of DMD. In some embodiments, a skipped exon is any exon whose skipping increased a desired function of DMD.

[001096] In some embodiments, more than one exon of DMD is skipped. In some embodiments, two or more exons of DMD are skipped. In some embodiments, two or more adjacent exons of DMD are skipped.

[001097] In some embodiments, for exon skipping of DMD transcript, or for treatment of DMD, a sequence of a provided plurality of oligonucleotides comprises a DMD sequence list herein. In some embodiments, a sequence comprises one of SEQ ID Nos 1-30 of US Patent No. 8,759,507. In some embodiments, a sequence comprises one of SEQ ID Nos 1-211 of US Patent No. US 8,486,907. In some embodiments, for exon skipping of DMD transcript, or for treatment of DMD, a sequence of a provided plurality of oligonucleotides is a DMD sequence disclosed herein. In some embodiments, a sequence is one of SEQ ID Nos 1-30 of US Patent No. 8,759,507. In some embodiments, a sequence is one of SEQ

ID Nos 1-211 of US Patent No. US 8,486,907. In some embodiments, a sequence is, comprises or comprises at least 15 consecutive bases of the sequence of any oligonucleotide list herein, e.g., in **Table A1**. In some embodiments, a sequence is one described in Kemaladewi, *et al.*, Dual exon skipping in myostatin and dystrophin for Duchenne muscular dystrophy, BMC Med Genomics. 2011 Apr 20;4:36. doi: 10.1186/1755-8794-4-36; or Malerba *et al.*, Dual Myostatin and Dystrophin Exon Skipping by Morpholino Nucleic Acid Oligomers Conjugated to a Cell-penetrating Peptide Is a Promising Therapeutic Strategy for the Treatment of Duchenne Muscular Dystrophy, Mol Ther Nucleic Acids. 2012 Dec 18;1:e62. doi: 10.1038/mtna.2012.54.

[001098] In some embodiments, a provided oligonucleotide composition is administered at a dose and/or frequency lower than that of an otherwise comparable reference oligonucleotide composition with comparable effect in altering the splicing of a target transcript. In some embodiments, a stereocontrolled (chirally controlled) oligonucleotide composition is administered at a dose and/or frequency lower than that of an otherwise comparable stereorandom reference oligonucleotide composition with comparable effect in altering the splicing of the target transcript. If desired, a provided composition can also be administered at higher dose/frequency due to its lower toxicities.

[001099] In some embodiments, provided oligonucleotides, compositions and methods have low toxicities, *e.g.*, when compared to a reference composition. As widely known in the art, oligonucleotides can induce toxicities when administered to, *e.g.*, cells, tissues, organism, *etc*. In some embodiments, oligonucleotides can induce undesired immune response. In some embodiments, oligonucleotide can induce complement activation. In some embodiments, oligonucleotides can induce activation of the alternative pathway of complement. In some embodiments, oligonucleotides can induce inflammation. Among other things, the complement system has strong cytolytic activity that can damages cells and should therefore be modulated to reduce potential injuries. In some embodiments, oligonucleotide-induced vascular injury is a recurrent challenge in the development of oligonucleotides for *e.g.*, pharmaceutical use. In some embodiments, a primary source of inflammation when high doses of oligonucleotides are administered involves activation of the alternative complement cascade. In some embodiments, complement activation is a common challenge associated with phosphorothioate-containing oligonucleotides, and there is also a potential of some sequences of phosphorothioates to induce innate immune cell activation. In some embodiments, cytokine release is associated with administration of oligonucleotides. For example, in some embodiments, increases in interleukin-6 (IL-6) monocyte chemoattractant protein (MCP-1) and/or interleukin-12 (IL-12) is observed. See, *e.g.*, Frazier, Antisense Oligonucleotide Therapies: The Promise and the Challenges from a Toxicologic Pathologist's Perspective. *Toxicol Pathol.*, 43: 78-89, 2015; and Engelhardt, *et al.*, Scientific and Regulatory Policy Committee Points-to-consider Paper: Drug-induced Vascular Injury Associated with Nonsmall Molecule

Therapeutics in Preclinical Development: Part 2. Antisense Oligonucleotides. *Toxicol Pathol.* 43: 935-944, 2015.

[001100] Oligonucleotide compositions as provided herein can be used as agents for modulating a number of cellular processes and machineries, including but not limited to, transcription, translation, immune responses, epigenetics, *etc.* In addition, oligonucleotide compositions as provided herein can be used as reagents for research and/or diagnostic purposes. One of ordinary skill in the art will readily recognize that the present disclosure disclosure herein is not limited to particular use but is applicable to any situations where the use of synthetic oligonucleitides is desirable. Among other things, provided compositions are useful in a variety of therapeutic, diagnostic, agricultural, and/or research applications.

[001101] Various dosing regimens can be utilized to administer .provided chirally controlled oligonucleotide compositions, e.g., those described in in US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, and/or WO 2017/210647, the dosing regimens of each of which is incorporated herein by reference.

[001102] In some embodiments, with their low toxicity, provided oligonucleotides and compositions can be administered in higher dosage and/or with higher frequency. In some embodiments, with their improved delivery (and other properties), provided compositions can be administered in lower dosages and/or with lower frequency to achieve biological effects, for example, clinical efficacy.

[001103] A single dose can contain various amounts of oligonucleotides. In some embodiments, a single dose can contain various amounts of a type of chirally controlled oligonucleotide, as desired suitable by the application. In some embodiments, a single dose contains about 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300 or more (*e.g.*, about 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000 or more) mg of a type of chirally controlled oligonucleotide. In some embodiments, a chirally controlled oligonucleotide is administered at a lower amount in a single dose, and/or in total dose, than a chirally uncontrolled oligonucleotide. In some embodiments, a chirally controlled oligonucleotide is administered at a lower amount in a single dose, and/or in total dose, than a chirally uncontrolled oligonucleotide due to improved efficacy. In some embodiments, a chirally controlled oligonucleotide is administered at a higher amount in a single dose, and/or in total dose, than a chirally uncontrolled oligonucleotide. In some embodiments, a chirally controlled oligonucleotide is administered at a higher amount in a single dose, and/or in total dose, than a chirally uncontrolled oligonucleotide due to improved safety.

Pharmaceutical Compositions

[001104] When used as therapeutics, a provided oligonucleotide or oligonucleotide

composition described herein is administered as a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of a provided oligonucleotides, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable inactive ingredient selected from pharmaceutically acceptable diluents, pharmaceutically acceptable excipients, and pharmaceutically acceptable carriers. In some embodiments, in provided compositions provided oligonucleotides may exist as salts, preferably pharmaceutically acceptable salts, *e.g.*, sodium salts, ammonium salts, *etc.* In some embodiments, a salt of a provided oligonucleotide comprises two or more cations, for example, in some embodiments, up to the number of negatively charged acidic groups (*e.g.*, phosphate, phosphorothioate, *etc.*) in an oligonucleotide. As appreciated by those skilled in the art, oligonucleotides described herein may be provided and/or utilized in a salt form, particularly a pharmaceutically acceptable salt form.

[001105] In some embodiments, the present disclosure provides salts of provided oligonucleotides, e.g., chirally controlled oligonucleotides, and pharmaceutical compositions thereof. In some embodiments, a salt is a pharmaceutically acceptable salt. In some embodiments, each hydrogen ion that may be donated to a base (e.g., under conditions of an aqueous solution, a pharmaceutical composition, etc.) is replaced by a non-H^+ cation. For example, in some embodiments, a pharmaceutically acceptable salt of an oligonucleotide is an all-metal ion salt, wherein each hydrogen ion (for example, of –OH, –SH, etc., acidic enough in water) of each internucleotidic linkage (e.g., a natural phosphate linkage, a phosphorothioate diester linkage, etc.) is replaced by a metal ion. In some embodiments, a provided salt is an all-sodium salt. In some embodiments, a provided pharmaceutically acceptable salt is an all-sodium salt. In some embodiments, a provided salt is an all-sodium salt, wherein each internucleotidic linkage which is a natural phosphate linkage (acid form –O–P(O)(OH)–O–), if any, exists as its sodium salt form (–O–P(O)(ONa)–O–), and each internucleotidic linkage which is a phosphorothioate diester linkage (phosphorothioate internucleotidic linkage; acid form –O–P(O)(SH)–O–), if any, exists as its sodium salt form (–O–P(O)(SNa)–O–).

[001106] In some embodiments, the pharmaceutical composition is formulated for intravenous injection, oral administration, buccal administration, inhalation, nasal administration, topical administration, ophthalmic administration or otic administration. In some embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a suspension, a gel, a colloid, a dispersion, a suspension, a solution, an emulsion, an ointment, a lotion, an eye drop or an ear drop.

[001107] In some embodiments, the present disclosure provides a pharmaceutical composition

comprising chirally controlled oligonucleotide, or composition thereof, in admixture with a pharmaceutically acceptable excipient. One of skill in the art will recognize that the pharmaceutical compositions include the pharmaceutically acceptable salts of the chirally controlled oligonucleotide, or composition thereof, described above.

[001108] A variety of supramolecular nanocarriers can be used to deliver nucleic acids. Example nanocarriers include, but are not limited to liposomes, cationic polymer complexes and various polymeric. Complexation of nucleic acids with various polycations is another approach for intracellular delivery; this includes use of PEGlyated polycations, polyethyleneamine (PEI) complexes, cationic block co-polymers, and dendrimers. Several cationic nanocarriers, including PEI and polyamidoamine dendrimers help to release contents from endosomes. Other approaches include use of polymeric nanoparticles, polymer micelles, quantum dots and lipoplexes. In some embodiments, an oligonucleotide is conjugated to another molecular.

[001109] Additional nucleic acid delivery strategies are known in addition to the example delivery strategies described herein.

[001110] In therapeutic and/or diagnostic applications, the compounds of the disclosure can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington, The Science and Practice of Pharmacy, (20th ed. 2000).

[001111] Provided oligonucleotides, and compositions thereof, are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.01 to about 1000 mg, from about 0.5 to about 100 mg, from about 1 to about 50 mg per day, and from about 5 to about 100 mg per day are examples of dosages that may be used. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[001112] Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art, and may include, by way of example but not limitation, acetate, benzenesulfonate, besylate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, carnsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington, The Science and Practice of Pharmacy (20th ed. 2000). Preferred pharmaceutically acceptable salts include, for example, acetate, benzoate, bromide, carbonate, citrate,

gluconate, hydrobromide, hydrochloride, maleate, mesylate, napsylate, pamoate (embonate), phosphate, salicylate, succinate, sulfate, or tartrate.

[001113] As appreciated by a person having oridinary skill in the art, oligonucleotides may be formulated as a number of salts for, *e.g.*, pharmaceutical uses. In some embodiments, a salt is a metal cation salt and/or ammonium salt. In some embodiments, a salt is a metal cation salt of an oligonucleotide. In some embodiments, a salt is an ammonium salt of an oligonucleotide. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. In some embodiments, a salt is a sodium salt of an oligonucleotide. In some embodiments, pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed with oligonucleotides. As appreciated by a person having oridinary skill in the art, a salt of an oligonucleotide may contain more than one cations, *e.g.*, sodium ions, as there may be more than one anions within an oligonucleotide.

[001114] Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained- low release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington, The Science and Practice of Pharmacy (20th ed. 2000). Suitable routes may include oral, buccal, by inhalation spray, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intra-articullar, intra-sternal, intra-synovial, intra-hepatic, intralesional, intracranial, intraperitoneal, intranasal, or intraocular injections or other modes of delivery.

[001115] For injection, the agents of the disclosure may be formulated and diluted in aqueous solutions, such as in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[001116] Use of pharmaceutically acceptable inert carriers to formulate the compounds herein disclosed for the practice of the disclosure into dosages suitable for systemic administration is within the scope of the disclosure. With proper choice of carrier and suitable manufacturing practice, the compositions of the present disclosure, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection.

[001117] Compounds, e.g., oligonucleotides, can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the disclosure to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject (*e.g.*, patient) to be treated.

[001118] For nasal or inhalation delivery, the agents of the disclosure may also be formulated by methods known to those of skill in the art, and may include, for example, but not limited to, examples of solubilizing, diluting, or dispersing substances such as, saline, preservatives, such as benzyl alcohol, absorption promoters, and fluorocarbons.

[001119] In certain embodiments, oligonucleotides and compositions are delivered to the CNS. In certain embodiments, oligonucleotides and compositions are delivered to the cerebrospinal fluid. In certain embodiments, oligonucleotides and compositions are administered to the brain parenchyma. In certain embodiments, oligonucleotides and compositions are delivered to an animal/subject by intrathecal administration, or intracerebroventricular administration. Broad distribution of oligonucleotides and compositions, described herein, within the central nervous system may be achieved with intraparenchymal administration, intrathecal administration, or intracerebroventricular administration.

[001120] In certain embodiments, parenteral administration is by injection, by, *e.g.*, a syringe, a pump, *etc*. In certain embodiments, the injection is a bolus injection. In certain embodiments, the injection is administered directly to a tissue, such as striatum, caudate, cortex, hippocampus and cerebellum.

[001121] In certain embodiments, methods of specifically localizing a pharmaceutical agent, such as by bolus injection, decreases median effective concentration (EC50) by a factor of 20, 25, 30, 35, 40, 45 or 50. In certain embodiments, the targeted tissue is brain tissue. In certain embodiments the targeted tissue is striatal tissue. In certain embodiments, decreasing EC50 is desirable because it reduces the dose required to achieve a pharmacological result in a patient in need thereof.

[001122] In certain embodiments, an oligonucleotide is delivered by injection or infusion once every month, every two months, every 90 days, every 3 months, every 6 months, twice a year or once a year.

[001123] Pharmaceutical compositions suitable for use in the present disclosure include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[001124] In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of an active compound into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

[001125] Pharmaceutical preparations for oral use can be obtained by combining an active compound with solid excipients, optionally grinding a resulting mixture, and processing the mixture of

granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[001126] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[001127] Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, an active compound may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

[001128] In some embodiments, any DMD oligonucleotide, or combination thereof, described herein, or any composition comprising a DMD oligonucleotide described herein, can be combined with any pharmaceutical preparation described herein or known in the art.

Certain Embodiments of Conjugates and Additional Chemical Moieties

[001129] In some embodiments, provided oligonucleotides comprise one or more additional chemical moieties (e.g., other than typical moieties of nucleobases, sugars and/or internucleotidic linkages, etc.), optionally through a linker. In some embodiments, a chemical moiety is a lipid moiety. In some embodiments, a chemical moiety is a carbohydrate moiety. In some embodiments, a chemical moiety is a targeting moiety. In some embodiments, a chemical moiety is a moiety of a ligand. In some embodiments, a chemical moiety can increase delivery of oligonucleotides to certain organelles, cells, tissues, organs, and/or organisms. In some embodiments, a chemical moiety enhances one or more of desired properties and/or activities. Certain example chemical moieties utilized in certain oligonucleotides are presented in the Tables (e.g., various Mod in Table A1). In some embodiments, a chemical moiety comprises one or more sugar moieties or derivatives thereof, e.g., glucose, mannose, etc. In some embodiments, a chemical moiety is or comprises a lipid moiety. In some embodiments, a chemical moiety is or comprises a vitamin E moiety. In some embodiments, a chemical moiety comprises

one or more peptide moieties. In some embodiments, a peptide is a cell-penetrating peptide. In some embodiments, a peptide is a ligand of a protein, e.g., a cell surface receptor. In some embodiments, a peptide is a Tfr1 peptide. Certain example peptide moieties are utilized to prepare oligonucleotides described in the Tables, e.g., Table 1A. In some embodiments, a chemical moiety comprises one or more basic moieties. In some embodiments, a basic moiety is positively charged at, e.g. about pH 7.4. In some embodiments, a basic moiety is or comprises a guanidine moiety. In some embodiments, a basic moiety is or comprises $-N(R^1)_2$, wherein each R^1 is independently as described in the present disclosure. In some embodiments, a basic moiety is or comprises $-N(R^1)_3$, wherein each R^1 is independently as described in the present disclosure. In some embodiments, a basic moiety is or comprises $-N=C(N(R^1)_2)_2$, wherein each R^1 is independently as described in the present disclosure. In some embodiments, each R^1 is independently R as described in the present disclosure. In some embodiments, each R^1 is independently optionally substituted C_{1-6} alkyl. In some embodiments, R^1 is methyl. In some embodiments, one or two R^1 are the same. In some embodiments, each R^1 is the same. In some embodiments, at least one R^1 is different from another R^1. In some embodiments, a basic moiety is $-N=C(N(CH_3)_2)_2$. In some embodiments, a chemical moiety comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more sugar, peptide, lipid, and/or basic moieties. In some embodiments, the number is 1. In some embodiments, the number is 2. In some embodiments, the number is 3. In some embodiments, the number is 4. In some embodiments, the number is 5. In some embodiments, the number is 6. In some embodiments, a chemical moiety comprises a ligand moiety of a protein, e.g., a receptor protein of a target cell. In some embodiments, a ligand is a ligand for a vitamin E receptor. In some embodiments, a ligand is for Tfr1 receptor. Chemical moieties as described and demonstrated in the present disclosure include and can be utilized as carbohydrate moieties, lipid moieties, targeting moieties, etc., and can provide a variety of functions, e.g., improving delivery, one or more properties, activities, etc.

[001130] In some embodiments, the present disclosure provides oligonucleotides comprising additional chemistry moieties, optionally connected to the oligonucleotide moiety through a linker. In some embodiments, the present disclosure provides oligonucleotides comprising $(R^D)b-L^{M1}-L^{M2}-L^{M3}-$, wherein:

each R^D is independently a chemical moiety;

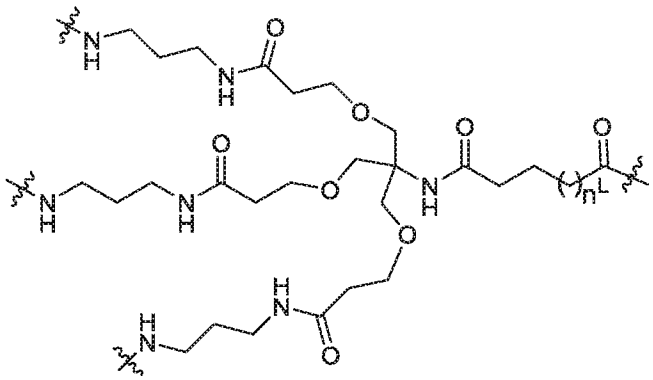
each of L^{M1}, L^{M2}, and L^{M3} is independently L; and

b is 1-1000.

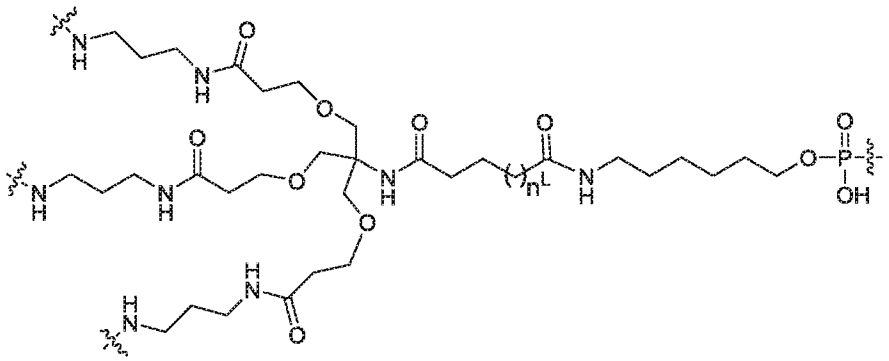
[001131] In some embodiments, each of L^{M1}, L^{M2}, and L^{M3} is independently a covalent bond, or a bivalent or multivalent, optionally substituted, linear or branched group selected from a C_{1-10} aliphatic group and a C_{1-10} heteroaliphatic group having 1-5 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, $-C\equiv C-$, $-C(R')_2-$, $-O-$,

–S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–; and one or more CH or carbon atoms are optionally and independently replaced with Cy^L.

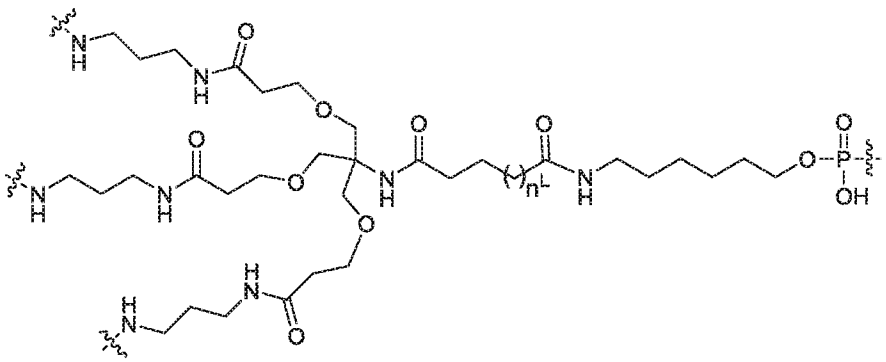
[001132] In some embodiments, L^{M1} comprises one or more –N(R')– and one or more –C(O)–. In some embodiments, a linker (e.g., L, L^M, etc.) or L^{M1} is or comprises



, wherein n^L is 1-8. In some embodiments, a linker or –L^{M1}–L^{M2}–L^{M3}– is



, or a salt form thereof, wherein n^L is 1-8. In some embodiments, a linker or –L^{M1}–L^{M2}–L^{M3}– is



,

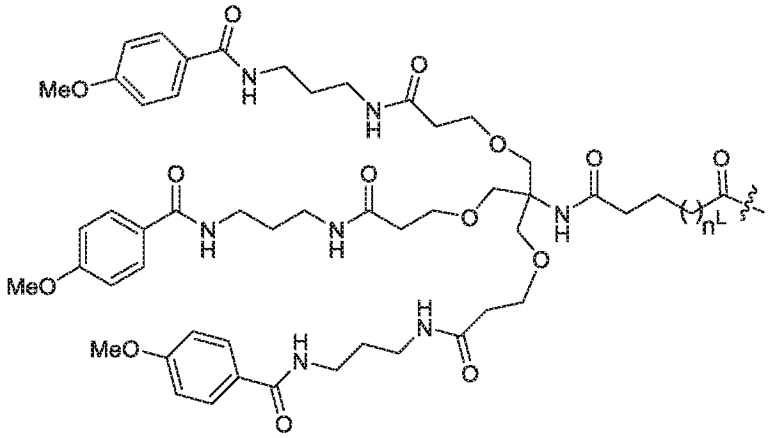
or a salt form thereof, wherein:

n^L is 1-8.

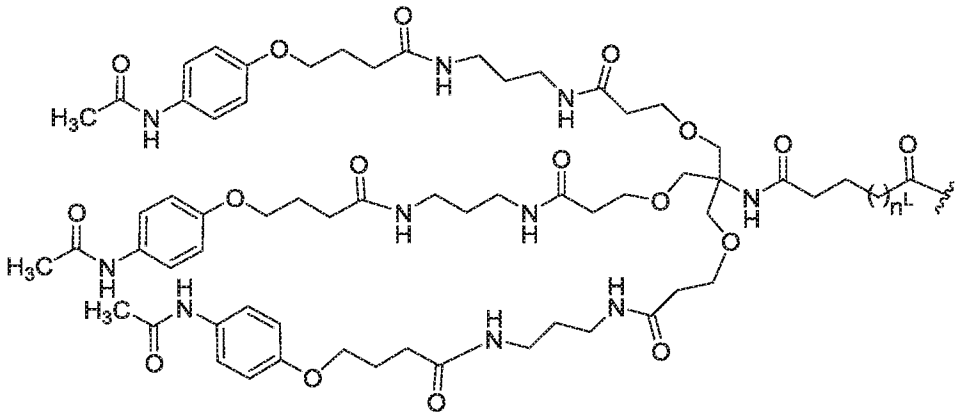
each amino group independently connects to a moiety; and

the P atom connects to the 5'-OH of the oligonucleotide.

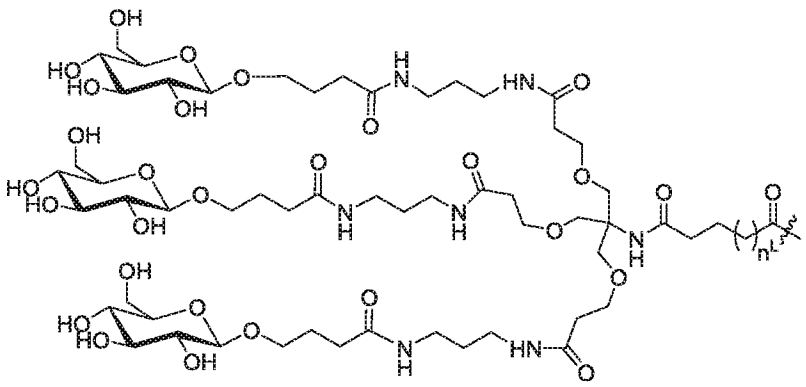
In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



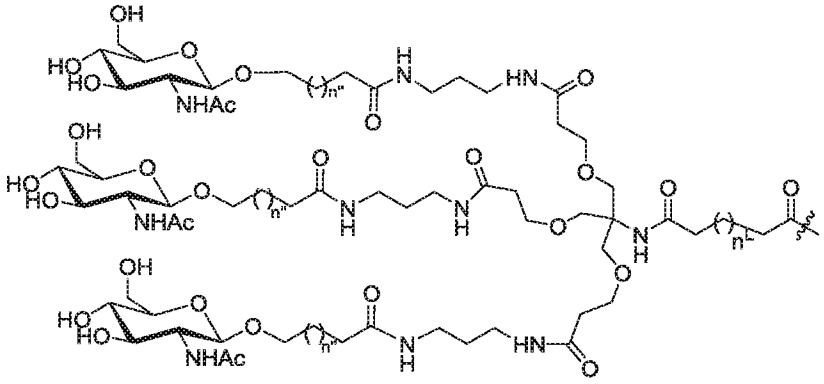
. In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



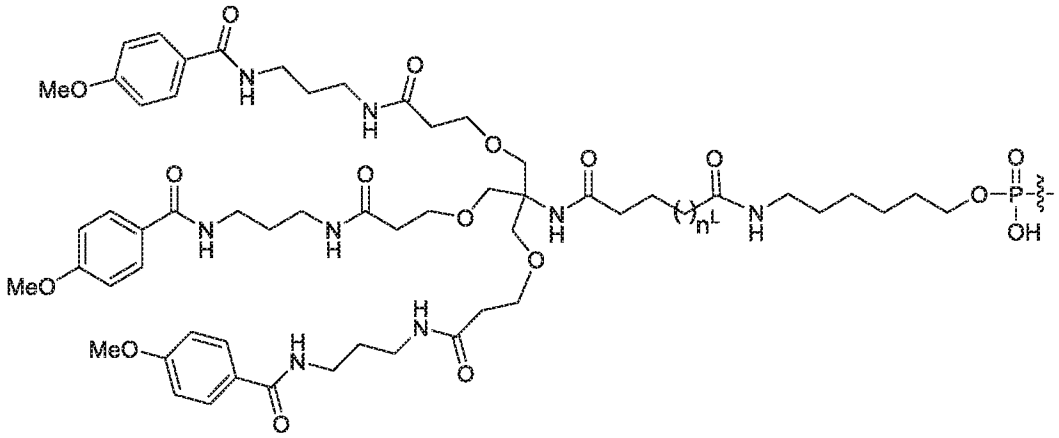
. In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



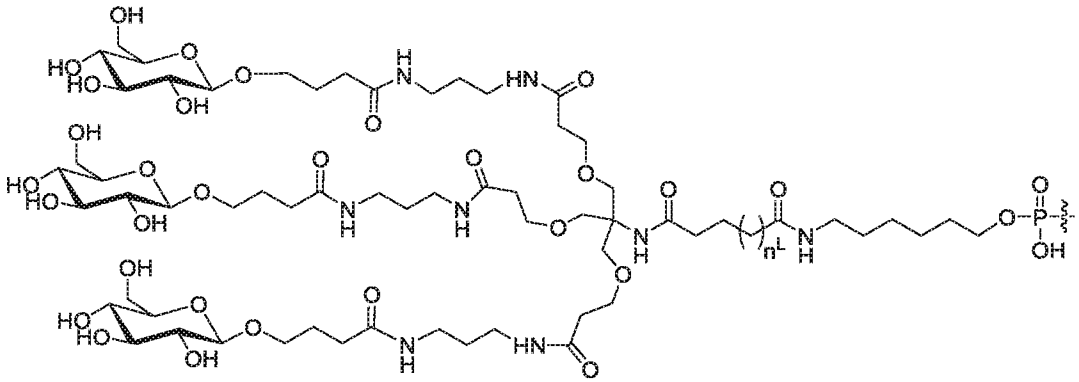
. In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



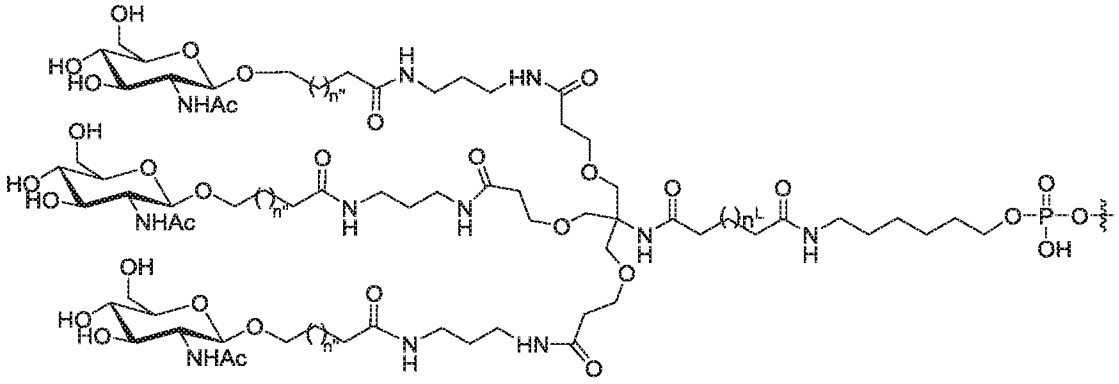
. In some embodiments, the moiety and the linker, or $(R^D)b$–L^{M1}–L^{M2}–L^{M3}–, is or comprises



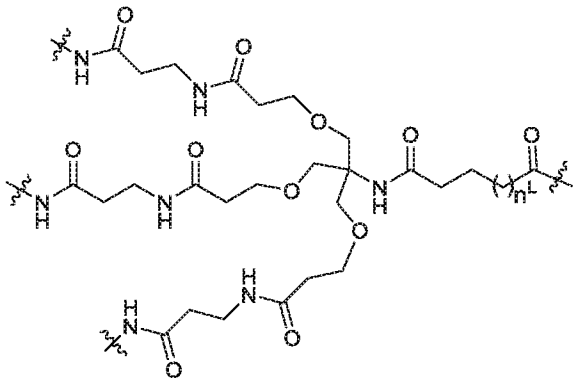
. In some embodiments, the moiety and the linker, or $(R^D)b$–L^{M1}–L^{M2}–L^{M3}–, is or comprises



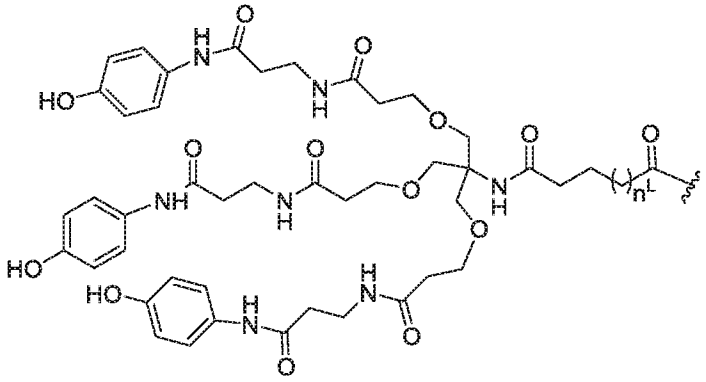
. In some embodiments, the moiety and the linker, or $(R^D)b$–L^{M1}–L^{M2}–L^{M3}–, is or comprises



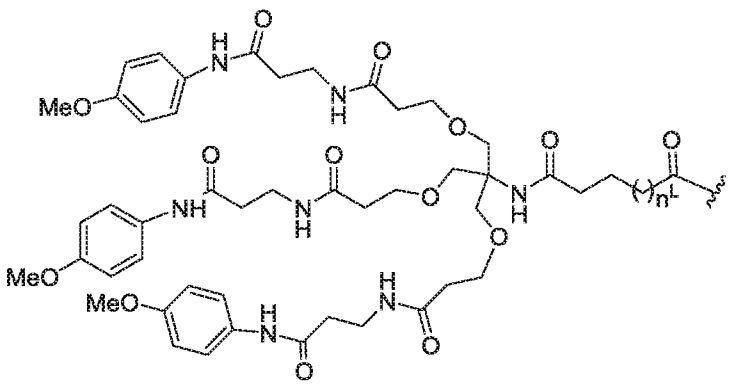
. In some embodiments, a linker, or L^{M1}, is or comprises



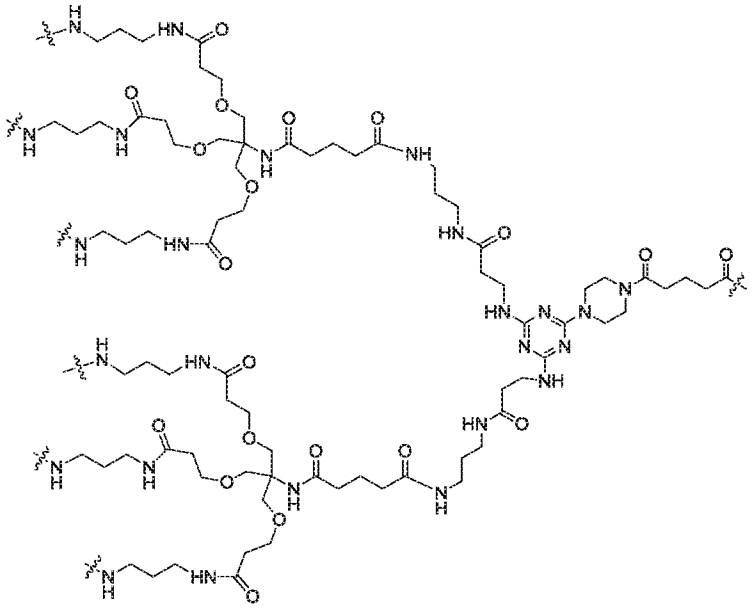
. In some embodiments, the moiety and linker, or $(R^D)b-L^{M1}-L^{M2}-L^{M3}-$, is or comprises:



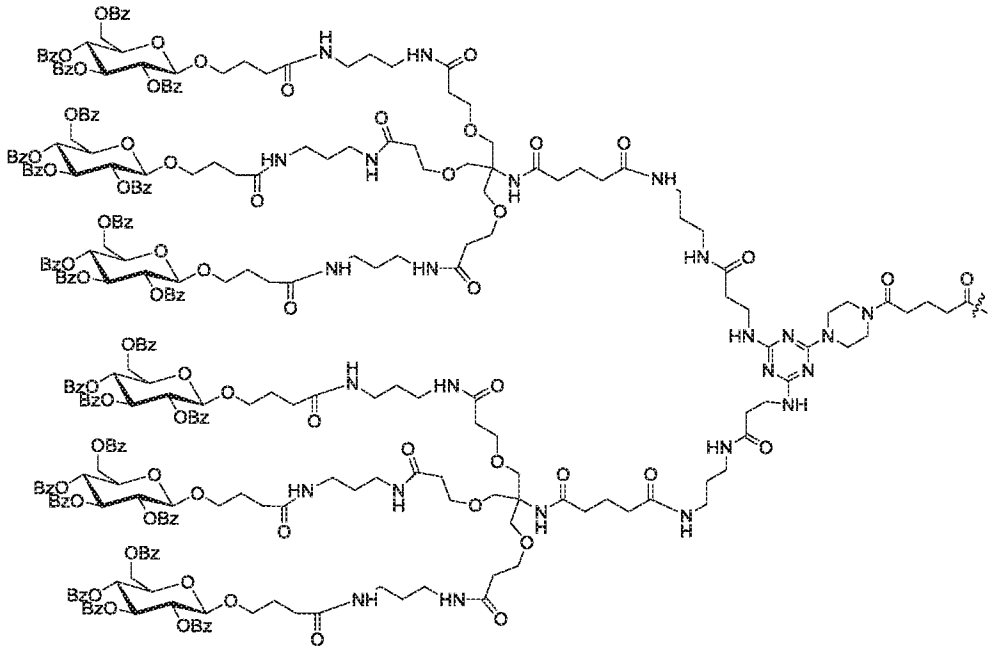
. In some embodiments, the moiety and linker, or $(R^D)b-L^{M1}-L^{M2}-L^{M3}-$, is or comprises:



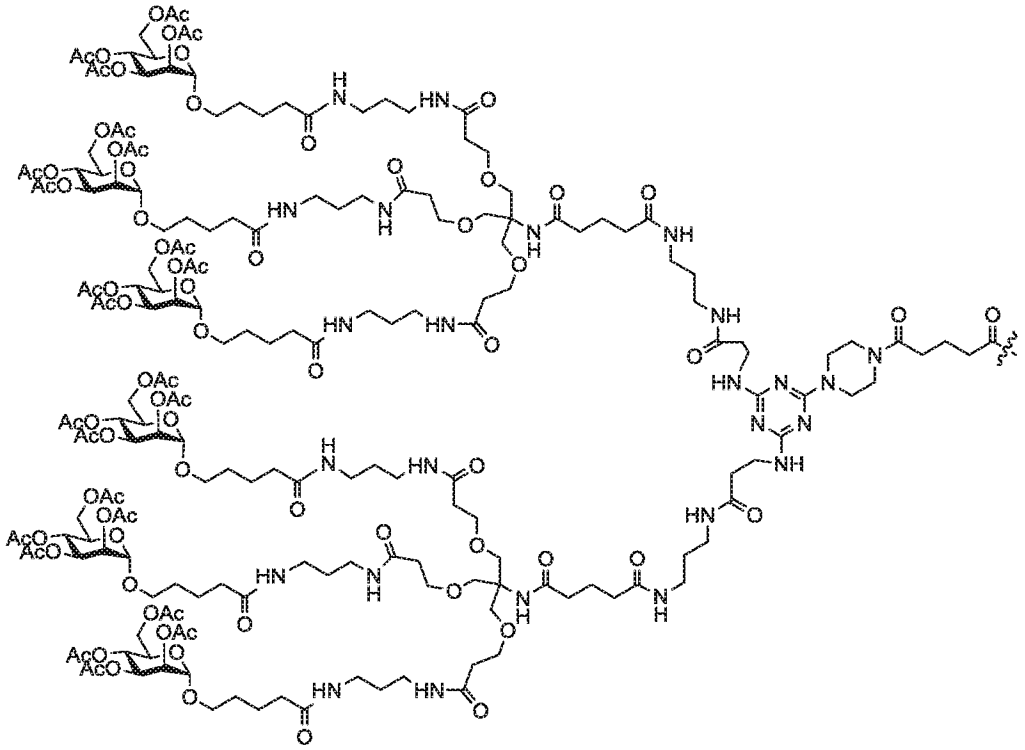
. In some embodiments, a linker is



. In some embodiments, the moiety and linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises:



. In some embodiments, the moiety and linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises:



[001133] In some embodiments, n^L is 1-8. In some embodiments, n^L is 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments, n^L is 1. In some embodiments, n^L is 2. In some embodiments, n^L is 3. In some embodiments, n^L is 4. In some embodiments, n^L is 5. In some embodiments, n^L is 6. In some embodiments, n^L is 7. In some embodiments, n^L is 8.

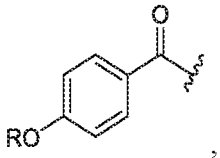
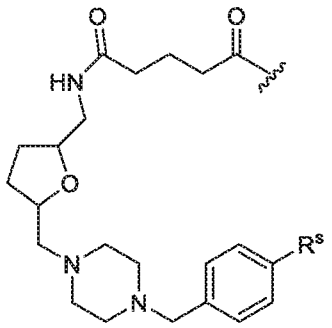
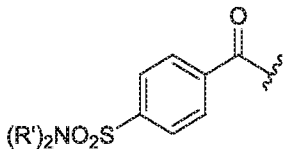
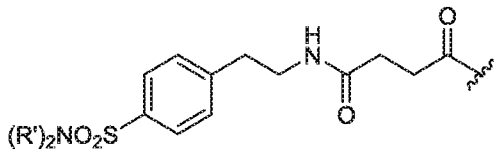
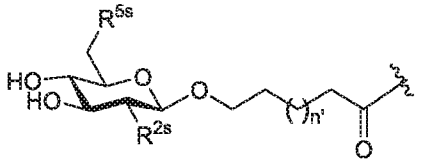
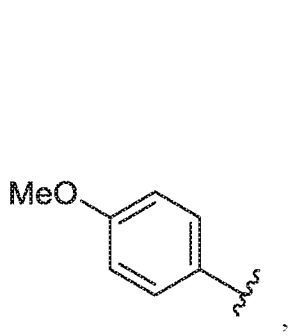
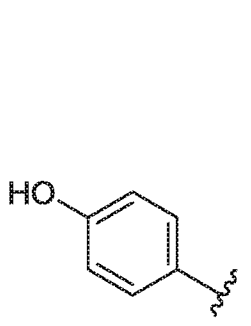
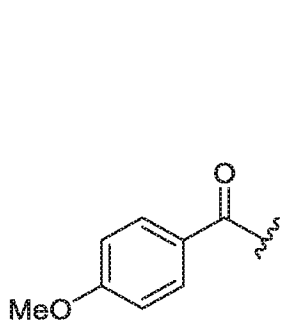
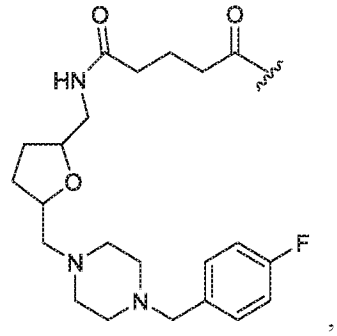
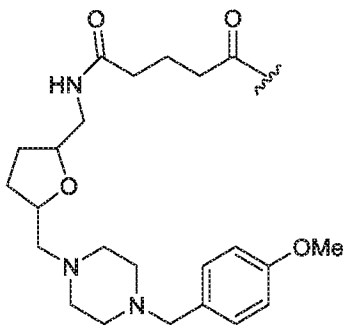
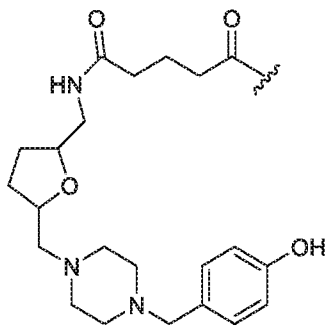
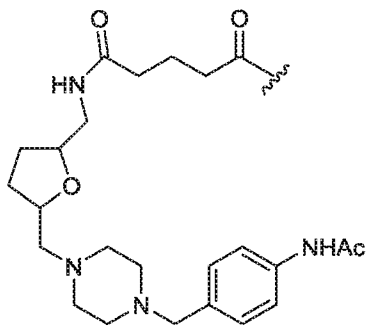
[001134] In some embodiments, L^{M2} is a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-10} aliphatic group and a C_{1-10} heteroaliphatic group having 1-5 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, $-C(R')_2-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$, $-OP(O)(NR')O-$, $-OP(OR')O-$, $-OP(SR')O-$, $-OP(NR')O-$, $-OP(R')O-$, or $-OP(OR')[B(R')_3]O-$; and one or more CH or carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L^{M2} is a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-10} aliphatic group and a C_{1-10} heteroaliphatic group having 1-5 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, $-C(R')_2-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, or $-P(O)(R')-$. In some

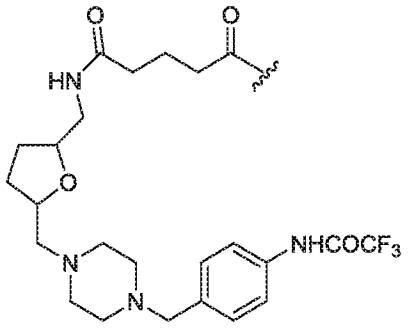
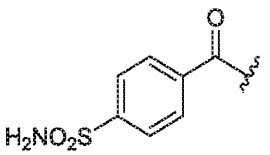
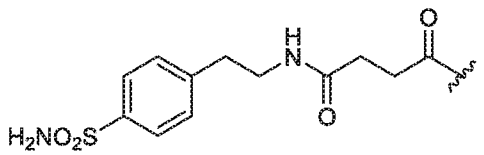
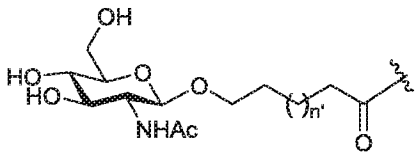
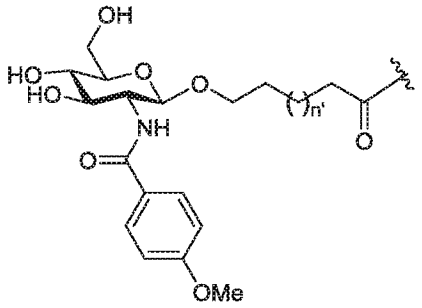
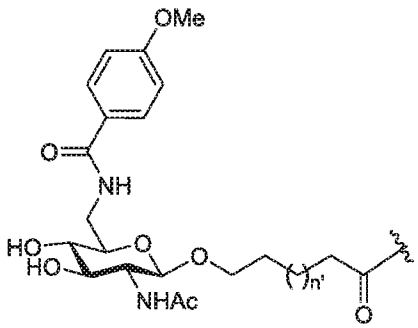
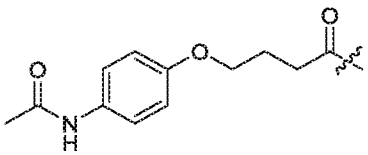
embodiments, L^{M2} is is a covalent bond, or a bivalent, optionally substituted, linear or branched C_{1-10} aliphatic wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, –C(R')$_2$–, –O–, –S–, –N(R')–, or –C(O)–. In some embodiments, L^{M2} is –NH–$(CH_2)_6$–, wherein –NH– is bonded to L^{M1}.

[001135] In some embodiments, L^{M3} is is –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')–, –OP(O)(SR')–, –OP(O)(R')–, –OP(O)(NR')–, –OP(S)(OR')–, –OP(S)(SR')–, –OP(S)(R')–, –OP(S)(NR')–, –OP(R')–, –OP(OR')–, –OP(SR')–, –OP(NR')–, or –OP(OR')[B(R')$_3$]–. In some embodiments, L^{M3} is –OP(O)(OR')–, or –OP(O)(SR')–, wherein –O– is bonded to L^{M2}. In some embodiments, the P atom is connected to a sugar unit, a nucleobase unit, or an internucleotidic linkage. In some embodiments, the P atom is connected to a –OH group through formation of a P–O bond. In some embodiments, the P atom is connected to the 5'–OH group through formation of a P–O bond.

[001136] In some embodiments, L^{M1} is a covalent bond. In some embodiments, L^{M2} is a covalent bond. In some embodiments, L^{M3} is a covalent bond. In some embodiments, L^{M1} is L^{M2} as described in the present disclosure. In some embodiments, L^{M1} is L^{M3} as described in the present disclosure. In some embodiments, L^{M2} is L^{M1} as described in the present disclosure. In some embodiments, L^{M2} is L^{M3} as described in the present disclosure. In some embodiments, L^{M3} is L^{M1} as described in the present disclosure. In some embodiments, L^{M3} is L^{M2} as described in the present disclosure. In some embodiments, L^{M} is L^{M1} as described in the present disclosure. In some embodiments, L^{M} is L^{M2} as described in the present disclosure. In some embodiments, L^{M} is L^{M3} as described in the present disclosure. In some embodiments, L^{M} is L^{M1}–L^{M2}, wherein each of L^{M1} and L^{M2} is independently as described in the present disclosure. In some embodiments, L^{M} is L^{M1}–L^{M3}, wherein each of L^{M1} and L^{M3} is independently as described in the present disclosure. In some embodiments, L^{M} is L^{M2}–L^{M3}, wherein each of L^{M2} and L^{M3} is independently as described in the present disclosure. In some embodiments, L^{M} is L^{M1}–L^{M2}–L^{M3}, wherein each of L^{M1}, L^{M2} and L^{M3} is independently as described in the present disclosure.

[001137] In some embodiments, each R^{D} is independently a chemical moiety as described in the present disclosure. In some embodiments, R^{D} is an additional chemical moiety. In some embodiments, R^{D} is targeting moiety. In some embodiments, R^{D} is or comprises a carbohydrate moiety. In some embodiments, R^{D} is or comprises a lipid moiety. In some embodiments, R^{D} is or comprises a ligand moiety for, e.g., cell receptors such as a sigma receptor, an asialoglycoprotein receptor, etc. In some embodiments, a ligand moiety is or comprises an anisamide moiety, which may be a ligand moiety for a sigma receptor. In some embodiments, a ligand moiety is or comprises a lipid. In some embodiments, a ligand moiety is or comprises a GalNAc moiety, which may be a ligand moiety for an asialoglycoprotein

receptor. In some embodiments, R^D is selected from optionally substituted phenyl,  ,  ,  ,  , and  , wherein n' is 0 or 1, and each other variable is independently as described in the present disclosure. In some embodiments, R^s is F. In some embodiments, R^s is OMe. In some embodiments, R^s is OH. In some embodiments, R^s is NHAc. In some embodiments, R^s is $NHCOCF_3$. In some embodiments, R' is H. In some embodiments, R is H. In some embodiments, R^{2s} is NHAc, and R^{5s} is OH. In some embodiments, R^{2s} is p-anisoyl, and R^{5s} is OH. In some embodiments, R^{2s} is NHAc and R^{5s} is p-anisoyl. In some embodiments, R^{2s} is OH, and R^{5s} is p-anisoyl. In some embodiments, R^D is selected from  ,  ,  ,  ,  ,  ,  ,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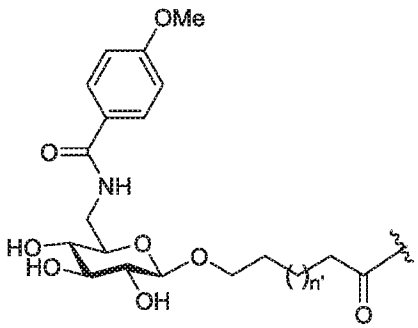

. Further embodiments of R^D includes additional chemical moiety embodiments, e.g., those described in the examples.

[001138] In some embodiments, n' is 1. In some embodiments, n' is 0.

[001139] In some embodiments, n" is 1. In some embodiments, n" is 2.

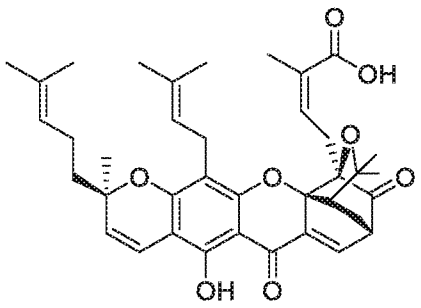
[001140] In some embodiments, a provided oligonucleotide, e.g., DMD oligonucleotide, is conjugated to an additional component (chemical moiety). In some embodiments, a composition comprises any DMD oligonucleotide, or combination thereof, described herein, can be conjugated to any

chemical moiety described herein or known in the art.

[001141] In some embodiments, a composition comprising a provided oligonucleotide, e.g., a DMD oligonucleotide, comprises an additional component which is any of: Sulfonamide (Carbonic Anhydrases IV inhibitor); Cleavable lipid; Transferrin Receptor 1 (CD71, TfR) ligand; OCTN2 transporter targeting (L-Cartinine); Glut4 and Glut1 Receptor ligand; Mannose Receptor C1 (Mrc1) and Mannose 6P Receptor (M6Pr) ligand; Cleavable Lipid; Cholesterol; or a Peptide (including, but not limited to, a short delivery peptide or cell-penetrating peptide (CPP)).

[001142] Variously oligonucleotides have been designed and/or constructed which comprise an additional component which is, comprises or is derived from: cholesterol; L-carnitine (amide and carbamate bond); Folic acid; Gambogic acid; Cleavable lipid (1,2-dilaurin and ester bond); Insulin receptor ligand; CPP; Glucose (tri- and hex-antennary); and Mannose (tri- and hex-antennary, alpha and beta); and various synthesis schemes for these additional components and oligonucleotides comprising them or molecules derived from them have been devised.

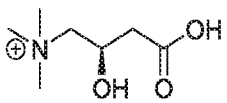
[001143] In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is derived from



WV-DL-14
Gambogic acid

. WV-DL-14 is also known as WV-DL-014. In some embodiments, gambogic acid or a derivative thereof binds to Transferrin receptor (CD71).

[001144] In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is derived from L-cartinine, which binds to the OCTN2 transporter. In some embodiments, a composition comprising a DMD oligonucleotide comprises an additional component which is derived from

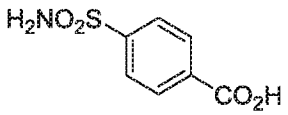


WV-DL-012

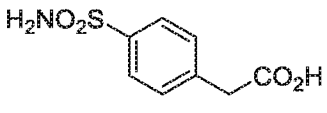
[001145] In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD

oligonucleotide comprises an additional component which is a sulfonamide or a derivative thereof.

[001146] In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is derived from any of:



WV-DL-05



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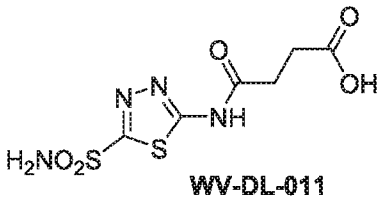

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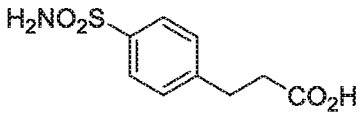

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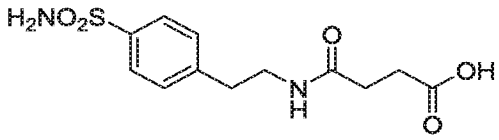

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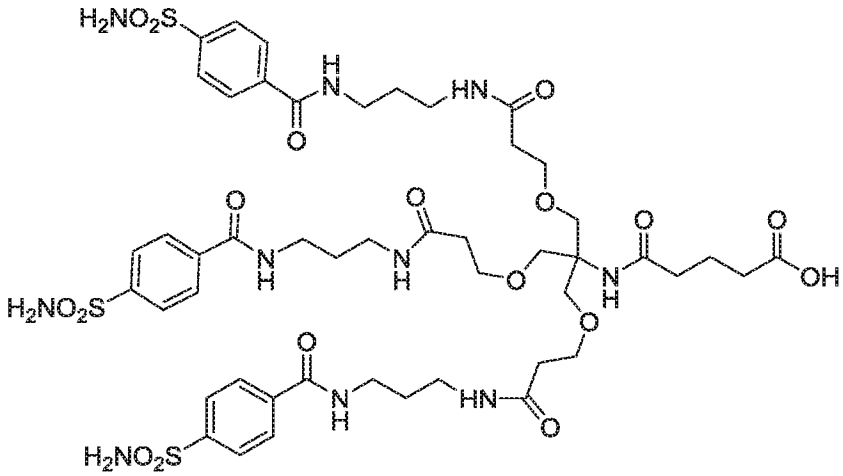

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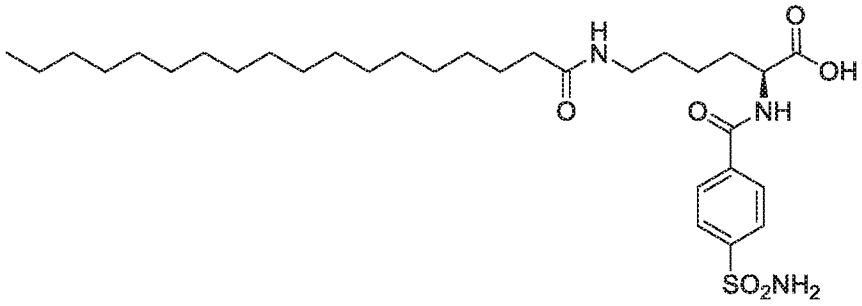
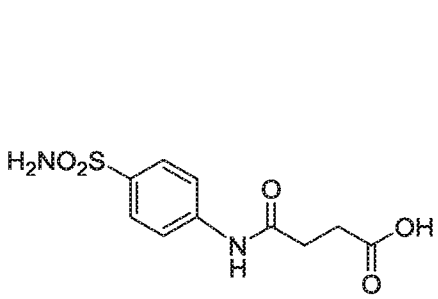
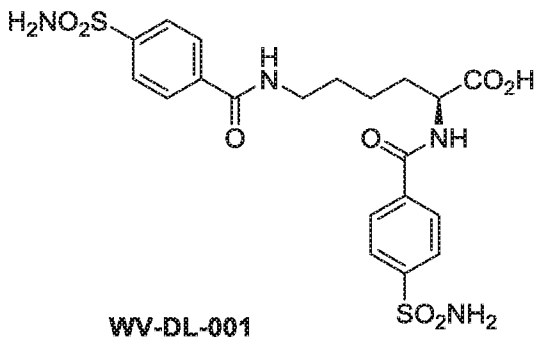


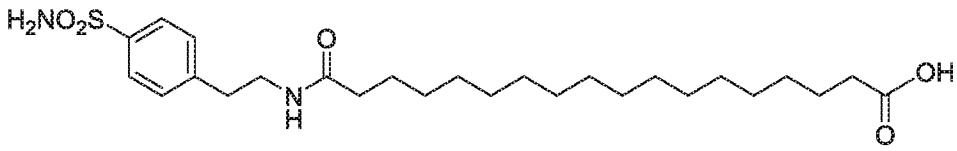
WV-DL-002



WV-DL-010

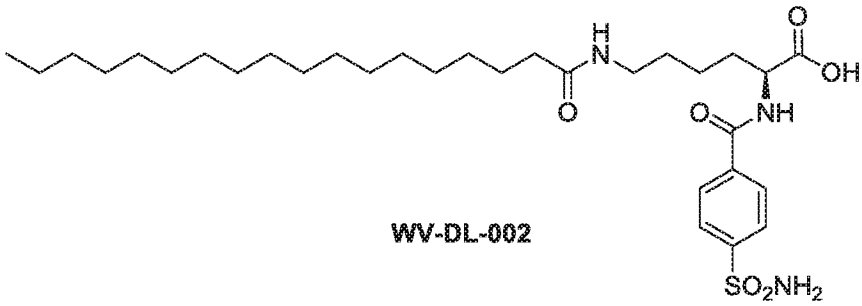


WV-DL-001



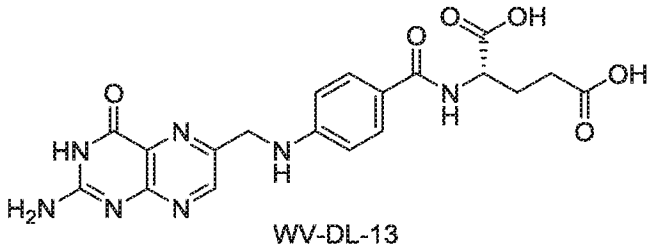
WV-DL-003

[001147] In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is or comprises or comprises a derivative of:



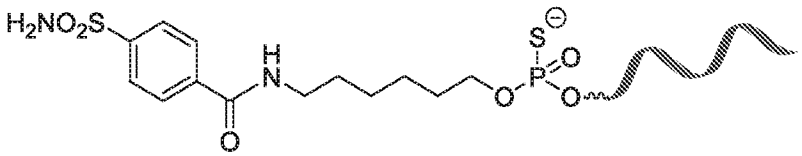
WV-DL-002

[001148] In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is or comprises or comprises a derivative of:



WV-DL-13
folic acid

[001149] In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is derived from any of: WV-DL-001, WV-DL-002, WV-DL-003, WV-DL-006, WV-DL-007, WV-DL-008, WV-DL-009, WV-DL-010, WV-DL-011, WV-DL-012, or WV-Dl-014, and other additional components, wherein the terminal -COOH is used to conjugate the additional component to a linker or to an oligonucleotide. In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is derived from any of: WV-DL-001, WV-DL-002, WV-DL-003, WV-DL-006, WV-DL-007, WV-DL-008, WV-DL-009, WV-DL-010, WV-DL-011, WV-DL-012, or WV-Dl-014, and other additional components, wherein the terminal -COOH is used to conjugate the additional component to a linker, wherein the conjugation process converts the -COOH to a −C(O)− which connects a linker. In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is derived from any of: WV-DL-001, WV-DL-002, WV-DL-003, WV-DL-006, WV-DL-007, WV-DL-008, WV-DL-009, WV-DL-010, WV-DL-011, WV-DL-012, or WV-Dl-014, and other additional components, wherein the terminal -COOH is used to conjugate the additional component to a linker, wherein the conjugation process replaces the -COOH with −C(O)− which connects to −NH− of a linker (e.g., L001). A non-limiting example of a product of this process for conjugation, using an additional component derived from WV-DL-006 is shown here:



WV-DL-005

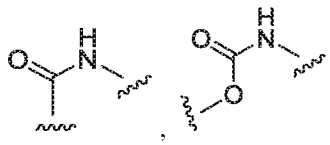
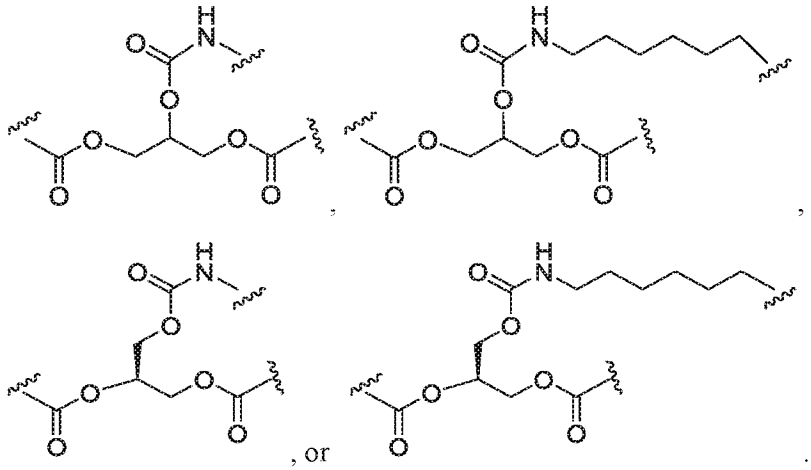
, wherein WV-DL-005 indicates the additional component.

[001150] In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is a lipid. In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is a lipid, including but not limited to a lipid described herein.

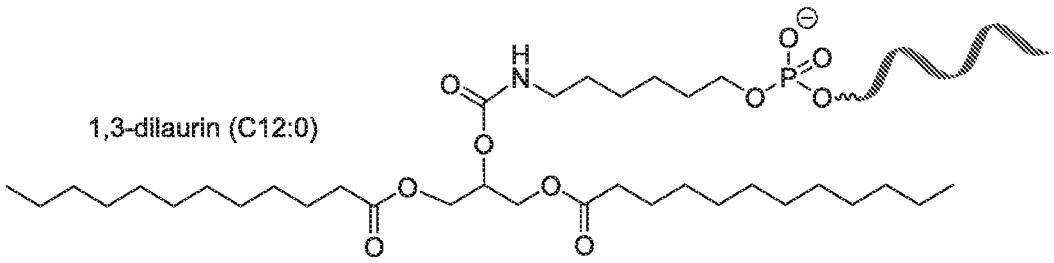
[001151] In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD

oligonucleotide, comprises an additional component, wherein the additional component is conjugated to the oligonucleotide via a cleavable linker. In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide, comprises an additional component which is a lipid, wherein the lipid is conjugated to the oligonucleotide via a cleavable linker. In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide, comprises an additional component which is a lipid, including but not limited to a lipid described herein, wherein the lipid is conjugated to the oligonucleotide via a cleavable linker.

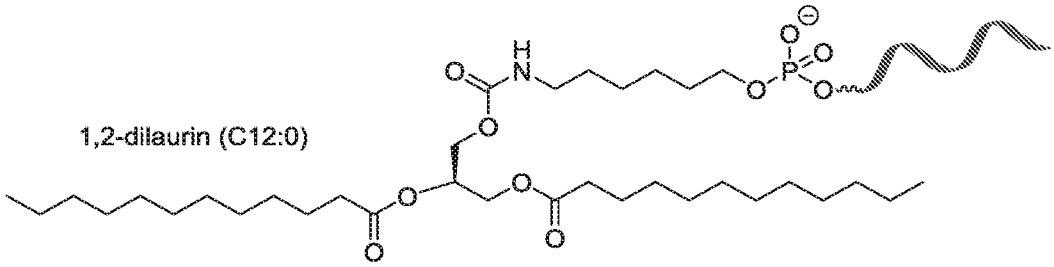
[001152] In some embodiments a cleavable linker comprises an ester. In some embodiments, a cleavable linker is cleavable within a cell, allowing the oligonucleotide to be physically separated from the additional component.

[001153] In some embodiments a cleavable linker is or comprises:  ,  , or .

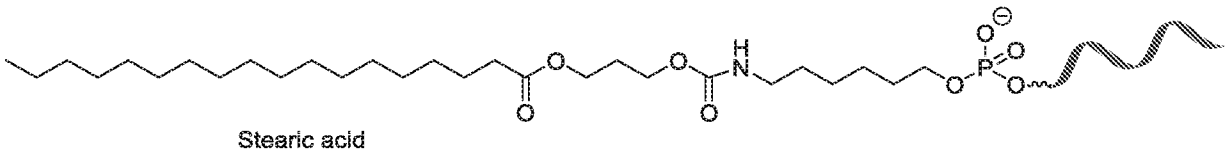
[001154] Non-limiting examples of an oligonucleotide conjugated to a lipid(s) via a cleavable linker are shown here:



, and

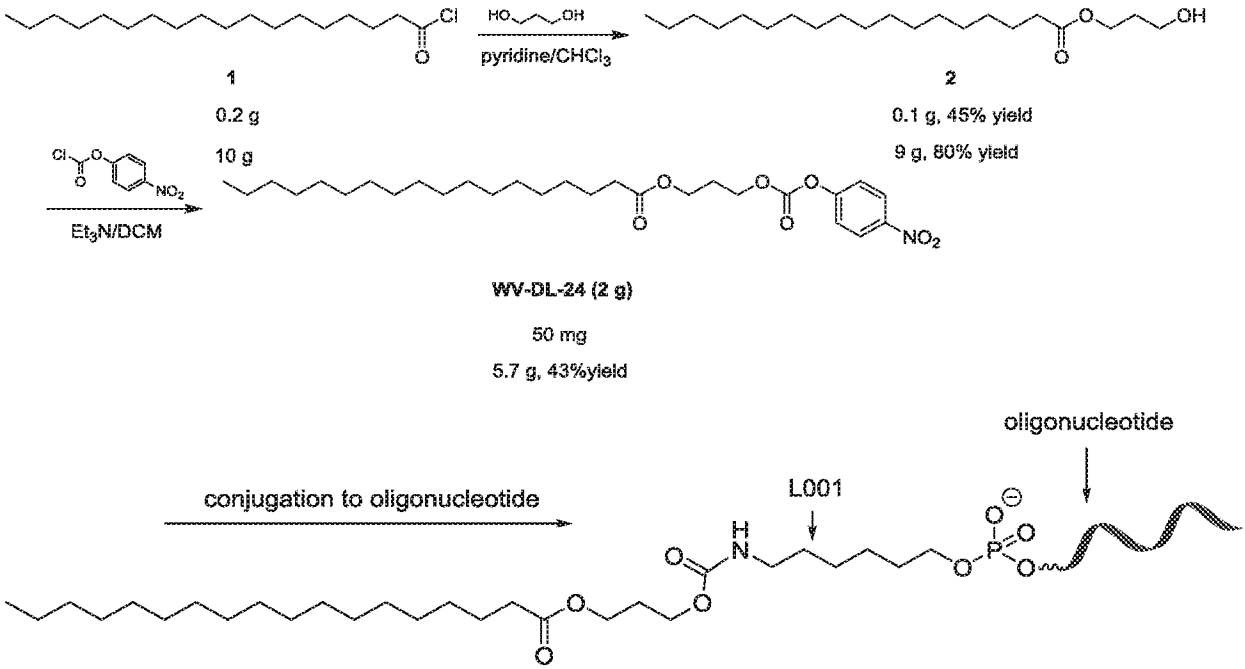


[001155] A non-limiting example of an oligonucleotide comprising an additional component which is stearic acid, linked to the oligonucleotide via a cleavable linker is shown here:

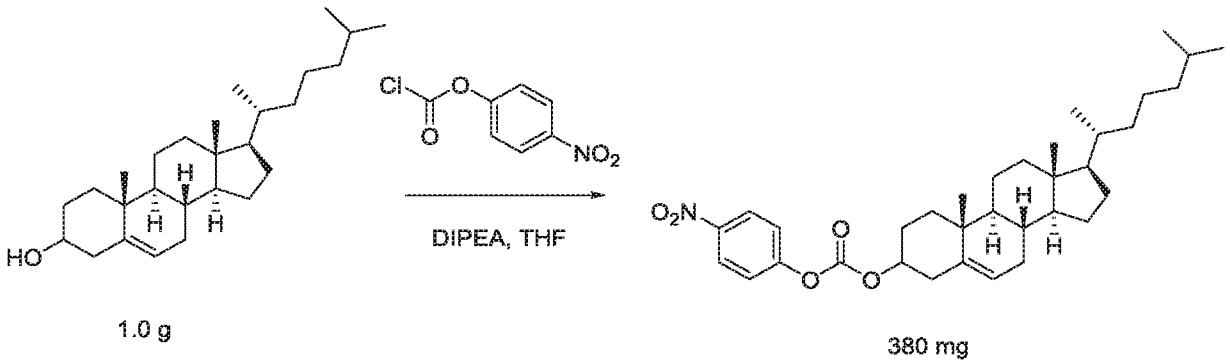


wherein stearic acid indicates the additional component.

[001156] A non-limiting reagent useful for conjugating stearic acid through a cleavable linker and its example preparation and use are shown below:



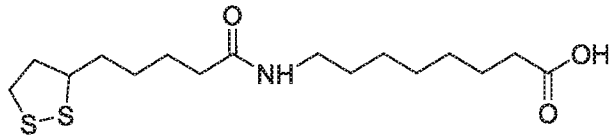
[001157] A non-limiting reagent useful for conjugating a cholesterol derivative through a cleavable linker, and its example preparation, are shown here:



1.0 g

380 mg

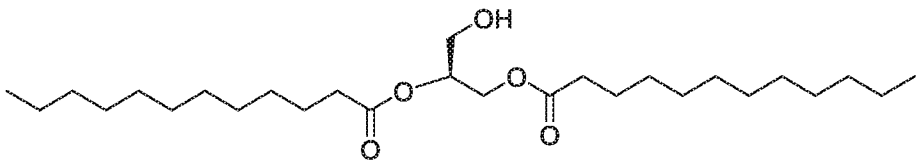
[001158] In some embodiments, a composition comprising an oligonucleotide comprises an additional component derived from:



WV-DL-019

.

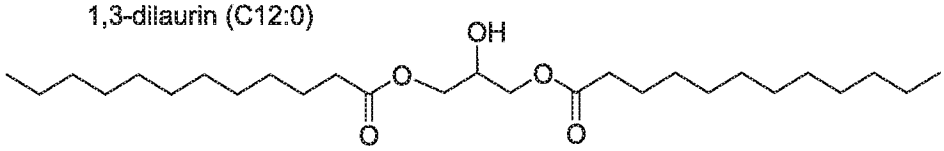
[001159] In some embodiments, a composition comprising an oligonucleotide comprises an additional component derived from either of:



1,2-dilaurin (C12:0)

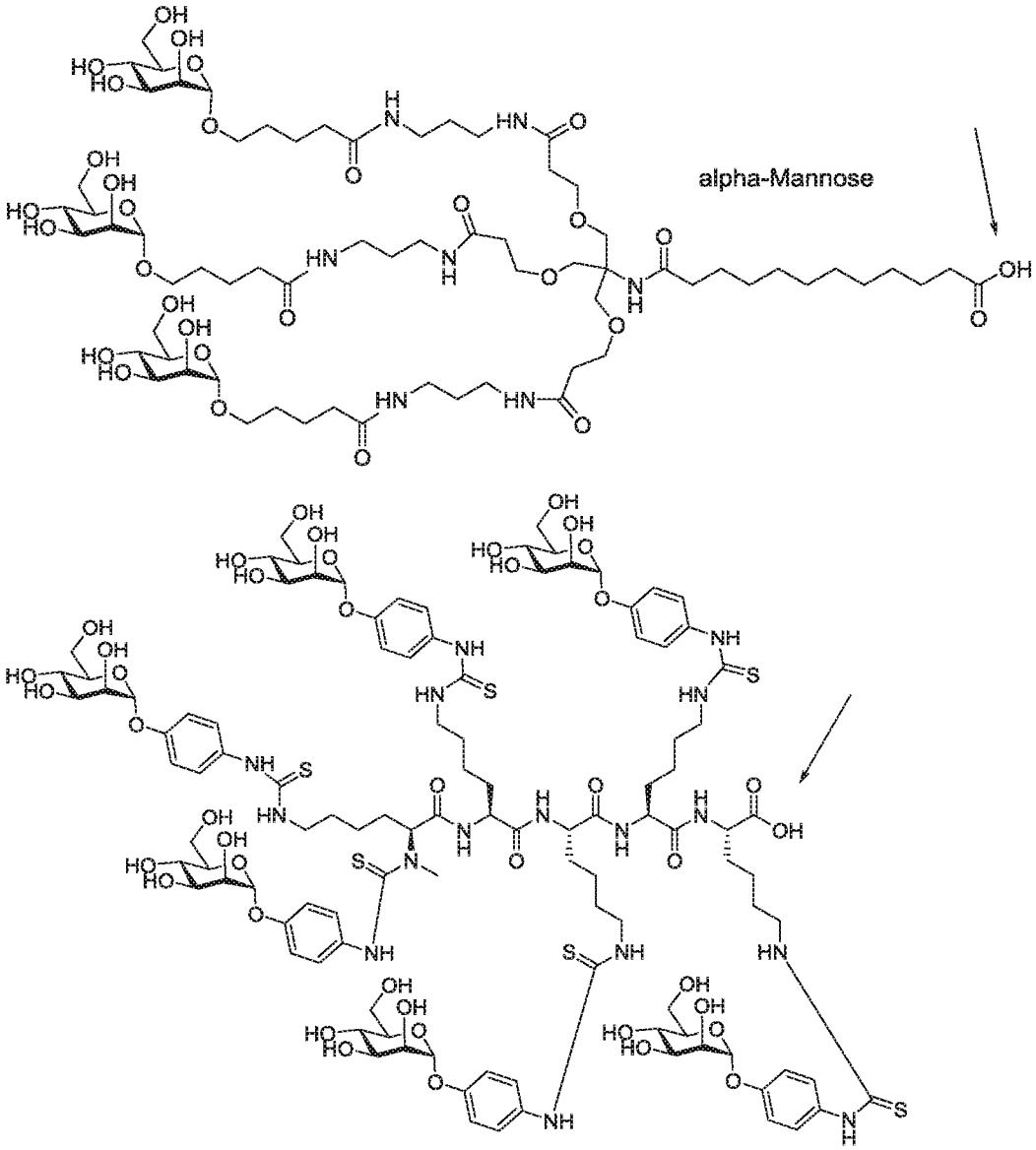
, and

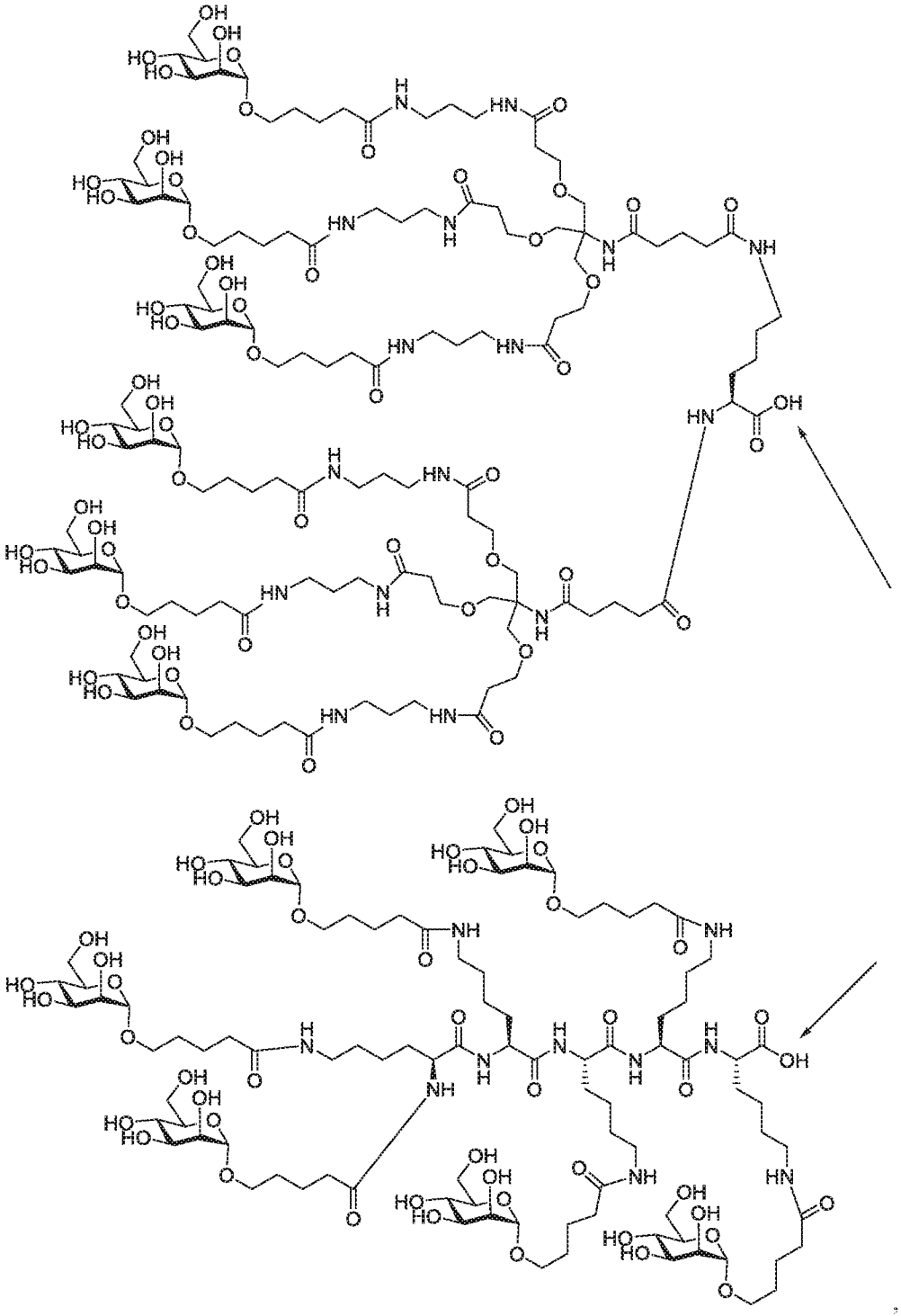
1,3-dilaurin (C12:0)



.

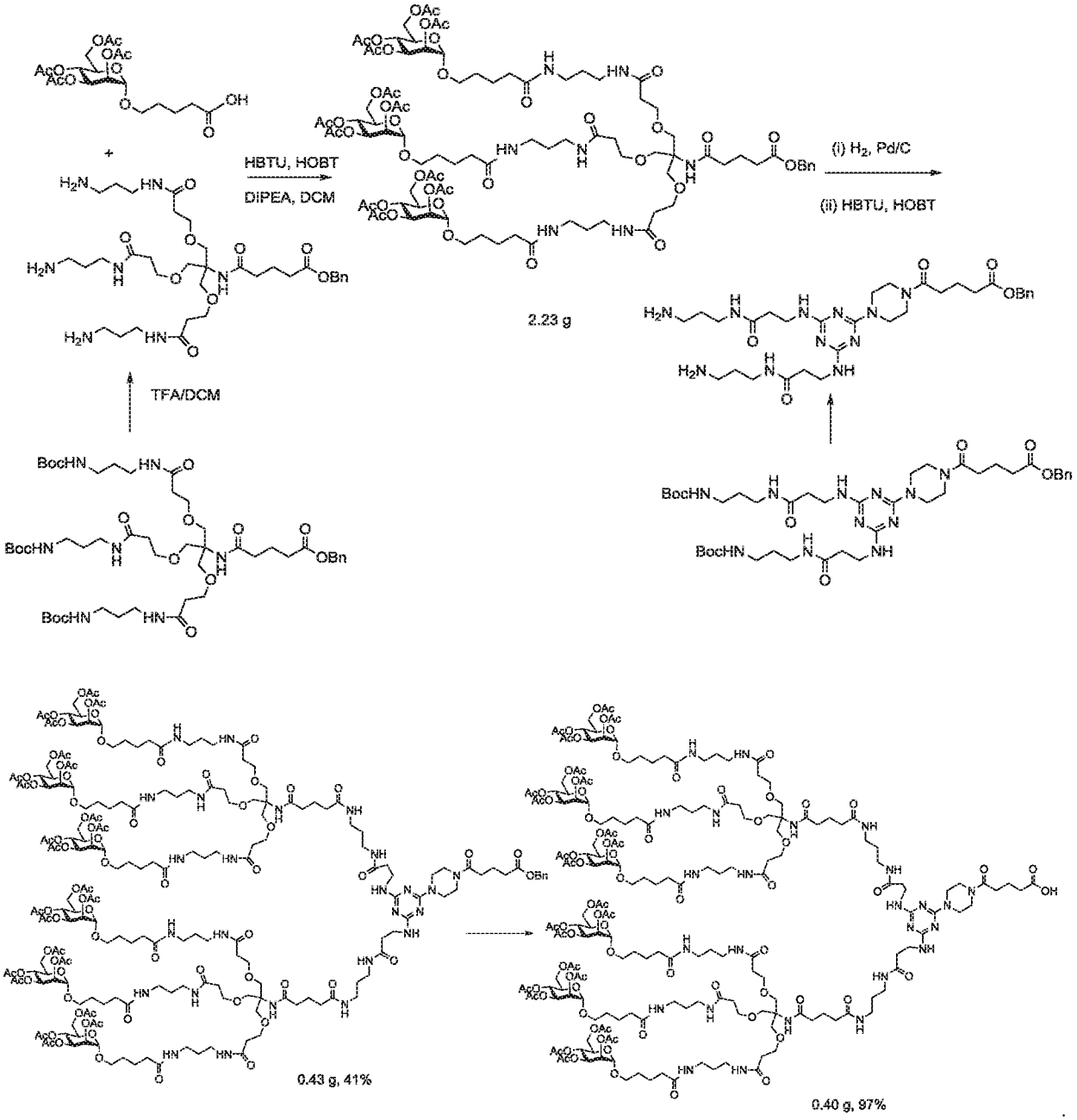
[001160] In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises a mannose receptor ligand. In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises a mannose receptor ligand which is a mannose receptor inhibitor. In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is derived from any of:


alpha-Mannose



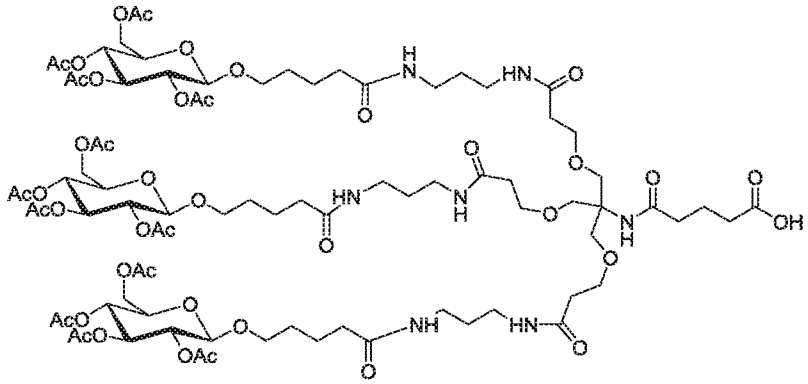
, where the arrow indicates a -COOH which can be used to conjugate the additional component to an oligonucleotide, optionally via a linker.

[001161] A non-limiting example of a procedure for preparing an additional component comprising a mannose receptor ligand is shown here:



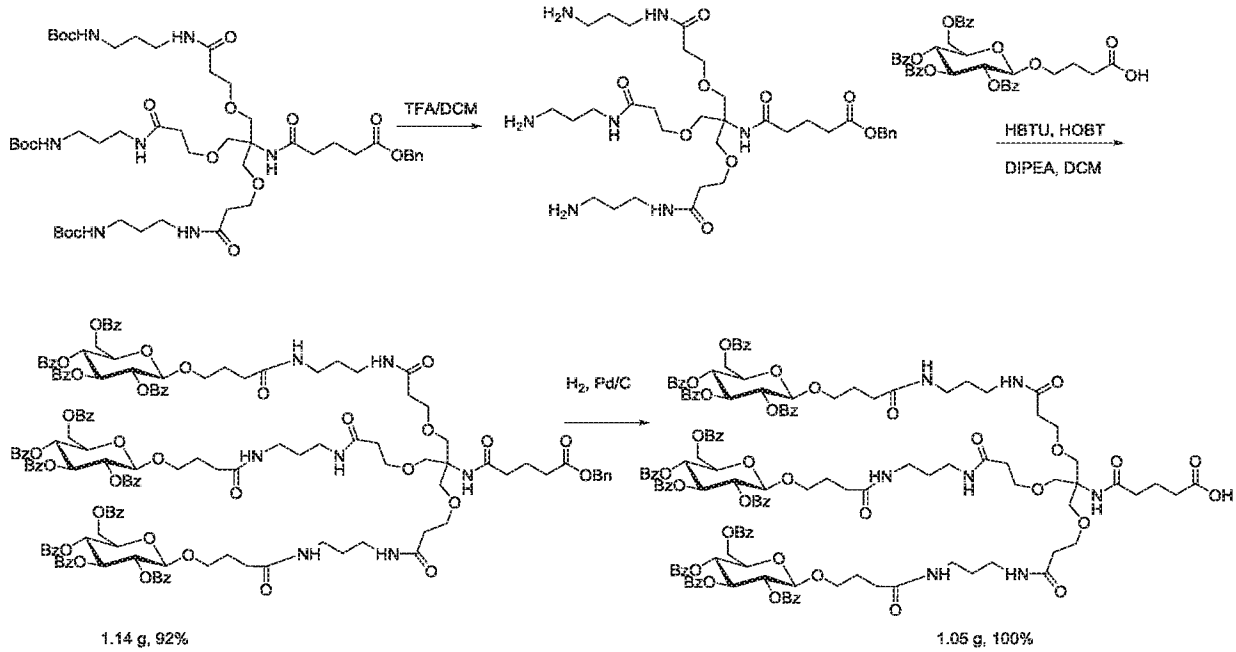
[001162] In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is a ligand (or derivative thereof) that binds to a glucose or Glut4 receptor. In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is a ligand (or derivative thereof) that binds to a glucose receptor. In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is a ligand (or derivative thereof) that binds to and inhibits a glucose receptor. In some embodiments, a ligand (or derivative thereof) that binds to a glucose or Glut4 receptor is mono-, bi-, tri, or hex-antennary. In some embodiments, a composition

comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component which is

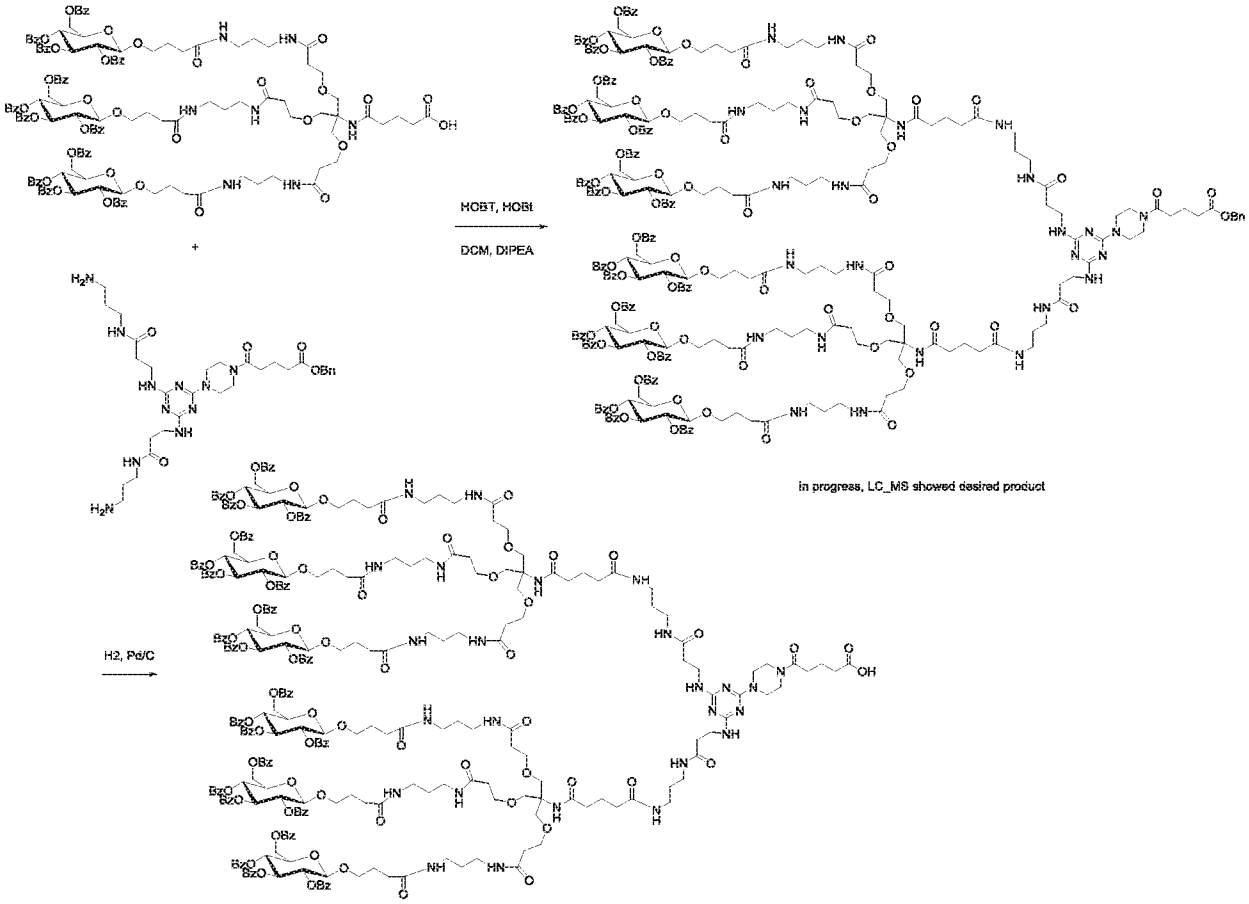


derived from:

[001163] A non-limiting example of a procedure for synthesis of a tri-antennary glucose receptor inhibitor is shown here:



[001164] A non-limiting example of a procedure for synthesis of a hex-antennary glucose receptor inhibitor is shown here:



[001165] In some embodiments, an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component, wherein the additional component increases internalization of the oligonucleotide via receptor-mediated endocytosis.

[001166] In some embodiments, an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component, wherein the additional component is an aptamer.

[001167] In some embodiments, an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component, wherein the additional component is an aptamer which is a peptide aptamer, a RNA apatamer, a DNA aptamer, or an aptamer which comprises a RNA nucleotide, a DNA nucleotide, a modified nucleotide, and/or an amino acid and/or peptide.

[001168] In some embodiments, an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component, wherein the additional component is an aptamer which binds to a receptor.

[001169] In some embodiments, an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component, wherein the additional component is an aptamer which binds to a receptor which is a mannose receptor, a mannose-6-phosphate receptor or transferrin receptor.

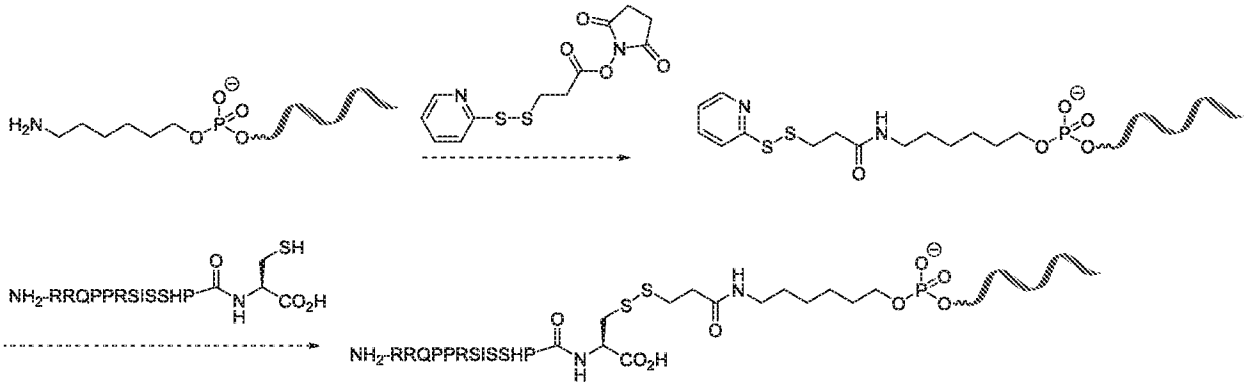
[001170] In some embodiments, an oligonucleotide, e.g., a DMD oligonucleotide comprises an

additional component, wherein the additional component is an aptamer that increases internalization of the oligonucleotide.

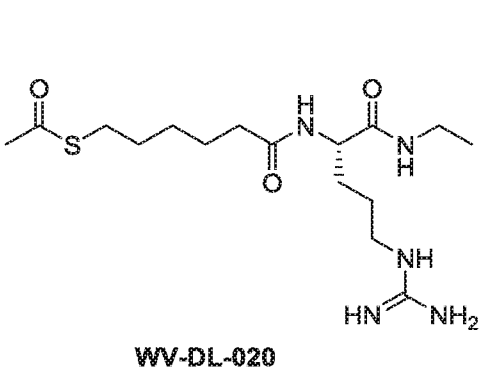
[001171] In some embodiments, an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component, wherein the additional component is an aptamer that increases internalization of the oligonucleotide via receptor-mediated endocytosis.

[001172] In some embodiments, an oligonucleotide, e.g., a DMD oligonucleotide comprises an additional component, wherein the additional component is or comprises a peptide. In some embodiments, a peptide is a cell-penetrating peptide (CPP). In some embodiments, a CPP is arginine-rich. In some embodiments, a CPP has or comprises the amino acid sequence of RRQPPRSISSHPC or RRQPPRSISSHP.

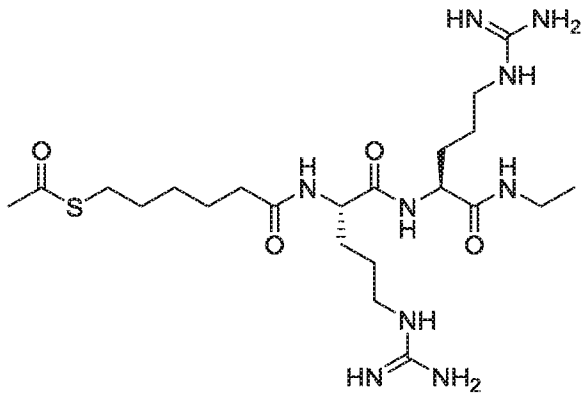
[001173] A non-limiting example of a procedure for conjugating a peptide to a DMD oligonucleotide is shown here:



[001174] In some embodiments, a peptide comprises the amino acid sequence of RC or RRC. In some embodiments, a peptide comprises a structure of either of:



WV-DL-020



WV-DL-021

[001175] Provided oligonucleotides, e.g., DMD oligonucleotides, may be conjugated as PMOs to cell-penetrating peptides. Yokota et al. 2012 Nucl. Acid Ther. 22: 306; Wu et al. 2009 Mol. Ther. 17:

864–871; Goyenvalle et al. 2010 Mol. Ther. 18, 198–205; Jearawiriyapaisarn et al. 2010 Cardiovasc. Res. 85, 444–453.; Crisp et al. 2011 Hum. Mol. Genet. 20, 413–421; Widrick et al. 2011; Wu et al. 2011 PLoS One 6, e19906.

[001176] In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises one or more peptide and/or peptide tag. In some embodiments, a peptide is or comprises a muscle-targeting heptapeptide (MSP). In some embodiments, the sequence of a muscle-targeting helptapeptide is or comprises the sequence of ASSLNIAXB. In some embodiments, a peptide is or comprises a cell-penetrating peptide. In some embodiments, the sequence of a cell-penetrating peptide comprises multiple arginines. In some embodiments, the sequence of a cell-penetrating peptide is or comprises RXRRBRRXRRBRXB.

[001177] In some embodiments, the sequence of a peptide is or comprises a sequence of: ASSLNIAXB, RXRRBRRXRRBRXB, RXRRXRRXRRXRXB, ASSLNIAXB-RXRRBRRXRRBRXB, RXRRBRRXRRBRXB-ASSLNIAXB, or any sequence comprising both ASSLNIAXB and either RXRRBRRXRRBRXB or RXRRXRRXRRXRXB, wherein R is L-arginine, X is 6-aminohexanoic acid, and B is beta-alanine.

[001178] A muscle-targeting heptapeptide (MSP) fused to an arginine-rich cell-penetrating peptide (B-peptide) may be conjugated to provided oligonucleotides in accordance with the present disclosure. Yin et al. 2009 Hum. Mol. Genet. 18: 4405-4414. Yokota et al. 2009 Arch. Neurol. 66: 32.

[001179] In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises anisamide or a derivative thereof.

[001180] In some embodiments, a composition comprising an oligonucleotide, e.g., a DMD oligonucleotide comprises one or more guanidinium group. vPMOs are reportedly morpholino oligomers conjugated with delivery moiety containing eight terminal guanidinium groups on a dendrimer scaffold that enable entry into cells. Morcos et al. 2008 Biotechniques 45: 613–618; Yokota et al. 2012 Nucl. Acid Ther. 22: 306.

[001181] In some embodiments, an oligonucleotide, e.g., DMD oligonucleotide is delivered using a leash. A non-limiting example of a leash is reported in: Gebski et al. 2003 Hum. Mol. Gen. 12: 1801–1811.

[001182] In some embodiments, an additional chemical moiety is cholesterol; L-carnitine (amide and carbamate bond); Folic acid; Cleavable lipid (1,2-dilaurin and ester bond); Insulin receptor ligand; Gambogic acid; CPP; Glucose (tri- and hex-antennary); or Mannose (tri- and hex-antennary, alpha and beta).

[001183] Certain chemical moieties, e.g., lipid moieties, carbohydrate moieties, targeting moieties, etc. and linker moieties for connecting such moieties to oligonucleotide chains (e.g., via sugars,

nucleobases, internucleotidic linkages, etc.) are described in the Tables as example; some of such chemical and linker moieties and related technologies for their preparation, conjugation with oligonucleotide chains, and uses are described in e.g., WO 2017/062862, WO 2017/192679, WO 2017/210647, etc.

Lipids

[001184] In some embodiments, an additional chemical moiety/component is a lipid moiety. In some embodiments, the present disclosure provided oligonucleotide compositions further comprise one or more lipids. In some embodiments, incorporation of lipid moieties into oligonucleotides can provide unexpected, greatly improved properties (*e.g.*, activities, toxicities, distribution, pharmacokinetics, *etc.*).

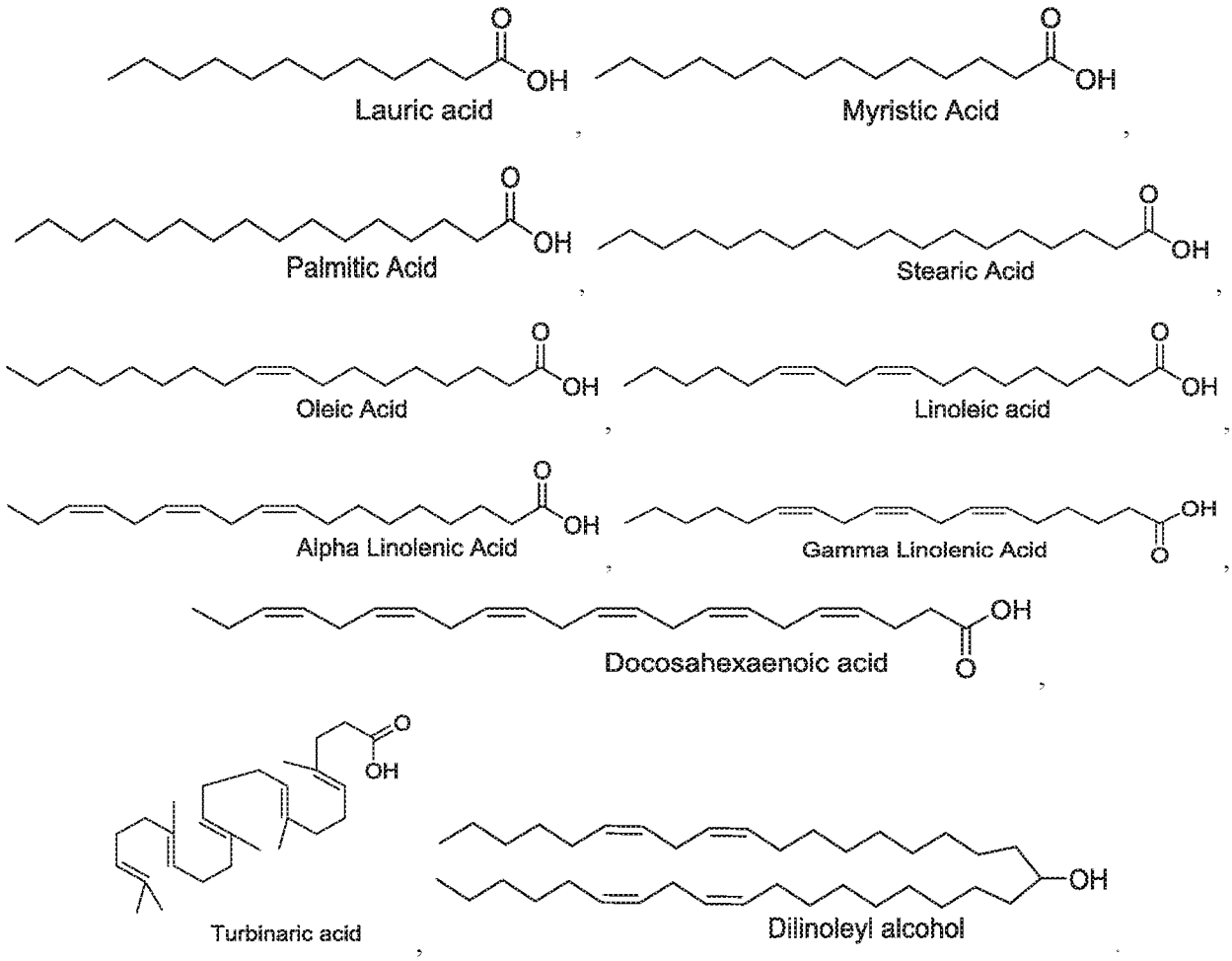
[001185] A composition can be obtained by combining an active compound with a lipid. In some embodiments, the lipid is conjugated to an active compound. In some embodiments, the lipid is not conjugated to an active compound. In some embodiments, a lipid comprises a C_{10}-C_{40} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises a C_{10}-C_{40} linear, saturated or partially unsaturated, aliphatic chain, optionally substituted with one or more C_{1-4} aliphatic group. In some embodiments, a lipid comprises a C_{10}-C_{60} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises a C_{10}-C_{60} linear, saturated or partially unsaturated, aliphatic chain, optionally substituted with one or more C_{1-4} aliphatic group. In some embodiments, a lipid comprises a C_{10}-C_{80} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises a C_{10}-C_{80} linear, saturated or partially unsaturated, aliphatic chain, optionally substituted with one or more C_{1-4} aliphatic group. In some embodiments, a lipid comprises a C_{10}-C_{100} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises a C_{10}-C_{100} linear, saturated or partially unsaturated, aliphatic chain, optionally substituted with one or more C_{1-4} aliphatic group.

[001186] In some embodiments, a lipid comprises an optionally substituted, C_{10}-C_{80} saturated or partially unsaturated aliphatic group, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, a C_1–C_6 heteroaliphatic moiety, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, and –C(O)O–, wherein each variable is independently as defined and described herein. In some embodiments, a lipid comprises an optionally substituted C_{10}-C_{80} saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises an optionally substituted C_{10}-C_{80} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises a C_{10}-C_{80}

linear, saturated or partially unsaturated, aliphatic chain, optionally substituted with one or more C_{1-4} aliphatic group. In some embodiments, a lipid comprises an optionally substituted, C_{10}-C_{60} saturated or partially unsaturated aliphatic group, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, a C_1–C_6 heteroaliphatic moiety, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, and –C(O)O–, wherein each variable is independently as defined and described herein. In some embodiments, a lipid comprises an optionally substituted C_{10}-C_{60} saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises an optionally substituted C_{10}-C_{60} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises a C_{10}-C_{60} linear, saturated or partially unsaturated, aliphatic chain, optionally substituted with one or more C_{1-4} aliphatic group. In some embodiments, a lipid comprises an optionally substituted, C_{10}-C_{40} saturated or partially unsaturated aliphatic group, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, a C_1–C_6 heteroaliphatic moiety, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, and –C(O)O–, wherein each variable is independently as defined and described herein. In some embodiments, a lipid comprises an optionally substituted C_{10}-C_{40} saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises an optionally substituted C_{10}-C_{40} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises a C_{10}-C_{40} linear, saturated or partially unsaturated, aliphatic chain, optionally substituted with one or more C_{1-4} aliphatic group. In some embodiments, a lipid comprises an unsubstituted C_{10}-C_{80} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises no more than one optionally substituted C_{10}-C_{80} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises two or more optionally substituted C_{10}-C_{80} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises an unsubstituted C_{10}-C_{60} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises no more than one optionally substituted C_{10}-C_{60} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises two or more optionally substituted C_{10}-C_{60} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises an unsubstituted C_{10}-C_{40} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises no more than

one optionally substituted C_{10}-C_{40} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises two or more optionally substituted C_{10}-C_{40} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises a C_{10}-C_{40} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid is selected from the group consisting of: lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, docosahexaenoic acid (cis-DHA), turbinaric acid and dilinoleyl. In some embodiments, a lipid is not conjugated to an oligonucleotide chain (whether through one or more linker moieties or not). In some embodiments, a lipid is conjugated to an oligonucleotide chain, optionally through one or more linker moieties.

[001187] In some embodiments, a lipid is selected from the group consisting of: lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, docosahexaenoic acid (cis-DHA), turbinaric acid and dilinoleyl. In some embodiments, a lipid has a structure of any of:



In some embodiments, an active compound is an oligonucleotide described herein. In some

embodiments, an active compound is an oligonucleotide capable of mediating skipping of an exon in dystrophin. In some embodiments, an active compound is an oligonucleotide capable of mediating skipping of exon 51 in dystrophin. In some embodiments, an active compound is a nucleic acid of a sequence comprising or consisting of any sequence of any nucleic acid described herein. In some embodiments, an active compound is a nucleic acid of a sequence comprising or consisting of any sequence of any oligonucleotide listed in Table A1. In some embodiments, a composition comprises a lipid and an an active compound, and further comprises another component selected from: another lipid, and a targeting compound or moiety. In some embodiments, a lipid includes, without limitation: an amino lipid; an amphipathic lipid; an anionic lipid; an apolipoprotein; a cationic lipid; a low molecular weight cationic lipid; a cationic lipid such as CLinDMA and DLinDMA; an ionizable cationic lipid; a cloaking component; a helper lipid; a lipopeptide; a neutral lipid; a neutral zwitterionic lipid; a hydrophobic small molecule; a hydrophobic vitamin; a PEG-lipid; an uncharged lipid modified with one or more hydrophilic polymers; phospholipid; a phospholipid such as 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; a stealth lipid; a sterol; a cholesterol; and a targeting lipid; and any other lipid described herein or reported in the art. In some embodiments, a composition comprises a lipid and a portion of another lipid capable of mediating at least one function of another lipid. In some embodiments, a targeting compound or moiety is capable of targeting a compound (*e.g.*, a composition comprising a lipid and a active compound) to a particular cell or tissue or subset of cells or tissues. In some embodiments, a targeting moiety is designed to take advantage of cell- or tissue-specific expression of particular targets, receptors, proteins, or other subcellular components; In some embodiments, a targeting moiety is a ligand (*e.g.*, a small molecule, antibody, peptide, protein, carbohydrate, aptamer, *etc.*) that targets a composition to a cell or tissue, and/or binds to a target, receptor, protein, or other subcellular component.

[001188] In some embodiments, incorporation of a lipid moiety for delivery of an active compound allow (*e.g.*, do not prevent or interfere with) the function of an active compound. Non-limiting example lipids include: lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, docosahexaenoic acid (cis-DHA), turbinaric acid and dilinoleyl.

[001189] In some embodiments, lipid conjugation, such as conjugation with fatty acids, may improve one or more properties of oligonucleotides. In some embodiments, lipid conjugation improves delivery.

[001190] In some embodiments, as supported by experimental data, conjugation with lipids can increase skipping efficiency.

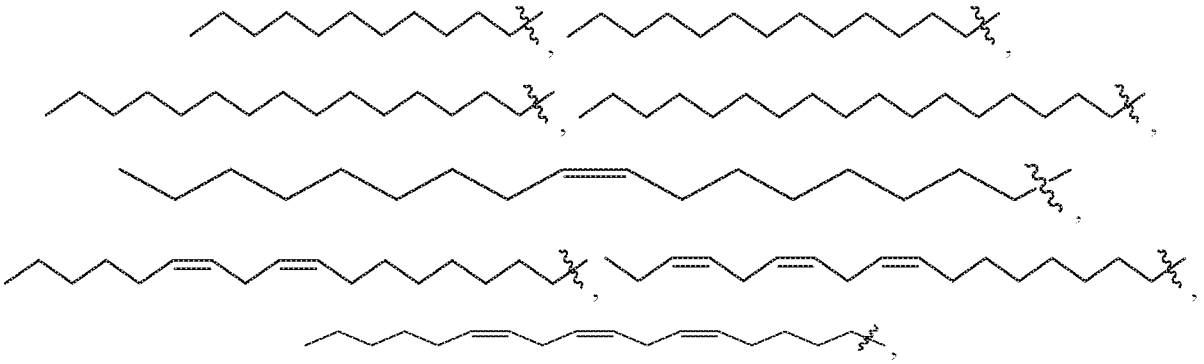
[001191] In some embodiments, a composition for delivery of an active compound is capable of targeting an active compound to particular cells or tissues, as desired. In some embodiments, a composition for delivery of an active compound is capable of targeting an active compound to a muscle

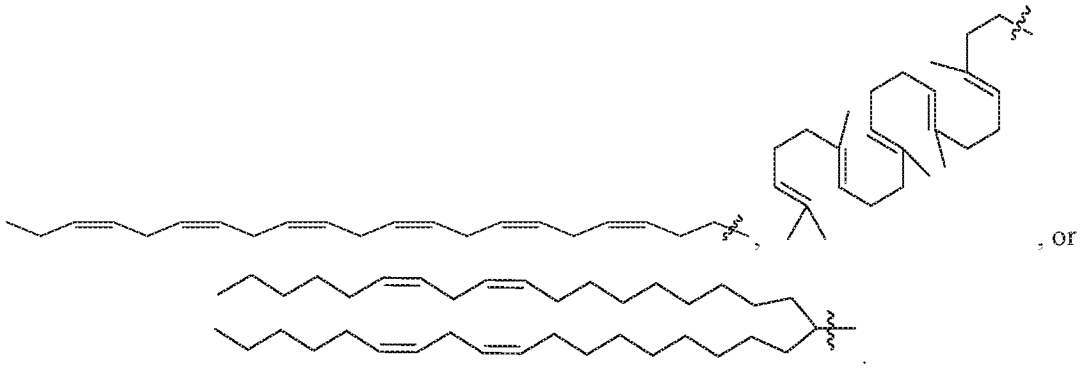
cell or tissue. In some embodiments, the present disclosure pertains to compositions and methods related to delivery of active compounds, wherein the compositions comprise an active compound a lipid. In some embodiments to a muscle cell or tissue, the lipid is selected from: lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, docosahexaenoic acid (cis-DHA), turbinaric acid and dilinoleyl. Example compositions were prepared comprising an active compound (WV-942) and a lipid, and these compositions were capable of delivering an active compound to target cells and tissues, *e.g.*, muscle cells and tissues. The example lipids used include stearic acid, oleic acid, alpha-linolenic acid, gamma-linolenic acids, cis-DHA, turbinaric acid and dilinoleyl acid.

[001192] Various compositions comprising an active compound and any of: stearic acid, oleic acid, alpha-linolenic acid, gamma-linolenic acid, cis-DHA or turbinaric acid, were able to deliver an active compound to various tissues, including gastrocnemius muscle tissue, heart muscle tissue, quadriceps muscle tissue, gastrocnemius muscle tissue, and diaphragm muscle tissue.

[001193] In some embodiments, a composition comprising a lipid, selected from: lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, docosahexaenoic acid (cis-DHA), turbinaric acid and dilinoleyl, and an active compound is capable of delivering an active compound to extra-hepatic cells and tissues, *e.g.*, muscle cells and tissues.

[001194] In some embodiments, a lipid has the structure of R^{LD}–OH, wherein wherein R^{LD} is an optionally substituted, C_{10}-C_{80} saturated or partially unsaturated aliphatic group, wherein one or more methylene units are optionally and independently replaced by C_1–C_6 alkylene, C_1–C_6 alkenylene, –C≡C–, a C_1–C_6 heteroaliphatic moiety, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$– –SC(O)–, –C(O)S–, –OC(O)–, and –C(O)O–. In some embodiments, a lipid has the structure of R^{LD}–C(O)OH. In some embodiments, R^{LD} is





Example oligonucleotides comprising such R^{LD} groups are described herein and in WO 2017/062862, the description of R^{LD} is incorporated herein by reference.

[001195] In some embodiments, a lipid is conjugated to an active compound optionally through a linker moiety. In some embodiments, a linker is L^M. In some embodiments, a linker is L. In some embodiments, –L– comprises a bivalent aliphatic chain. In some embodiments, –L– comprises a phosphate group. In some embodiments, –L– comprises a phosphorothioate group. In some embodiments, –L– has the structure of $-C(O)NH-(CH_2)_6-OP(=O)(S^-)-$. In some embodiments, –L– has the structure of $-C(O)NH-(CH_2)_6-OP(=O)(O^-)-$.

[001196] Lipids, optionally through linkers, can be conjugated to oligonucleotides at various suitable locations. In some embodiments, lipids are conjugated through the 5'-OH group. In some embodiments, lipids are conjugated through the 3'-OH group. In some embodiments, lipids are conjugated through one or more sugar moieties. In some embodiments, lipids are conjugated through one or more bases. In some embodiments, lipids are incorporated through one or more internucleotidic linkages. In some embodiments, an oligonucleotide may contain multiple conjugated lipids which are independently conjugated through its 5'-OH, 3'-OH, sugar moieties, base moieties and/or internucleotidic linkages.

[001197] In some embodiments, a composition comprises an oligonucleotide, e.g., DMD oligonucleotide and a lipid selected from: lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, docosahexaenoic acid (cis-DHA), turbinaric acid, arachidonic acid, and dilinoleyl, wherein the lipid is directly conjugated to the biologically active agent (without a linker interposed between the lipid and the biologically active agent). In some embodiments, a composition comprises an oligonucleotide and a lipid selected from: lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, docosahexaenoic acid (cis-DHA), turbinaric acid and dilinoleyl, wherein the lipid is directly conjugated to the biologically active agent (without a linker interposed between the lipid and the biologically active agent).

[001198] In some embodiments, a composition comprises a DMD oligonucleotide and any lipid known in the art, wherein the lipid is conjugated or not conjugated to the oligonucleotide.

[001199] Non-limiting examples of lipids, and methods of making them and conjugating them are provided in, for example, WO 2017/062862, the lipids and related methods of which are incorporated herein by reference.

Targeting moieties

[001200] In some embodiments, an additional chemical moiety/component is a targeting moiety. In some embodiments, a provided composition further comprises a targeting moiety. In some embodiments, a targeting moiety is conjugated to an oligonucleotide chain. In some embodiments, a biologically active agent is conjugated to both a lipid and an oligonucleotide chain. Various targeting moieties can be used in accordance with the present disclosure, *e.g.*, lipids, antibodies, peptides, carbohydrates, *etc.*

[001201] Targeting moieties can be incorporated into provided technologies through many types of methods in accordance with the present disclosure. In some embodiments, targeting moieties are chemically conjugated with oligonucleotides.

[001202] In some embodiments, provided compositions comprise two or more targeting moieties. In some embodiments, provided oligonucleotides comprise two or more conjugated targeting moieties. In some embodiments, the two or more conjugated targeting moieties are the same. In some embodiments, the two or more conjugated targeting moieties are different. In some embodiments, provided oligonucleotides comprise no more than one targeting moiety. In some embodiments, oligonucleotides of a provided composition comprise different types of conjugated targeting moieties. In some embodiments, oligonucleotides of a provided composition comprise the same type of targeting moieties.

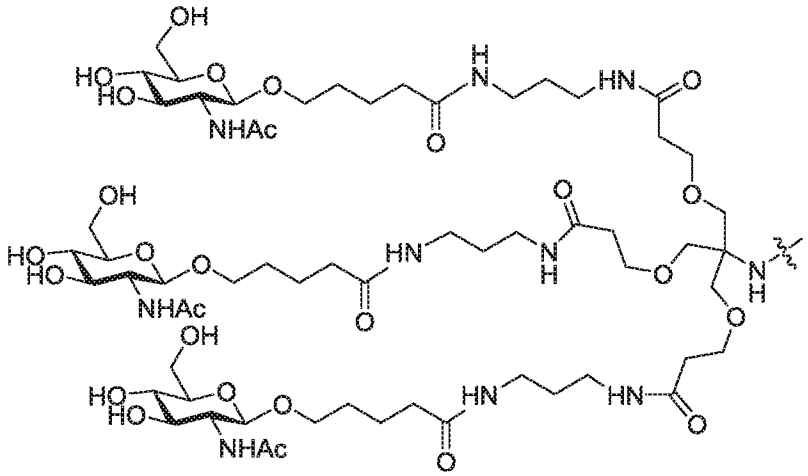
[001203] Targeting moieties can be conjugated to oligonucleotides optionally through linkers. Various types of linkers in the art can be utilized in accordance of the present disclosure. In some embodiments, a linker comprises a phosphate group, which can, for example, be used for conjugating targeting moieties through chemistry similar to those employed in oligonucleotide synthesis. In some embodiments, a linker comprises an amide, ester, or ether group. In some embodiments, a linker is L^M. In some embodiments, a linker has the structure of −L−. Targeting moieties can be conjugated through either the same or different linkers compared to lipids.

[001204] Targeting moieties, optionally through linkers, can be conjugated to oligonucleotides at various suitable locations. In some embodiments, targeting moieties are conjugated through the 5'-OH group. In some embodiments, targeting moieties are conjugated through the 3'-OH group. In some embodiments, targeting moieties are conjugated through one or more sugar moieties. In some

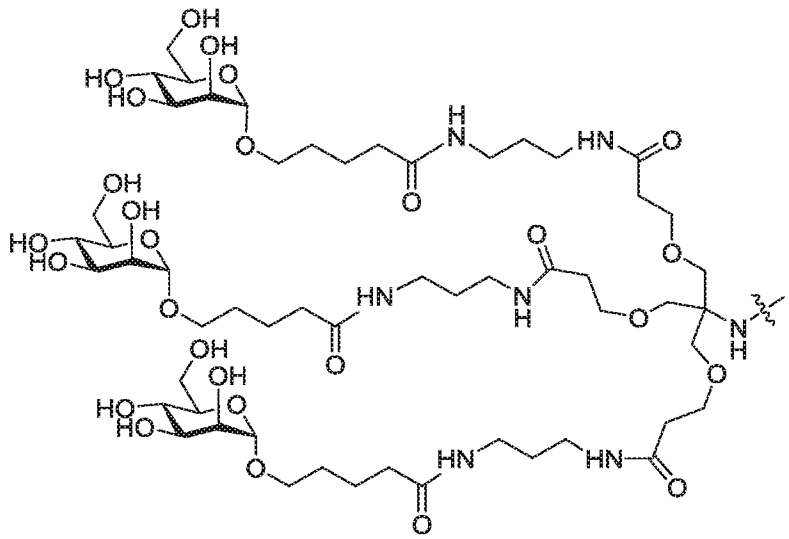
embodiments, targeting moieties are conjugated through one or more bases. In some embodiments, targeting moieties are incorporated through one or more internucleotidic linkages. In some embodiments, an oligonucleotide may contain multiple conjugated targeting moieties which are independently conjugated through its 5'-OH, 3'-OH, sugar moieties, base moieties and/or internucleotidic linkages. Targeting moieties and lipids can be conjugated either at the same, neighboring and/or separated locations. In some embodiments, a targeting moiety is conjugated at one end of an oligonucleotide, and a lipid is conjugated at the other end.

[001205] In some embodiments, a targeting moiety interacts with a protein on the surface of targeted cells. In some embodiments, such interaction facilitates internalization into targeted cells. In some embodiments, a targeting moiety comprises a sugar moiety. In some embodiments, a targeting moiety comprises a polypeptide moiety. In some embodiments, a targeting moiety comprises an antibody. In some embodiments, a targeting moiety is an antibody. In some embodiments, a targeting moiety comprises an inhibitor. In some embodiments, a targeting moiety is a moiety from a small molecule inhibitor. In some embodiments, an inhibitor is an inhibitor of a protein on the surface of targeted cells. In some embodiments, an inhibitor is a carbonic anhydrase inhibitor. In some embodiments, an inhibitor is a carbonic anhydrase inhibitor expressed on the surface of target cells. In some embodiments, a carbonic anhydrase is I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV or XVI. In some embodiments, a carbonic anhydrase is membrane bound. In some embodiments, a carbonic anhydrase is IV, IX, XII or XIV. In some embodiments, an inhibitor is for IV, IX, XII and/or XIV. In some embodiments, an inhibitor is a carbonic anhydrase III inhibitor. In some embodiments, an inhibitor is a carbonic anhydrase IV inhibitor. In some embodiments, an inhibitor is a carbonic anhydrase IX inhibitor. In some embodiments, an inhibitor is a carbonic anhydrase XII inhibitor. In some embodiments, an inhibitor is a carbonic anhydrase XIV inhibitor. In some embodiments, an inhibitor comprises or is a sulfonamide (*e.g.*, those described in Supuran, CT. *Nature Rev Drug Discover* **2008**, *7*, 168-181, which sulfonamides are incorporated herein by reference). In some embodiments, an inhibitor is a sulfonamide. In some embodiments, targeted cells are muscle cells.

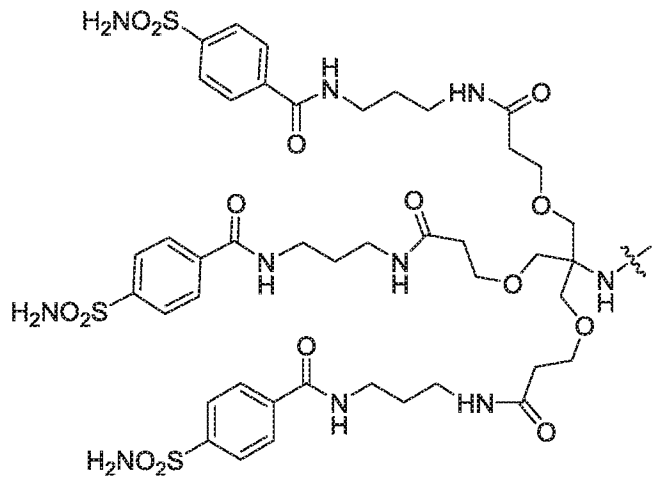
[001206] In some embodiments, a targeting moiety is R^{LD} or R^{CD} or R^{TD} as defined and described in the present disclosure. In some embodiments, R^{CD} comprises or is



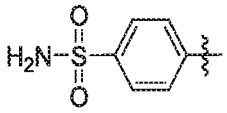
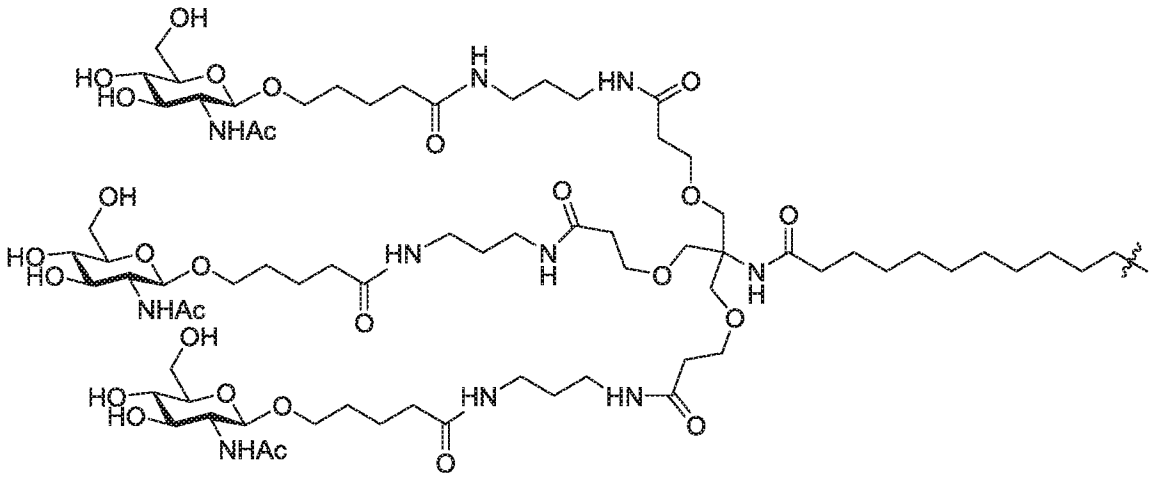
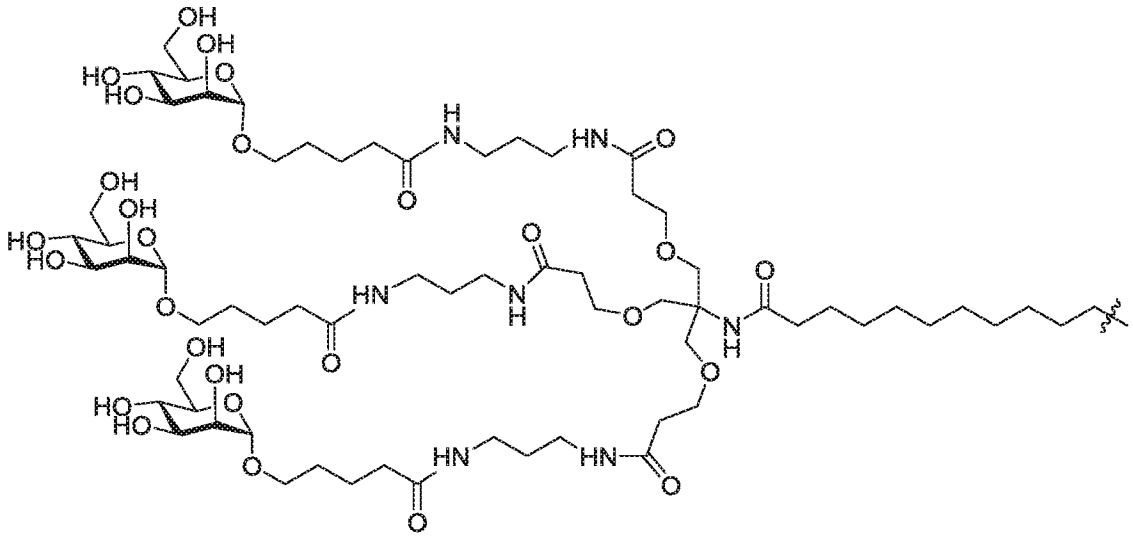
. In some embodiments, R^{CD} comprises or is

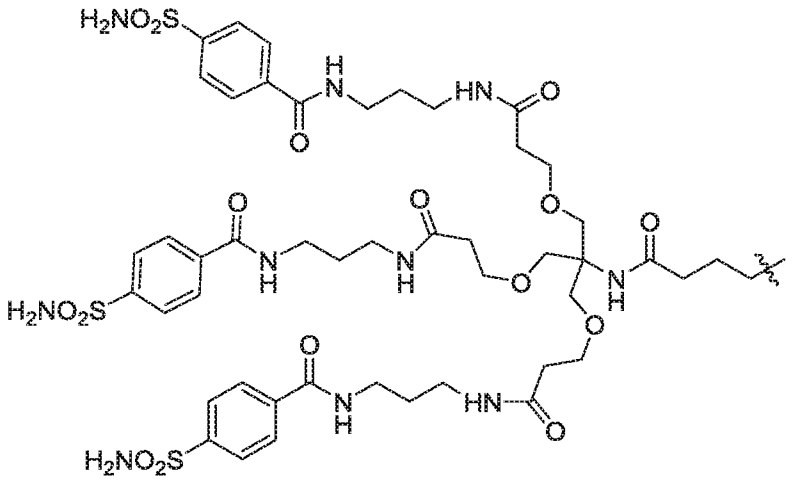


. In some embodiments, R^{CD} comprises or is

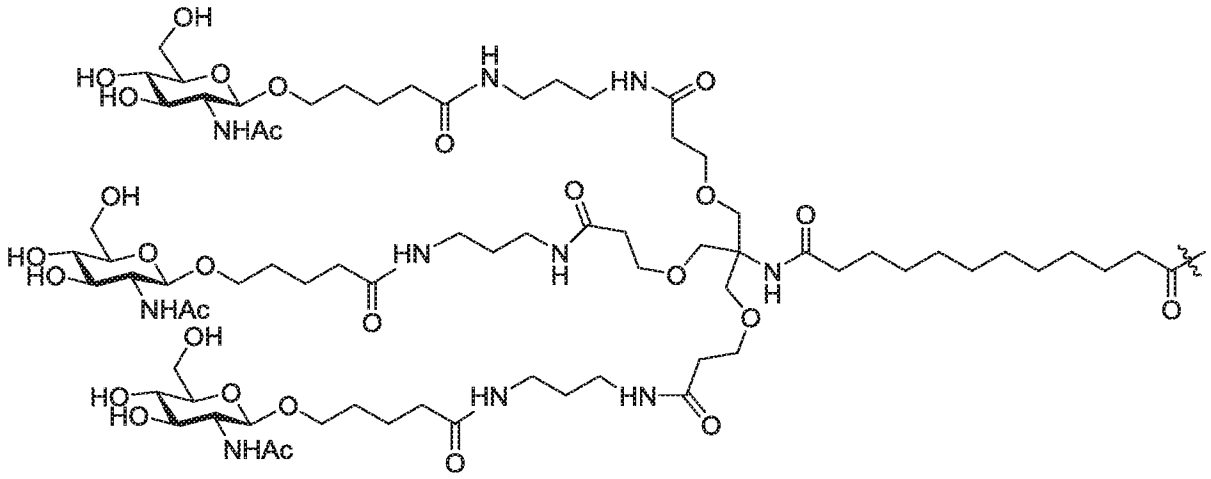


. In some embodiments, R^{TD} is a sulfonamide moiety as described in the present disclosure. In some embodiments,

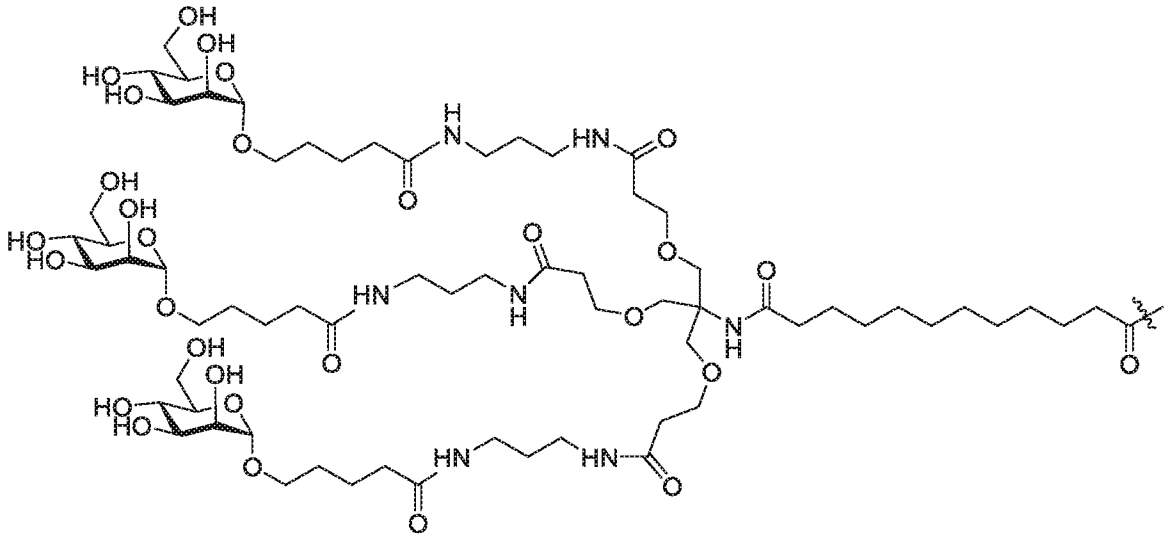
R^{TD} comprises or is  . In some embodiments, R^{TD} or R^{CD} comprises or is  . In some embodiments, R^{TD} or R^{CD} comprises or is  . In some embodiments, R^{TD} comprises or is



. In some embodiments, R^{TD} or R^{CD} comprises or is



. In some embodiments, R^{TD} or R^{CD} comprises or is



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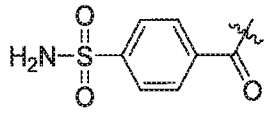
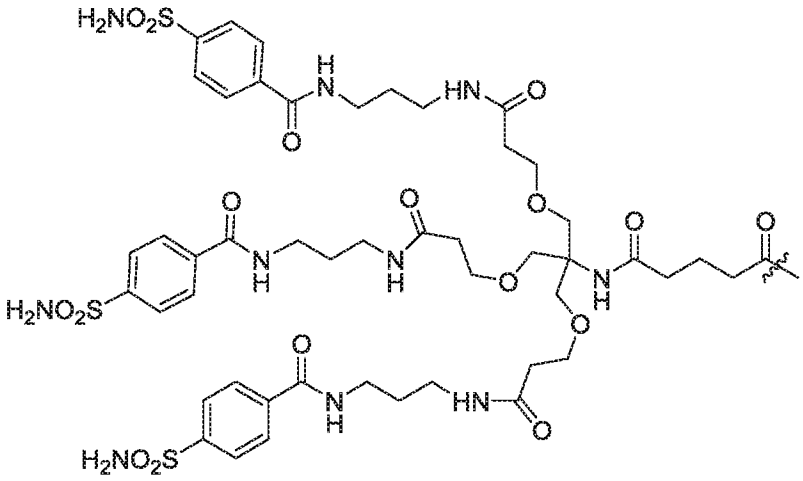
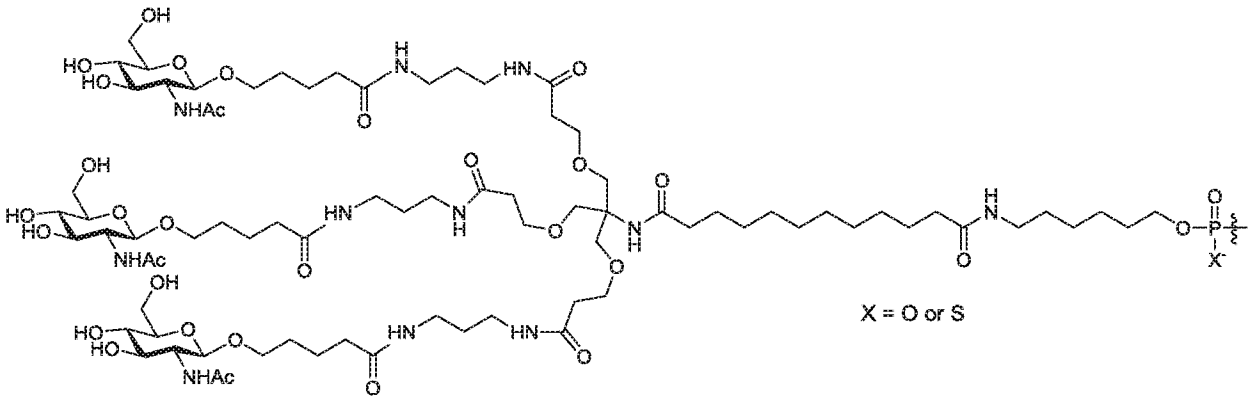
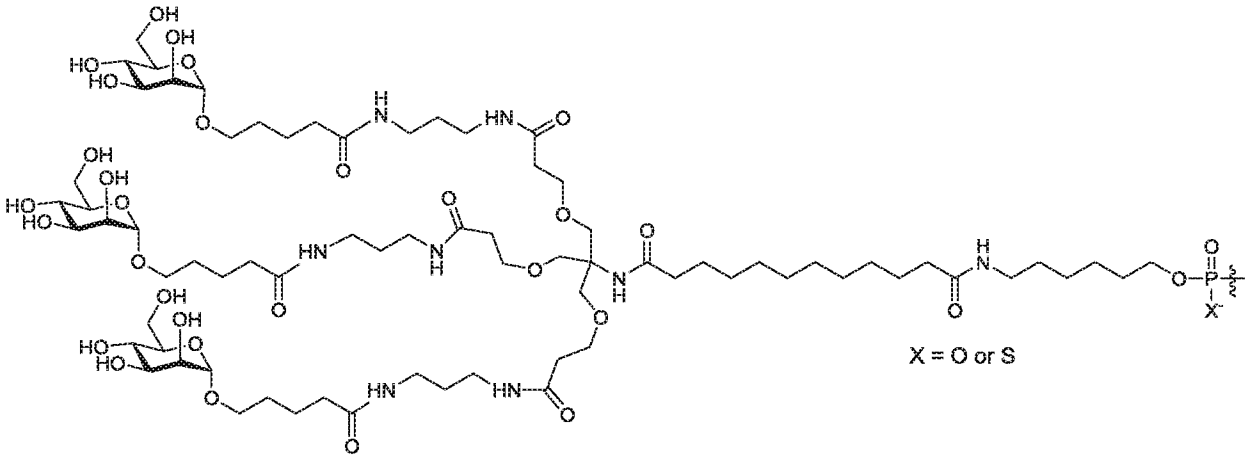
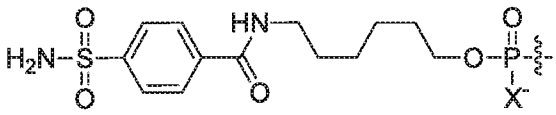
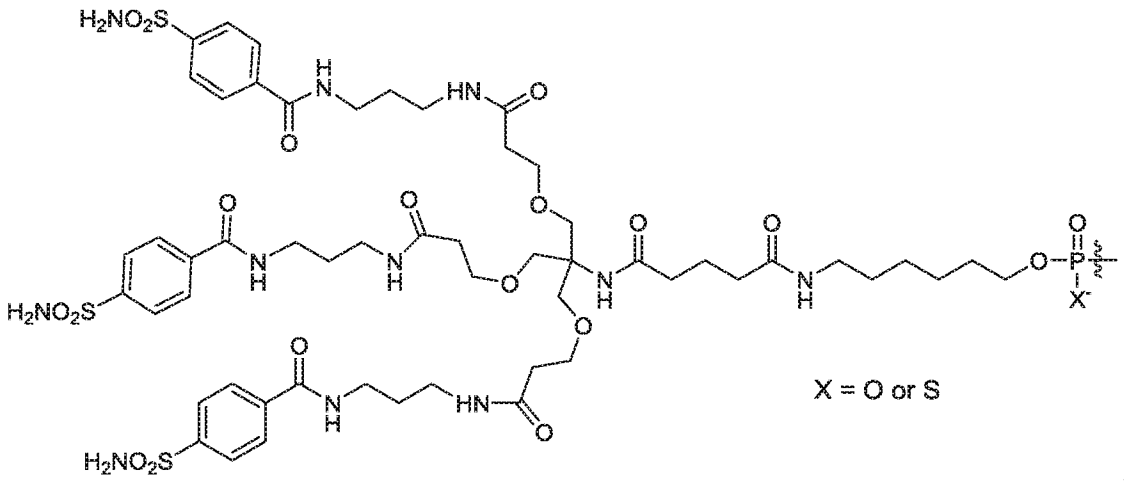
some embodiments, R^{TD} comprises or is  . In some embodiments, R^{TD} comprises or is  . In some embodiments, R^{TD} or R^{CD} comprises or is 

. In some embodiments, R^{TD} or R^{CD} comprises or is 

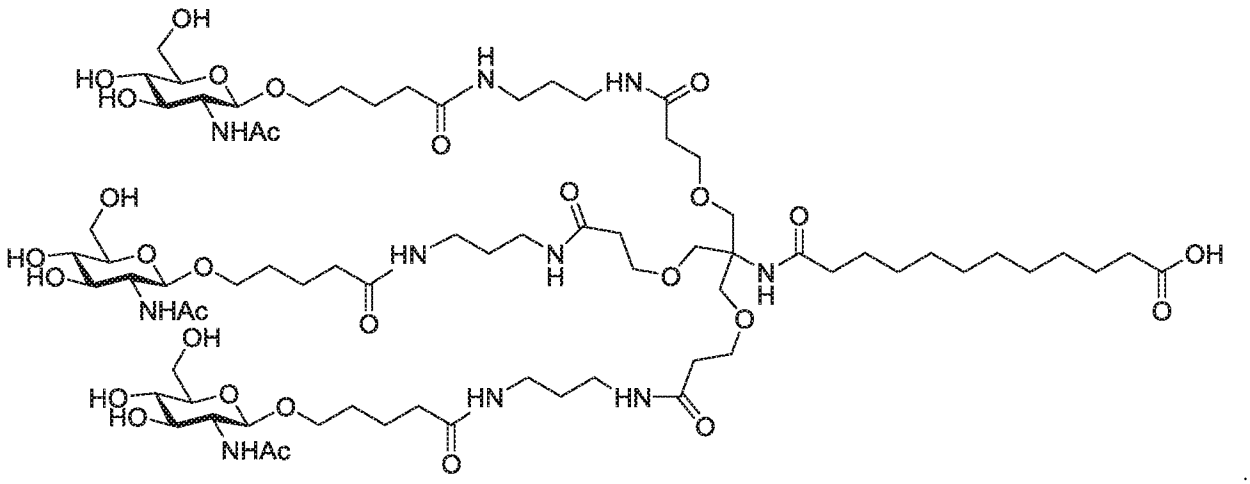
. In some embodiments, R^{TD} comprises or is 

. In some embodiments, R^{TD} comprises or is



. In some embodiments, R^{LD} is a targeting moiety that comprises or is a lipid moiety. In some embodiments, X is O. In some embodiments, X is S.

[001207] In some embodiments, the present disclosure provides technologies (*e.g.*, reagents, methods, *etc.*) for conjugating various moieties to oligonucleotide chains. In some embodiments, the present disclosure provides technologies for conjugating targeting moiety to oligonucleotide chains. In some embodiments, the present disclosure provides acids comprising targeting moieties for conjugation, *e.g.*, R^{LD}–COOH. In some embodiments, the present disclosure provides linkers for conjugation, *e.g.*, L^{LD}. A person having ordinary skill in the art understands that many known and widely practiced technologies can be utilized for conjugation with oligonucleotide chains in accordance with the present disclosure. In some embodiments, a provided acid is



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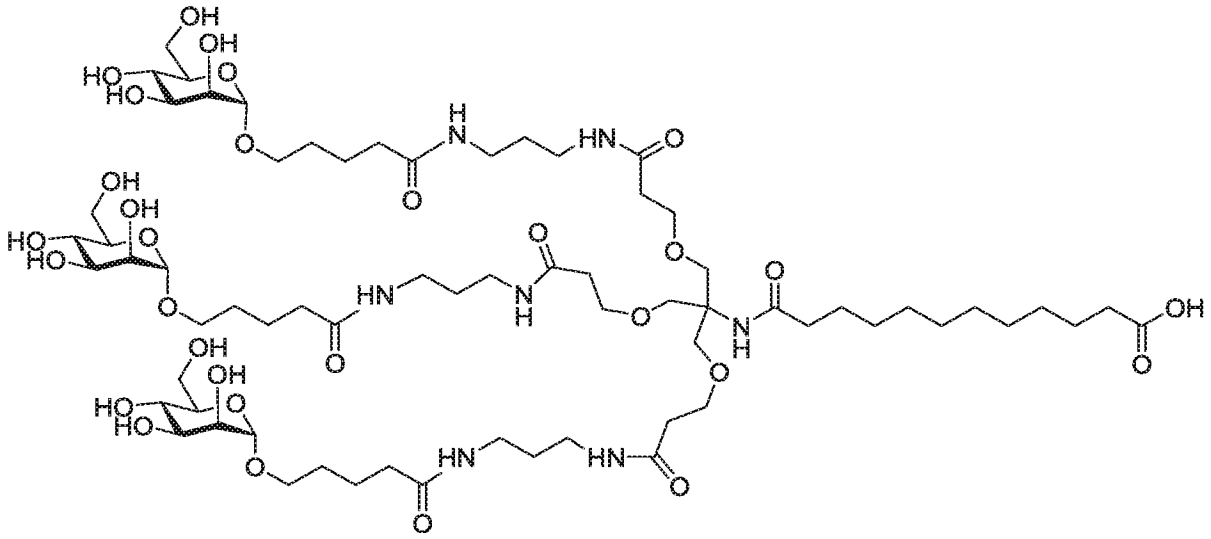
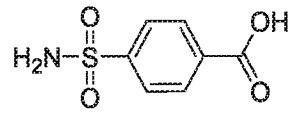
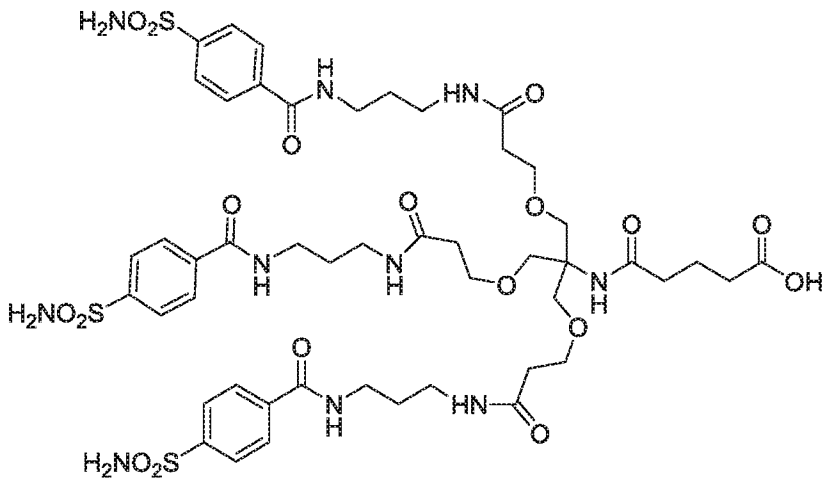
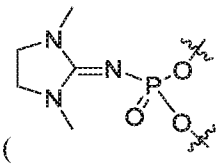
In some embodiments, a provided acid is

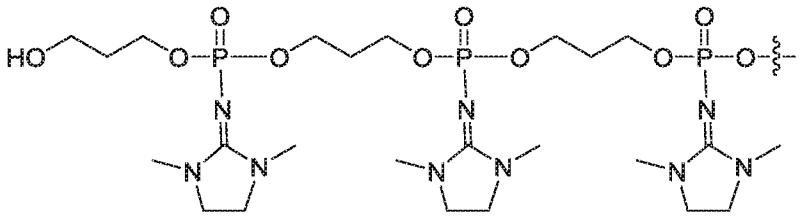




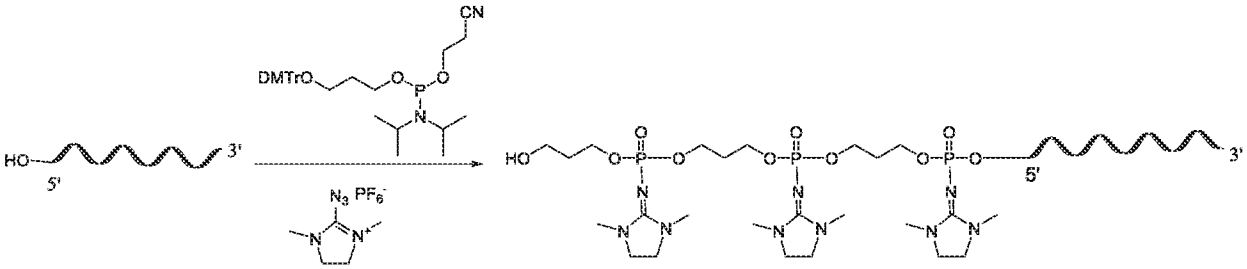
In some embodiments, a provided acid is . In some embodiments, a provided acid is  . In some embodiments, a provided acid is a fatty acid, which can provide a lipid moiety as a targeting moiety. In some embodiments, the present disclosure provides methods and reagents for preparing such acids.

[001208] In some embodiments, an additional chemical moiety, *e.g.*, one comprising a guanidine moiety, may be incorporated into an oligonucleotide to improve one or more properties and/or activities. In some embodiments, such an additional chemical moiety is useful for improving delivery. In some embodiments, an additional chemical moiety comprises one or more group having the structure of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, or **II-d-2** as described herein. In some embodiments, an additional chemical moiety comprises one or more group having the structure of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, or **II-d-2** as described herein. In some embodiments, such a chemical moiety has the structure of

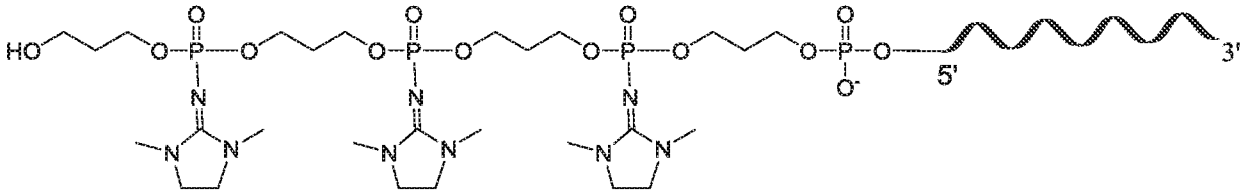
formula R^1–[–L–L^P]n–, wherein each L^P independently has the structure of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, or **II-d-2** as described herein, and each other variable is independently as described herein. In some embodiments, R^1 is –OH. In some embodiments, R^1 is –H. In some embodiments, each L is independently optionally substituted bivalent C_{1-10} aliphatic. In some embodiments, each L is independently $-(CH_2)_3-$ alkylene. In some embodiments, each L is independently C_{1-6} alkylene. In some embodiments, each L^P is independently n001 (). In some embodiments, an additional chemical moiety is

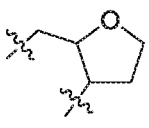


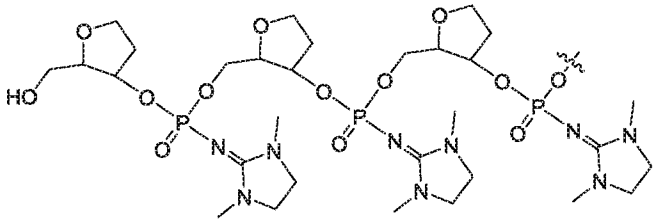
. In some embodiments, an additional chemical moiety is bonded to 5'-end carbon of an oligonucleotide chain. In some embodiments, it may be incorporated, *e.g.*, using reagents including those illustrated below:

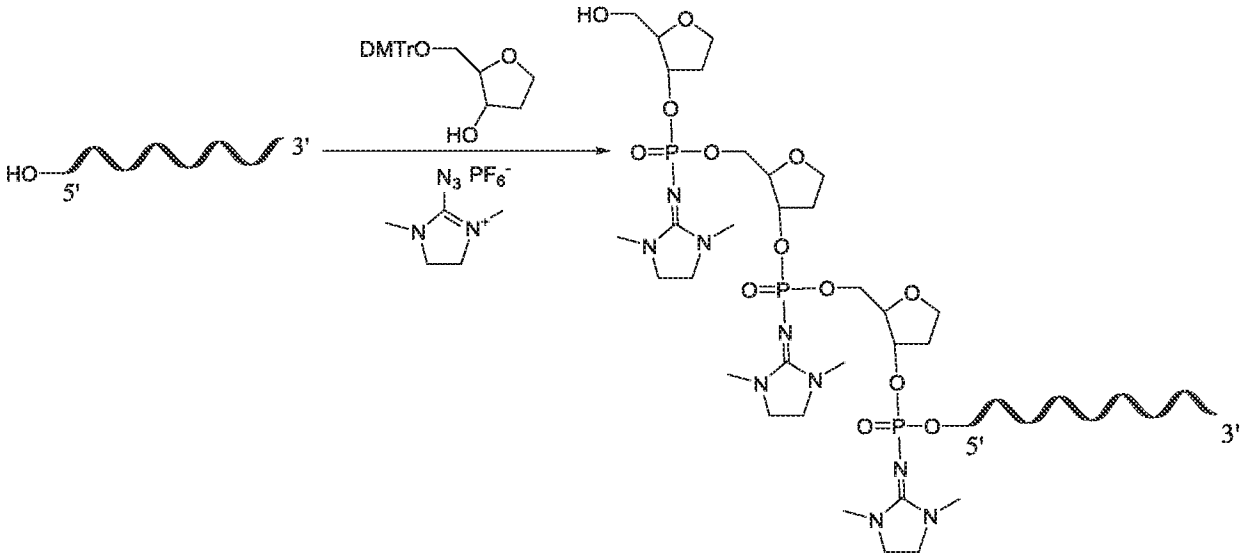


In some embodiments, an additional chemical moiety may be linked to an oligonucleotide chain through a cleavable group, *e.g.*, a phosphate group, to an oligonucleotide chain (*e.g.*, at the 5'-end carbon):

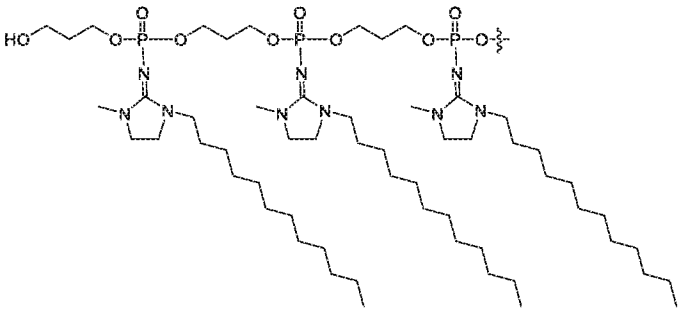


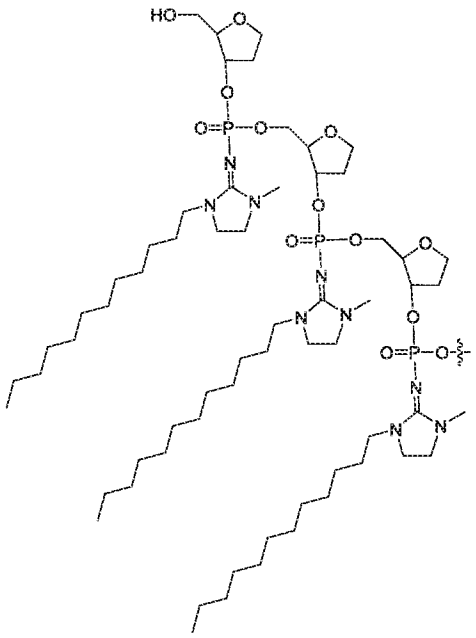
In some embodiments, L is a sugar moiety as described herein. For example, in some embodiments, L is  . In some embodiments, an additional chemical moiety is


. In some embodiments, it is bonded to 5'-end carbon of an oligonucleotide chain. In some embodiments, it may be incorporated, *e.g.*, using reagents including those illustrated below:

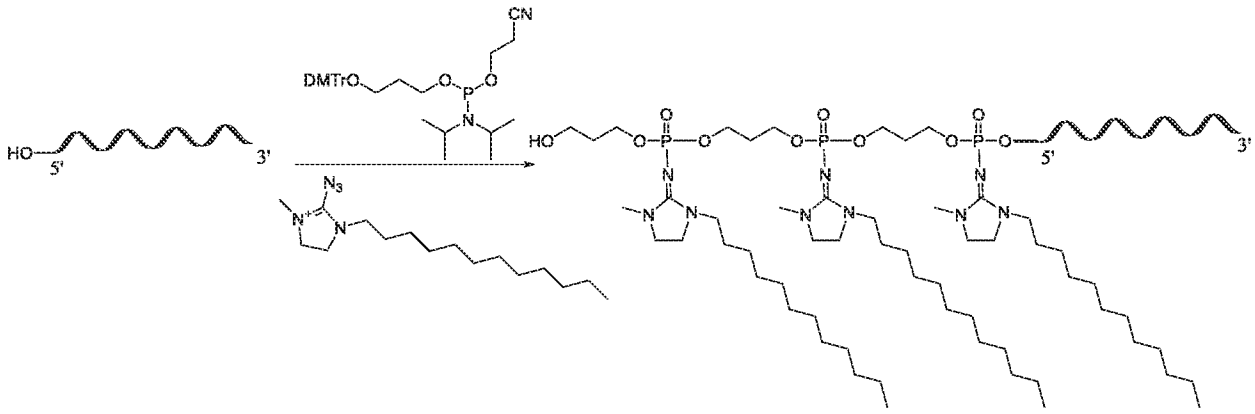


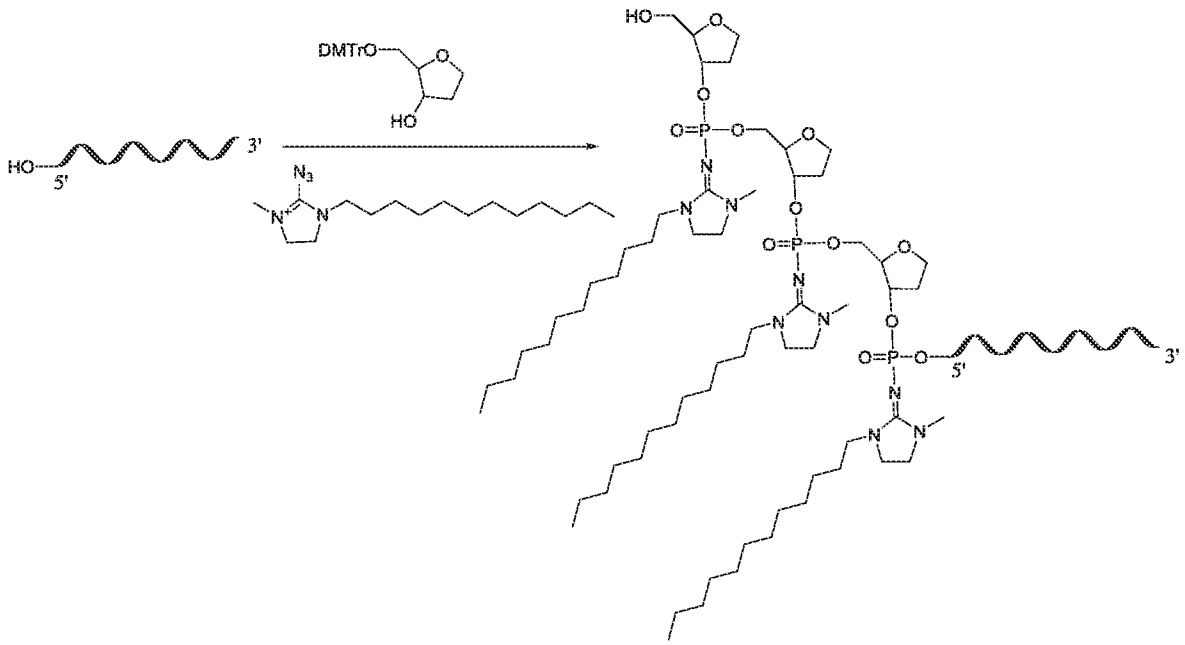
In some embodiments, additional chemical moieties described herein may comprise one or more alkyl chain. In some embodiments, additional chemical moieties described herein may comprise one or more lipid moieties. Those skilled in the art appreciates that many other embodiments of L^P, including neutral internucleotidic linkage moieties, may be utilized in additional chemical moieties, *e.g.*, n009. In some embodiments, an additional chemical moiety is


. In some embodiments, an additional



chemical moiety is . As described herein, in some embodiments, an additional chemical moiety may be bonded to the 5'-end carbon of an oligonucleotide chain. In some embodiments, an additional chemical moiety may be incorporated , *e.g.*, using reagents including those illustrated below:





Those skilled in the art will appreciate that many other technologies, including synthetic chemical technologies, can be utilized in accordance with the present disclosure to provide compounds, *e.g.*, oligonucleotides, reagents for incorporating additional chemical moieties, *etc.*

[001209] In some embodiments, provided compounds, *e.g.*, reagents, products (*e.g.*, oligonucleotides, amidites, *etc.*) *etc.* are at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 97% or 99% pure. In some embodiments, the purity is at least 50%. In some embodiments, the purity is at least 75%. In some embodiments, the purity is at least 80%. In some embodiments, the purity is at least 85%. In some embodiments, the purity is at least 90%. In some embodiments, the purity is at least 95%. In some embodiments, the purity is at least 96%. In some embodiments, the purity is at least 97%. In some embodiments, the purity is at least 98%. In some embodiments, the purity is at least 99%.

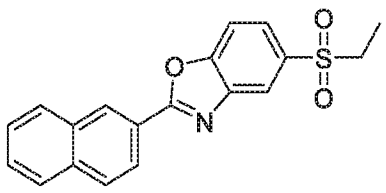
Combination Therapy

[001210] In some embodiments, a subject is administered an additional treatment (including, but not limited to, a therapeutic agent or method) in additional to provided oligonucleotide or oligonucleotide composition, e.g., a composition comprising a DMD oligonucleotide. In some embodiments, a composition comprising a DMD oligonucleotide(s) (or two or more compositions, each comprising a DMD oligonucleotide) is administered to a patient along with an additional treatment.

[001211] In some embodiments, the present disclosure pertains to a method for treating muscular dystrophy, Duchenne (Duchenne's) muscular dystrophy (DMD), or Becker (Becker's) muscular dystrophy (BMD), comprising (a) administering to a subject susceptible thereto or suffering therefrom a

composition comprising a provided oligonucleotide, and (b) administering to the subject an additional treatment which is capable of preventing, treating, ameliorating or slowing the progress of muscular dystrophy. In some embodiments, an additional treatment is a composition comprising a second oligonucleotide.

[001212] In some embodiments, an additional treatment is capable of preventing, treating, ameliorating or slowing the progress of muscular dystrophy by itself. In some embodiments, an additional treatment is capable of preventing, treating, ameliorating or slowing the progress of muscular dystrophy when administered with a provided oligonucleotide.

[001213] In some embodiments, an additional treatment is administered to the subject prior to, after or simultaneously with a composition comprising a provided oligonucleotide, e.g., a provided DMD oligonucleotide. In some embodiments, a composition comprises both a DMD oligonucleotide(s) and an additional treatment. In some embodiments, a DMD oligonucleotide(s) and an additional treatment(s) are in separate compositions. In some embodiments, the present disclosure provides technologies (*e.g.*, compositions, methods, *etc.*) for combination therapy, for example, with other therapeutic agents and/or medical procedures. In some embodiments, provided oligonucleotides and/or compositions may be used together with one or more other therapeutic agents. In some embodiments, provided compositions comprise provided oligonucleotides, and one or more other therapeutic agents. In some embodiments, the one or more other therapeutic agents may have one or more different targets, and/or one or more different mechanisms toward targets, when compared to provided oligonucleotides in the composition. In some embodiments, a therapeutic agent is an oligonucleotide. In some embodiments, a therapeutic agent is a small molecule drug. In some embodiments, a therapeutic agent is a protein. In some embodiments, a therapeutic agent is an antibody. A number of therapeutic agents may be utilized in accordance with the present disclosure. For example, oligonucleotides for DMD may be used together with one or more therapeutic agents that modulate utrophin production (utrophin modulators). In some embodiments, a utrophin modulator promotes production of utrophin. In some embodiments, a utrophin modulator is ezutromid. In some embodiments, a utrophin modulator is  , or a pharmaceutically acceptable salt thereof. In some embodiments, provided oligonucleotides or compositions thereof are administered prior to, concurrently with, or subsequent to one or more other therapeutic agents and/or medical procedures. In some embodiments, provided oligonucleotides or compositions thereof are administered concurrently with one or more other therapeutic agents and/or medical procedures. In some embodiments, provided oligonucleotides or compositions thereof are

administered prior to one or more other therapeutic agents and/or medical procedures. In some embodiments, provided oligonucleotides or compositions thereof are administered subsequent to one or more other therapeutic agents and/or medical procedures. In some embodiments, provide compositions comprise one or more other therapeutic agents.

[001214] In some embodiments, a composition comprising a DMD oligonucleotide is co-administered with an additional agent in order to improve skipping of a DMD exon of interest. In some embodiments, an additional agent is an antibody, oligonucleotide, protein or small molecule. In some embodiments, an additional agent interferes with a protein involved in splicing. In some embodiments, an additional agent interferes with a protein involved in splicing, wherein the protein is a SR protein.

[001215] In some embodiments, an additional agent interferes with a protein involved in splicing, wherein the protein is a SR protein, which contains a protein domain with one or more long repeats of serine (S) and arginine (R) amino acid residues. SR proteins are reportedly heavily phosphorylated in cells and are involved in constitutive and alternative splicing. Long et al. 2009 Biochem. J. 417: 15-27; Shepard et al. 2009 Genome Biol. 10: 242. In some embodiments, an additional agent is a chemical compound that inhibits or decreases a SR protein kinase. In some embodiments, a chemical compound that inhibits or decreases a SR protein kinase is SRPIN340. SRPIN340 is reported in, for example, Fukuhura et al. 2006 Proc. Natl. Acad. Sci. USA 103: 11329-11333. In some embodiments, a chemical compound is a kinase inhibitor specific for Cdc-like kinases (Clks) that are also able to phosphorylate SR proteins. In some embodiments, a kinase inhibitor specific for Cdc-like kinases (Clks) that are also able to phosphorylate SR proteins is TG003. TG003 reportedly affected splicing both in vitro and in vivo. Nowak et al. 2010 J. Biol. Chem. 285: 5532-5540; Muraki et al. 2004 J. Biol. Chem. 279: 24246-24254; Yomoda et al. 2008 Genes Cells 13: 233-244; and Nishida et al. 2011 Nat Commun. 2:308.

[001216] In some embodiments, in a patient afflicted with muscular dystrophy, muscle tissue is replaced by fat and connective tissue, and affected muscles may look larger due to increased fat content, a condition known as pseudohypertrophy. In some embodiments, a composition comprising a DMD oligonucleotide(s) is administered along with a treatment which reduces or prevents development of fat or fibrous or connective tissue, or replacement of muscle tissue by fat or fibrous or connective tissue.

[001217] In some embodiments, a composition comprising a DMD oligonucleotide(s) is administered along with a treatment which reduces or prevents development of fat or fibrous or connective tissue, or replacement of muscle tissue by fat or fibrous or connective tissue, wherein the treatment is an antibody to connective tissue growth factor (CTGF), a central mediator of fibrosis (e.g., FG-3019). In some embodiments, a composition comprising a DMD oligonucleotide(s) is administered along with an agent which reduces the fat content of the human body.

[001218] Additional treatments incude: slowing the progression of the disease by immune

modulators (eg, steroids and transforming growth factor-beta inhibitors), inducing or introducing proteins that may compensate for dystrophin deficiency in the myofiber (eg, utrophin, biglycan, and laminin), or bolstering the muscle's regenerative response (eg, myostatin and activin 2B).

[001219] In some embodiments, an additional treatment is a small molecule capable of restoring normal balance of calcium within muscle cells.

[001220] In some embodiments, an additional treatment is a small molecule capable of restoring normal balance of calcium within muscle cells by correcting the activity of a type of channel called the ryanodine receptor calcium channel complex (RyR). In some embodiments, such a small molecule is Rycal ARM210 (ARMGO Pharma, Tarry Town, NY).

[001221] In some embodiments, an additional treatment is a flavonoid.

[001222] In some embodiments, an additional treatment is a flavonoid such as Epicatechin. Epicatechin is a flavonoid found in dark chocolate harvested from the cacao tree which has been reported in animals and humans to increase the production of new mitochondria in heart and muscle (e.g., mitochondrial biogenesis) while concurrently stimulating the regeneration of muscle tissue.

[001223] In some embodiments, an additional treatment is follistatin gene therapy.

[001224] In some embodiments, an additional treatment is adeno-associated virus delivery of follistatin 344 to increase muscle strength and prevent muscle wasting and fibrosis.

[001225] In some embodiments, an additional treatment is glucocorticoid.

[001226] In some embodiments, an additional treatment is prednisone.

[001227] In some embodiments, an additional treatment is deflazacort.

[001228] In some embodiments, an additional treatment is vamorolone (VBP15).

[001229] In some embodiments, an additional treatment is delivery of an exogenous Dystrophin gene or synthetic version or portion thereof, such as a microdystrophin gene.

[001230] In some embodiments, an additional treatment is delivery of an exogenous Dystrophin gene or portion thereof, such as a microdystrophin gene, such as SGT-001, an adeno-associated viral (AAV) vector-mediated gene transfer system for delivery of a synthetic dystrophin gene or microdystrophin (Solid BioSciences, Cambridge, Mass.).

[001231] In some embodiments, an additional treatment is stem cell treatment.

[001232] In some embodiments, an additional treatment is a steroid.

[001233] In some embodiments, an additional treatment is a corticosteroid.

[001234] In some embodiments, an additional treatment is prednisone.

[001235] In some embodiments, an additional treatment is a beta-2 agonist.

[001236] In some embodiments, an additional treatment is an ion channel inhibitor.

[001237] In some embodiments, an additional treatment is a calcium channel inhibitor.

[001238] In some embodiments, an additional treatment is a calcium channel inhibitor which is a xanthin. In some embodiments, an additional treatment is a calcium channel inhibitor which is methylxanthine. In some embodiments, an additional treatment is a calcium channel inhibitor which is pentoxifylline. In some embodiments, an additional treatment is a calcium channel inhibitor which is a methylxanthine derivative selected from: pentoxifylline, furafylline, lisofylline, propentofylline, pentifylline, theophylline, torbafylline, albifylline, enprofylline and derivatives thereof.

[001239] In some embodiments, an additional treatment is a treatment for heart disease or cardiovascular disease.

[001240] In some embodiments, an additional treatment is a blood pressure medicine.

[001241] In some embodiments, an additional treatment is surgery.

[001242] In some embodiments, an additional treatment is surgery to fix shortened muscles, straighten the spine, or treat a heart or lung problem.

[001243] In some embodiments, an additional treatment is a brace, walker, standing walker, or other mechanical aid for walking.

[001244] In some embodiments, an additional treatment is exercise and/or physical therapy.

[001245] In some embodiments, an additional treatment is assisted ventilation.

[001246] In some embodiments, an additional treatment is anticonvulsant, immunosuppressant or treatment for constipation.

[001247] In some embodiments, an additional treatment is an inhibitor of NF-κB.

[001248] In some embodiments, an additional treatment comprises salicylic acid and/or docosahexaenoic acid (DHA).

[001249] In some embodiments, an additional treatment is edasalonexent (CAT-1004, Catabasis), a conjugate of salicylic acid and docosahexaenoic acid (DHA).

[001250] In some embodiments, an additional treatment is a cell-based therapeutic.

[001251] In some embodiments, an additional treatment is comprises allogeneic cardiosphere-derived cells.

[001252] In some embodiments, an additional treatment is CAP-1002 (Capricor).

Certain Embodiments of Variables

[001253] Embodiments of variables are extensive described in the present disclosure. Those skilled in the art appreciate that an embodiment described for one variable may be optionally and independently combined with embodiments for other variables, and such combinations, wherever and

whenever appropriate, are within the scope of the present disclosure. Embodiments of a variable (e.g. R) given when describing one variable that can be such variable (e.g., R^1, which can be R) are generally applicable to other variables that can be the same variable (e.g., R^s, which can be R). Various embodiments of many variables are also described in other sections of the present disclosure.

[001254] In some embodiments, P^L is P(=W). In some embodiments, P^L is P. In some embodiments, P^L is a chiral P (P*). In some embodiments, P^L is $P{\rightarrow}B(R')_3$.

[001255] In some embodiments, W is O. In some embodiments, W is S. In some embodiments, W is Se. In some embodiments, W is $-N(-L-R^5)$.

[001256] In some embodiments, X is O. In some embodiments, X is S. In some embodiments, X is $-N(-L-R^5)-$. In some embodiments, $-L-R^5$ is $-R$, which is taken together with a R group of $-L-R^1$ (e.g., a $-C(R')-$ in L) to form a double bond or a ring as described in the present disclosure. In some embodiments, X is L.

[001257] In some embodiments, Y is O. In some embodiments, Y is S. In some embodiments, Z is O. In some embodiments, Z is S. In some embodiments, Y is O and Z is O.

[001258] In some embodiments, W is O, Y is O and Z is O. In some embodiments, W is S, Y is O and Z is O.

[001259] In some embodiments, R^1 is $-H$. In some embodiments, R^1 is $-L-R$. In some embodiments, R^1 is halogen. In some embodiments, R^1 is $-CN$. In some embodiments, R^1 is $-NO_2$. In some embodiments, R^1 is $-L-Si(R)_3$. In some embodiments, R^1 is $-OR$. In some embodiments, R^1 is $-SR$. In some embodiments, R^1 is $-N(R)_2$.

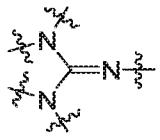
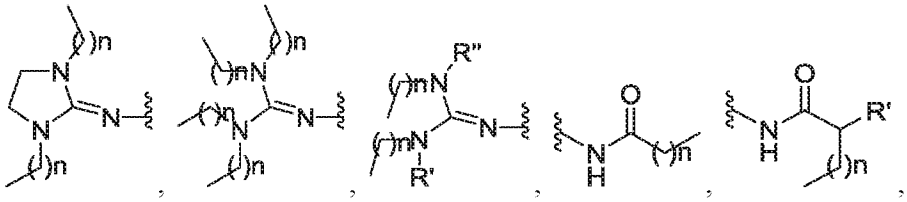
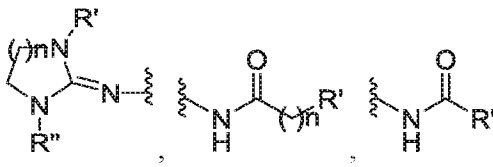
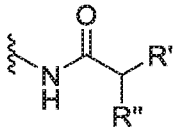
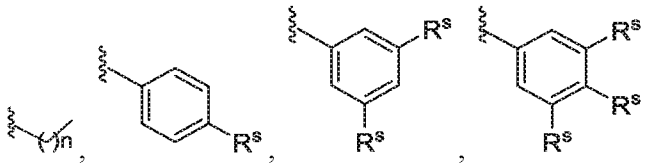
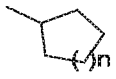
[001260] In some embodiments, R^1 is R as described in the present disclosure.

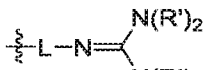
[001261] In some embodiments, $-X-L-R^1$ comprises or is an optionally substituted moiety of a chiral auxiliary (e.g., $H-X-L-R^1$ is an optionally substituted (e.g., capped) chiral auxiliary), e.g., as used in chirally controlled oligonucleotide synthesis, such as those described in US 20150211006, US 20150211006, WO 2017015555, WO 2017015575, WO 2017062862, or WO 2017160741, chiral auxiliaries of each of which are incorporated herein by reference.

[001262] In some embodiments, $-X-L-R^1$ is $-OR$. In some embodiments, $-X-L-R^1$ is $-OH$. In some embodiments, $-X-L-R^1$ is $-SR$. In some embodiments, $-X-L-R^1$ is $-SH$.

[001263] In some embodiments, $-X-L-R^1$ is $-R$. In some embodiments, R is $-CH_3$. In some embodiments, R is $-CH_2CH_3$. In some embodiments, R is $-CH_2CH_2CH_3$. In some embodiments, R is $-CH_2OCH_3$. In some embodiments, R is $CH_3CH_2OCH_2-$. In some embodiments, R is $PhCH_2OCH_2-$. In some embodiments, R is $HC{\equiv}C-CH_2-$. In some embodiments, R is $H_3C-C{\equiv}C-CH_2-$. In some embodiments, R is $CH_2{=}CHCH_2-$. In some embodiments, R is CH_3SCH_2-. In some embodiments, R is

$-CH_2COOCH_3$. In some embodiments, R is $-CH_2COOCH_2CH_3$. In some embodiments, R is $-CH_2CONHCH_3$.

[001264] In some embodiments, $-X-L-R^1$ is comprises a guanidine moiety. In some embodiments, $-X-L-R^1$ is or comprises  . In some embodiments, $-X-L-R^1$ is $-L-W^z$, wherein W^z is selected from  ,  , and  , wherein R" is R' and n is 0-15. In some embodiments, R' and R" are independently  , or  . In some embodiments, L is $-O-CH_2CH_2-$. In some embodiments, n is 0-3. In some embodiments, each R^s is independently $-H$, $-OCH_3$, $-F$, $-CN$, $-CH_3$, $-NO_2$, $-CF_3$, or $-OCF_3$. In some embodiments, R' and R" are the same. In some embodiments, R' and R" are different.

[001265] In some embodiments, In some embodiments, $-X-L-R^1$ is  , wherein each R' is independently as described in the present disclosure. In some embodiments, two R' on two different nitrogen atoms are taken together to form an optionally substituted ring as described in the present disclosure. In some embodiments, a ring is saturated. In some embodiments, a ring is monocyclic. In some embodiments, a ring is 3-10 membered. In some embodiments, a ring is 3-membered. In some embodiments, a ring is 4-membered. In some embodiments, a ring is 5-membered. In some embodiments, a ring is 6-membered. In some embodiments, a ring is 7-membered. In some embodiments, a ring has no additional ring heteroatoms in addition to the two nitrogen atoms.

[001266] In some embodiments, R^5 is R^1 as described in the present disclosure. In some embodiments, R^5 is $-H$. In some embodiments, R^5 is R as described in the present disclosure.

[001267] In some embodiments, L is a bivalent optionally substituted methylene group. In some

embodiments, L is $-CH_2-$. In some embodiments, each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, $-C\equiv C-$, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, $-C(R')_2-$, $-Cy-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$, $-OP(O)(NR')O-$, $-OP(OR')O-$, $-OP(SR')O-$, $-OP(NR')O-$, $-OP(R')O-$, or $-OP(OR')[B(R')_3]O-$, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L.

[001268] In some embodiments, L is a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, $-C\equiv C-$, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, $-C(R')_2-$, $-Cy-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$, $-OP(O)(NR')O-$, $-OP(OR')O-$, $-OP(SR')O-$, $-OP(NR')O-$, $-OP(R')O-$, or $-OP(OR')[B(R')_3]O-$, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L is a covalent bond, or a bivalent, optionally substituted, linear or branched C_{1-30} aliphatic group, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, $-C\equiv C-$, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, $-C(R')_2-$, $-Cy-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$, $-OP(O)(NR')O-$, $-OP(OR')O-$, $-OP(SR')O-$,

–OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L is a covalent bond, or a bivalent, optionally substituted, linear or branched C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L is a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, or –C(O)O–, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L is a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-10} aliphatic group and a C_{1-10} heteroaliphatic group having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, and –C(O)O–, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L is a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-10} aliphatic group and a C_{1-10} heteroaliphatic group having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–,

–$S(O)_2N(R')$–, –C(O)S–, and –C(O)O–.

[001269] In some embodiments, L is a covalent bond. In some embodiments, L is optionally substituted bivalent C_{1-30} aliphatic. In some embodiments, L is optionally substituted bivalent C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from boron, oxygen, nitrogen, sulfur, phosphorus and silicon.

[001270] In some embodiments, aliphatic moieties, *e.g.* those of L, L^s, L^M, R, *etc.*, either monovalent or bivalent or multivalent, and can contain any number of carbon atoms (before any optional substitution) within its range, *e.g.*, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, C_{25}, C_{26}, C_{27}, C_{28}, C_{29}, C_{30}, *etc.* In some embodiments, heteroaliphatic moieties, *e.g.* those of L, R, *etc.*, either monovalent or bivalent or multivalent, and can contain any number of carbon atoms (before any optional substitution) within its range, *e.g.*, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, C_{25}, C_{26}, C_{27}, C_{28}, C_{29}, C_{30}, *etc.*

[001271] In some embodiments, a methylene unit of a linker, e.g., L, L^s, L^M, etc., is replaced with –Cy–, wherein –Cy– is as described in the present disclosure. In some embodiments, one or more methylene unit is optionally and independently substituted with –O–, –S–, –N(R')–, –C(O)–, –S(O)–, –$S(O)_2$–, –P(O)(OR')–, –P(O)(SR')–, –P(S)(OR')–, or –P(S)(OR')–. In some embodiments, a methylene unit is replaced with –O–. In some embodiments, a methylene unit is replaced with –S–. In some embodiments, a methylene unit is replaced with –N(R')–. In some embodiments, a methylene unit is replaced with –C(O)–. In some embodiments, a methylene unit is replaced with –S(O)–. In some embodiments, a methylene unit is replaced with –$S(O)_2$–. In some embodiments, a methylene unit is replaced with –P(O)(OR')–. In some embodiments, a methylene unit is replaced with –P(O)(SR')–. In some embodiments, a methylene unit is replaced with –P(O)(R')–. In some embodiments, a methylene unit is replaced with –P(O)(NR')–. In some embodiments, a methylene unit is replaced with –P(S)(OR')–. In some embodiments, a methylene unit is replaced with –P(S)(SR')–. In some embodiments, a methylene unit is replaced with –P(S)(R')–. In some embodiments, a methylene unit is replaced with –P(S)(NR')–. In some embodiments, a methylene unit is replaced with –P(R')–. In some embodiments, a methylene unit is replaced with –P(OR')–. In some embodiments, a methylene unit is replaced with –P(SR')–. In some embodiments, a methylene unit is replaced with –P(NR')–. In some embodiments, a methylene unit is replaced with –P(OR')[$B(R')_3$]–. In some embodiments, one or more methylene unit is optionally and independently substituted with –O–, –S–, –N(R')–, –C(O)–, –S(O)–, –$S(O)_2$–, –P(O)(OR')–, –P(O)(SR')–, –P(S)(OR')–, or –P(S)(OR')–. In some embodiments, a methylene unit is replaced with –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[$B(R')_3$]O–, each of which may independently be an internucleotidic linkage.

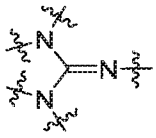
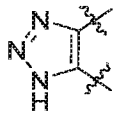
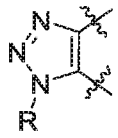
[001272] In some embodiments, L or L^s (e.g., when L^s is L), *e.g.*, when connected to R^s or a sugar ring, is $-CH_2-$. In some embodiments, L is $-C(R)_2-$, wherein at least one R is not hydrogen. In some embodiments, L is −CHR−. In some embodiments, R is hydrogen. In some embodiments, L is −CHR−, wherein R is not hydrogen. In some embodiments, C of −CHR− is chiral. In some embodiments, L is −(*R*)−CHR−, wherein C of −CHR− is chiral. In some embodiments, L is −(*S*)−CHR−, wherein C of −CHR− is chiral. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted C_{1-5} aliphatic. In some embodiments, R is optionally substituted C_{1-5} alkyl. In some embodiments, R is optionally substituted C_{1-4} aliphatic. In some embodiments, R is optionally substituted C_{1-4} alkyl. In some embodiments, R is optionally substituted C_{1-3} aliphatic. In some embodiments, R is optionally substituted C_{1-3} alkyl. In some embodiments, R is optionally substituted C_2 aliphatic. In some embodiments, R is optionally substituted methyl. In some embodiments, R is C_{1-6} aliphatic. In some embodiments, R is C_{1-6} alkyl. In some embodiments, R is C_{1-5} aliphatic. In some embodiments, R is C_{1-5} alkyl. In some embodiments, R is C_{1-4} aliphatic. In some embodiments, R is C_{1-4} alkyl. In some embodiments, R is C_{1-3} aliphatic. In some embodiments, R is C_{1-3} alkyl. In some embodiments, R is C_2 aliphatic. In some embodiments, R is methyl. In some embodiments, R is C_{1-6} haloaliphatic. In some embodiments, R is C_{1-6} haloalkyl. In some embodiments, R is C_{1-5} haloaliphatic. In some embodiments, R is C_{1-5} haloalkyl. In some embodiments, R is C_{1-4} haloaliphatic. In some embodiments, R is C_{1-4} haloalkyl. In some embodiments, R is C_{1-3} haloaliphatic. In some embodiments, R is C_{1-3} haloalkyl. In some embodiments, R is C_2 haloaliphatic. In some embodiments, R is methyl substituted with one or more halogen. In some embodiments, R is $-CF_3$. In some embodiments, L is optionally substituted −CH=CH−. In some embodiments, L is optionally substituted (*E*)−CH=CH−. In some embodiments, L is optionally substituted (*Z*)−CH=CH−. In some embodiments, L is −C≡C−.

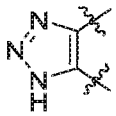
[001273] In some embodiments, L comprises at least one phosphorus atom. In some embodiments, at least one methylene unit of L is replaced with −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, −P(OR')[$B(R')_3$]−, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or −OP(OR')[$B(R')_3$]O−.

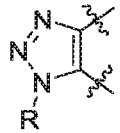
[001274] In some embodiments, L is bonded to a phosphorus of an linkage (e.g., when X is a covalent bond), e.g., the phosphorus of a linkage having formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof. In some embodiments, such an linkage is an internucleotidic linkage. In some embodiments, such an linkage is a chirally controlled internucleotidic linkage.

[001275] In some embodiments, L is −Cy−. In some embodiments, L is .

[001276] In some embodiments, L is a bivalent, optionally substituted, linear or branched C_{1-30} aliphatic group wherein one or more methylene units are optionally and independently replaced as described in the present disclosure. In some embodiments, L is a bivalent, optionally substituted, linear or branched C_{1-30} heteroaliphatic group having 1-10 heteroatoms wherein one or more methylene units are optionally and independently replaced as described in the present disclosure.

[001277] In some embodiments, a heteroaliphatic group in the present disclosure, e.g., of L, R (including any variable that can be R), etc., comprises a  moiety. In some embodiments, =N– is directly bonded to a phosphorus atom. In some embodiments, a heteroaliphatic group comprises a  moiety. In some embodiments, a heteroaliphatic group comprises a  moiety. In some embodiments, such a moiety is directly bonded to a phosphorus atom. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is isopropyl.

[001278] In some embodiments, –Cy– is optionally substituted bivalent monocyclic, bicyclic or polycyclic C_{3-20} cycloaliphatic. In some embodiments, –Cy– is optionally substituted bivalent monocyclic, bicyclic or polycyclic C_{6-20} aryl. In some embodiments, –Cy– is optionally substituted monocyclic, bicyclic or polycyclic 3-20 membered heterocyclyl ring having 1-5 heteroatoms. In some embodiments, –Cy– is optionally substituted monocyclic, bicyclic or polycyclic 5-20 membered heterocyclyl ring having 1-5 heteroatoms, wherein at least one heteroatom is oxygen. In some embodiments, –Cy– is 3-10 membered. In some embodiments, –Cy– is 3-membered. In some embodiments, –Cy– is 4-membered. In some embodiments, –Cy– is 5-membered. In some embodiments, –Cy– is 6-membered. In some embodiments, –Cy– is 7-membered. In some embodiments, –Cy– is 8-membered. In some embodiments, –Cy– is 9-membered. In some embodiments, –Cy– is 10-membered. In some embodiments, –Cy– is optionally substituted bivalent tetrahydrofuran ring. In some embodiments, –Cy– is an optionally substituted furanose moiety. In some embodiments, –Cy– is an optionally substituted bivalent 5-membered heteroaryl ring having 1-4 heteroatoms. In some embodiments, at least one heteroatom is nitrogen. In some embodiments, each heteroatom is nitrogen. In some embodiments, –Cy– is an optionally substituted bivalent triazole ring. In some embodiments, In some embodiments, –Cy– is optionally substituted  . In some

embodiments, –Cy– is  . In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is isopropyl.

[001279] In some embodiments, Cy^L is an optionally substituted trivalent or tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus, boron and silicon. In some embodiments, Cy^L is trivalent. In some embodiments, Cy^L is tetravalent. In some embodiments, one or more CH in a moiety, e.g., L, L^s, L^M, etc. are independently substituted with a trivalent Cy^L group. In some embodiments, one or more carbon atoms in a moiety, e.g., L, L^s, L^M, etc. are independently substituted with a tetravalent Cy^L group. In some embodiments, one or more CH in a moiety, e.g., L, L^s, L^M, etc. are independently substituted with a trivalent Cy^L group, and one or more carbon atoms in a moiety, e.g., L, L^s, L^M, etc. are independently substituted with a tetravalent Cy^L group.

[001280] In some embodiments, Cy^L is monocyclic. In some embodiments, Cy^L is bicyclic. In some embodiments, Cy^L is polycyclic.

[001281] In some embodiments, Cy^L is saturated. In some embodiments, Cy^L is partially unsaturated. In some embodiments, Cy^L is aromatic. In some embodiments, Cy^L is or comprises a saturated ring moiety. In some embodiments, Cy^L is or comprises a partially unsaturated ring moiety. In some embodiments, Cy^L is or comprises an aromatic ring moiety.

[001282] In some embodiments, Cy^L is an optionally substituted C_{3-20} cycloaliphatic ring as described in the present disclosure (for example, those described for R but tetravalent). In some embodiments, a ring is an optionally substituted saturated C_{3-20} cycloaliphatic ring. In some embodiments, a ring is an optionally substituted partially unsaturated C_{3-20} cycloaliphatic ring. A cycloaliphatic ring can be of various sizes as described in the present disclosure. In some embodiments, a ring is 3, 4, 5, 6, 7, 8, 9, or 10-membered. In some embodiments, a ring is 3-membered. In some embodiments, a ring is 4-membered. In some embodiments, a ring is 5-membered. In some embodiments, a ring is 6-membered. In some embodiments, a ring is 7-membered. In some embodiments, a ring is 8-membered. In some embodiments, a ring is 9-membered. In some embodiments, a ring is 10-membered. In some embodiments, a ring is an optionally substituted cyclopropyl moiety. In some embodiments, a ring is an optionally substituted cyclobutyl moiety. In some embodiments, a ring is an optionally substituted cyclopentyl moiety. In some embodiments, a ring is an optionally substituted cyclohexyl moiety. In some embodiments, a ring is an optionally substituted

cycloheptyl moiety. In some embodiments, a ring is an optionally substituted cyclooctanyl moiety. In some embodiments, a cycloaliphatic ring is a cycloalkyl ring. In some embodiments, a cycloaliphatic ring is monocyclic. In some embodiments, a cycloaliphatic ring is bicyclic. In some embodiments, a cycloaliphatic ring is polycyclic. In some embodiments, a ring is a cycloaliphatic moiety as described in the present disclosure for R with more valences.

[001283] In some embodiments, Cy^L is an optionally substituted 6-20 membered aryl ring. In some embodiments, a ring is an optionally substituted trivalent or tetravalent phenyl moiety. In some embodiments, a ring is a tetravalent phenyl moiety. In some embodiments, a ring is an optionally substituted naphthalene moiety. A ring can be of different size as described in the present disclosure. In some embodiments, an aryl ring is 6-membered. In some embodiments, an aryl ring is 10-membered. In some embodiments, an aryl ring is 14-membered. In some embodiments, an aryl ring is monocyclic. In some embodiments, an aryl ring is bicyclic. In some embodiments, an aryl ring is polycyclic. In some embodiments, a ring is an aryl moiety as described in the present disclosure for R with more valences.

[001284] In some embodiments, Cy^L is an optionally substituted 5-20 membered heteroaryl ring having 1-10 heteroatoms, e.g., independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, Cy^L is an optionally substituted 5-20 membered heteroaryl ring having 1-10 heteroatoms, e.g., independently selected from oxygen, nitrogen, and sulfur. In some embodiments, Cy^L is an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms, e.g., independently selected from oxygen, nitrogen, and sulfur. In some embodiments, Cy^L is an optionally substituted 5-membered heteroaryl ring having 1-4 heteroatoms, e.g., independently selected from oxygen, nitrogen, and sulfur. In some embodiments, Cy^L is an optionally substituted 6-membered heteroaryl ring having 1-4 heteroatoms, e.g., independently selected from oxygen, nitrogen, and sulfur. In some embodiments, as described in the present disclosure, heteroaryl rings can be of various sizes and contain various numbers and/or types of heteroatoms. In some embodiments, a heteroaryl ring contains no more than one heteroatom. In some embodiments, a heteroaryl ring contains more than one heteroatom. In some embodiments, a heteroaryl ring contains no more than one type of heteroatom. In some embodiments, a heteroaryl ring contains more than one type of heteroatoms. In some embodiments, a heteroaryl ring is 5-membered. In some embodiments, a heteroaryl ring is 6-membered. In some embodiments, a heteroaryl ring is 8-membered. In some embodiments, a heteroaryl ring is 9-membered. In some embodiments, a heteroaryl ring is 10-membered. In some embodiments, a heteroaryl ring is monocyclic. In some embodiments, a heteroaryl ring is bicyclic. In some embodiments, a heteroaryl ring is polycyclic. In some embodiments, a heteroaryl ring is a nucleobase moiety, e.g., A, T, C, G, U, etc. In some embodiments, a ring is a heteroaryl moiety as described in the present disclosure for R with more valences. In some embodiments, as in linkers described in the present disclosure, Cy^L is

[001285] In some embodiments, Cy^L is a 3-20 membered heterocyclyl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, Cy^L is a 3-20 membered heterocyclyl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, a heterocyclyl ring is saturated. In some embodiments, a heterocyclyl ring is partially unsaturated. A heterocyclyl ring can be of various sizes as described in the present disclosure. In some embodiments, a ring is 3, 4, 5, 6, 7, 8, 9, or 10-membered. In some embodiments, a ring is 3-membered. In some embodiments, a ring is 4-membered. In some embodiments, a ring is 5-membered. In some embodiments, a ring is 6-membered. In some embodiments, a ring is 7-membered. In some embodiments, a ring is 8-membered. In some embodiments, a ring is 9-membered. In some embodiments, a ring is 10-membered. Heterocyclyl rings can contain various numbers and/or types of heteroatoms. In some embodiments, a heterocyclyl ring contains no more than one heteroatom. In some embodiments, a heterocyclyl ring contains more than one heteroatom. In some embodiments, a heterocyclyl ring contains no more than one type of heteroatom. In some embodiments, a heterocyclyl ring contains more than one type of heteroatoms. In some embodiments, a heterocyclyl ring is monocyclic. In some embodiments, a heterocyclyl ring is bicyclic. In some embodiments, a heterocyclyl ring is polycyclic. In some embodiments, a ring is a heterocyclyl moiety as described in the present disclosure for R with more valences.

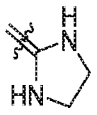
[001286] As readily appreciated by a person having ordinary skill in the art, many suitable ring moieties are extensively described in and can be used in accordance with the present disclosure, for example, those described for R (which may have more valences for Cy^L).

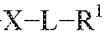
[001287] In some embodiments, Cy^L is a sugar moiety in a nucleic acid. In some embodiments, Cy^L is an optionally substituted furanose moiety. In some embodiments, Cy^L is a pyranose moiety. In some embodiments, Cy^L is an optionally substituted furanose moiety found in DNA. In some embodiments, Cy^L is an optionally substituted furanose moiety found in RNA. In some embodiments, Cy^L is an optionally substituted 2'-deoxyribofuranose moiety. In some embodiments, Cy^L is an optionally substituted ribofuranose moiety. In some embodiments, substitutions provide sugar modifications as described in the present disclosure. In some embodiments, an optionally substituted 2'-deoxyribofuranose moiety and/or an optionally substituted ribofuranose moiety comprise substitution at a 2'-position. In some embodiments, a 2'-position is a 2'-modification as described in the present disclosure. In some embodiments, a 2'-modification is –F. In some embodiments, a 2'-modification is –OR, wherein R is as described in the present disclosure. In some embodiments, R is not hydrogen. In some embodiments, Cy^L is a modified sugar moiety, such as a sugar moiety in LNA, alpha-L-LNA or GNA. In some embodiments, Cy^L is a modified sugar moiety, such as a sugar moiety in ENA. In some embodiments, Cy^L is a terminal sugar moiety of an oligonucleotide, connecting an internucleotidic

linkage and a nucleobase. In some embodiments, Cy^L is a terminal sugar moiety of an oligonucleotide, for example, when that terminus is connected to a solid support optionally through a linker. In some embodiments, Cy^L is a sugar moiety connecting two internucleotidic linkages and a nucleobase. Example sugars and sugar moieties are extensively described in the present disclosure.

[001288] In some embodiments, Cy^L is a nucleobase moiety. In some embodiments, a nucleobase is a natural nucleobase, such as A, T, C, G, U, etc. In some embodiments, a nucleobase is a modified nucleobase. In some embodiments, Cy^L is optionally substituted nucleobase moiety selected from A, T, C, G, U, and 5mC. Example nucleobases and nucleobase moieties are extensively described in the present disclosure.

[001289] In some embodiments, two Cy^L moieties are bonded to each other, wherein one Cy^L is a sugar moiety and the other is a nucleobase moiety. In some embodiments, such a sugar moiety and nucleobase moiety forms a nucleoside moiety. In some embodiments, a nucleoside moiety is natural. In some embodiments, a nucleoside moiety is modified. In some embodiments, Cy^L is an optionally substituted natural nucleoside moiety selected from adenosine, 5-methyluridine, cytidine, guanosine, uridine, 5-methylcytidine, 2'-deoxyadenosine, thymidine, 2'-deoxycytidine, 2'-deoxyguanosine, 2'-deoxyuridine, and 5-methyl-2'-deoxycytidine. Example nucleosides and nucleosides moieties are extensive described in the present disclosure.

[001290] Ring A^L can be either be monovalent, bivalent or polyvalent. In some embodiments, Ring A^L is monovalent (e.g., when g is 0 and no substitution). In some embodiments, Ring A^L is bivalent. In some embodiments, Ring A^L is polyvalent. In some embodiments, Ring A^L is bivalent and is −Cy−. In some embodiments, Ring A^L is an optionally substituted bivalent triazole ring. In some embodiments, Ring A^L is trivalent and is Cy^L. In some embodiments, Ring A^L is tetravalent and is Cy^L. In some embodiments, Ring A^L is optionally substituted  .

[001291] In some embodiments, $-X-L-R^1$ is optionally substituted alkynyl. In some embodiments, $-X-L-R^1$ is  . In some embodiments, an alkynyl group, e.g., , can react with a number of reagents through various reactions to provide further modifications. For example, in some embodiments, an alkynyl group can react with azides through click chemistry. In some embodiments, an azide has the structure of R^1-N_3.

[001292] In some embodiments, each R^S is independently −H, halogen, −CN, $-N_3$, −NO, $-NO_2$, −L−R', −L−Si(R)$_3$, −L−OR', −L−SR', −L−N(R')$_2$, −O−L−R', −O−L−Si(R)$_3$, −O−L−OR', −O−L^SSR', or −O−L^SN(R')$_2$ as described in the present disclosure.

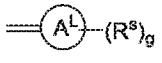
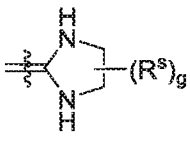
[001293] In some embodiments, R^S is R', wherein R' is as described in the present disclosure. In

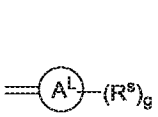
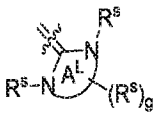
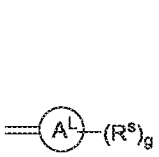
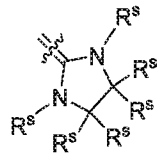
some embodiments, R^s is R, wherein R is as described in the present disclosure. In some embodiments, R^s is optionally substituted C_{1-6} aliphatic. In some embodiments, R^s is methyl. In some embodiments, R^s is optionally substituted C_{1-30} heteroaliphatic. In some embodiments, R^s comprises one or more silicon atoms. In some embodiments, R^s is $-CH_2Si(Ph)_2CH_3$.

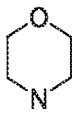
[001294] In some embodiments, R^s is $-L-R'$. In some embodiments, R^s is $-L-R'$ wherein $-L-$ is a bivalent, optionally substituted C_{1-30} heteroaliphatic group. In some embodiments, R^s is $-CH_2Si(Ph)_2CH_3$.

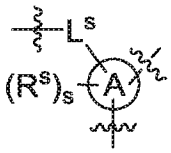
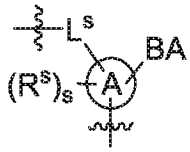
[001295] In some embodiments, R^s is $-F$. In some embodiments, R^s is $-Cl$. In some embodiments, R^s is $-Br$. In some embodiments, R^s is $-I$. In some embodiments, R^s is $-CN$. In some embodiments, R^s is $-N_3$. In some embodiments, R^s is $-NO$. In some embodiments, R^s is $-NO_2$. In some embodiments, R^s is $-L-Si(R)_3$. In some embodiments, R^s is $-Si(R)_3$. In some embodiments, R^s is $-L-R'$. In some embodiments, R^s is $-R'$. In some embodiments, R^s is $-L-OR'$. In some embodiments, R^s is $-OR'$. In some embodiments, R^s is $-L-SR'$. In some embodiments, R^s is $-SR'$. In some embodiments, R^s is $-L-N(R')_2$. In some embodiments, R^s is $-N(R')_2$. In some embodiments, R^s is $-O-L-R'$. In some embodiments, R^s is $-O-L-Si(R)_3$. In some embodiments, R^s is $-O-L-OR'$. In some embodiments, R^s is $-O-L-SR'$. In some embodiments, R^s is $-O-L-N(R')_2$. In some embodiments, R^s is a 2'-modification as described in the present disclosure. In some embodiments, R^s is $-OR$, wherein R is as described in the present disclosure. In some embodiments, R^s is $-OR$, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, R^s is $-OMe$. In some embodiments, R^s is $-OCH_2CH_2OMe$. In some embodiments, R^s is R^{1s}, R^{2s}, R^{3s}, R^{4s}, or R^{5s} as described in the present disclosure.

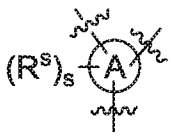
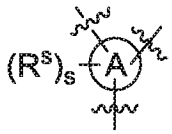
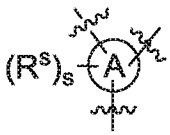
[001296] In some embodiments, g is 0-20. In some embodiments, g is 1-20. In some embodiments, g is 1-5. In some embodiments, g is 1. In some embodiments, g is 2. In some embodiments, g is 3. In some embodiments, g is 4. In some embodiments, g is 5. In some embodiments, g is 6. In some embodiments, g is 7. In some embodiments, g is 8. In some embodiments, g is 9. In some embodiments, g is 10. In some embodiments, g is 11. In some embodiments, g is 12. In some embodiments, g is 13. In some embodiments, g is 14. In some embodiments, g is 15. In some embodiments, g is 16. In some embodiments, g is 17. In some embodiments, g is 18. In some embodiments, g is 19. In some embodiments, g is 20.

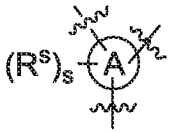
[001297] In some embodiments,  is  . In some embodiments,

 is  . In some embodiments,  is  .

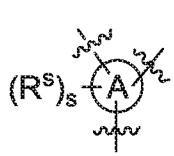
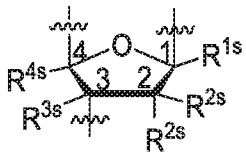
[001298] In some embodiments, each Ring A is independently an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms, e.g., independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, Ring A is an optionally substituted ring, which ring is as described in the present disclosure. In some embodiments, Ring A comprises an oxygen ring atom. In some embodiments, Ring A is or comprises a ring of a sugar moiety. In some embodiments, a ring is . In some embodiments, a ring is . In some embodiments, a ring is  . In some embodiments, a ring is a bicyclic ring, e.g., found in a sugar moiety of LNA.

[001299] In some embodiments, a sugar unit is of the structure  , wherein each variable is independently as described in the present disclosure. In some embodiments, a nucleoside unit is of the structure  , wherein each variable is independently as described in the present disclosure.

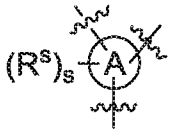
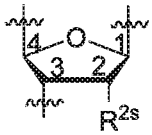
[001300] In some embodiments, L^s is $-C(R^{5s})_2-$ and  is as described in the present disclosure. In some embodiments, L^s is $-CHR^{5s}-$ and  is as described in the present disclosure. In some embodiments, L^s is $-C(R)_2-$ and  is as described in the present



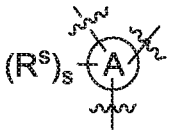
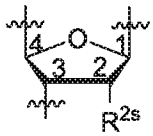
disclosure. In some embodiments, L^s is –CHR– and is as described in the present disclosure.

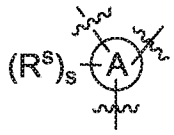
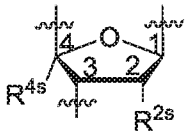
[001301] In some embodiments, is , BA is connected at C1, and each of R^{1s}, R^{2s}, R^{3s}, R^{4s} and R^{5s} is independently as described in the present disclosure. In some

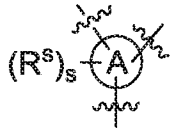
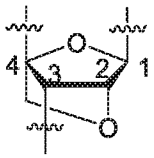
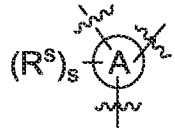
embodiments, is , wherein R^{2s} is as described in the present disclosure. In

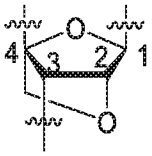
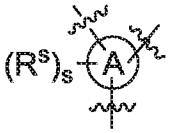
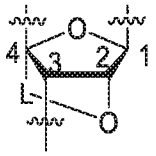
some embodiments, is , wherein R^{2s} is not –OH. In some embodiments,

is , wherein R^{2s} and R^{4s} are R, and the two R groups are taken together with their intervening atoms to form an optionally substituted ring. In some embodiments,

, or Ring A, is optionally substituted . In some embodiments,

, or Ring A, is . In some embodiments, , or Ring A, is .

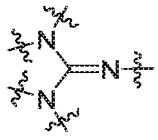
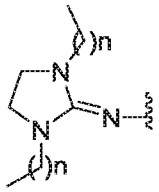
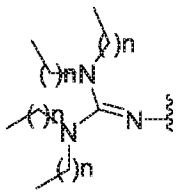
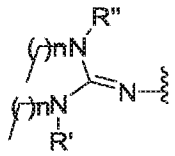
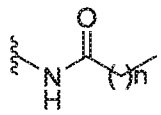
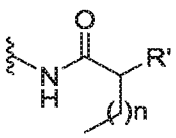
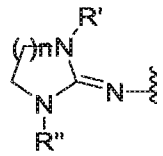
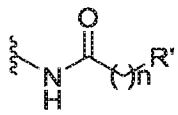
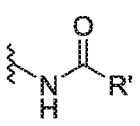
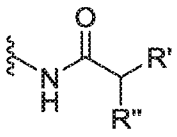
[001302] In some embodiments, each of R^{1s}, R^{2s}, R^{3s}, R^{4s}, and R^{5s} is independently R^s, wherein R^s is as described in the present disclosure.

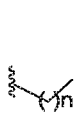
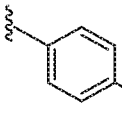
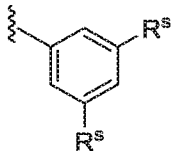
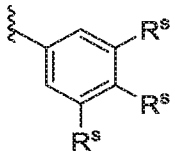
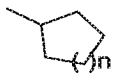
[001303] In some embodiments, R^{1s} is R^s wherein R^s is as described in the present disclosure. In some embodiments, R^{1s} is at 1'-position (BA is at 1'-position). In some embodiments, R^{1s} is –H. In some embodiments, R^{1s} is –F. In some embodiments, R^{1s} is –Cl. In some embodiments, R^{1s} is –Br. In some embodiments, R^{1s} is –I. In some embodiments, R^{1s} is –CN. In some embodiments, R^{1s} is $-N_3$. In some embodiments, R^{1s} is –NO. In some embodiments, R^{1s} is $-NO_2$. In some embodiments, R^{1s} is –L–R'. In some embodiments, R^{1s} is –R'. In some embodiments, R^{1s} is –L–OR'. In some

embodiments, R^{1s} is –OR'. In some embodiments, R^{1s} is –L–SR'. In some embodiments, R^{1s} is –SR'. In some embodiments, R^{1s} is L–L–N(R')$_2$. In some embodiments, R^{1s} is –N(R')$_2$. In some embodiments, R^{1s} is –OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{1s} is –OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{1s} is –OMe. In some embodiments, R^{1s} is –MOE. In some embodiments, R^{1s} is hydrogen. In some embodiments, R^s at one 1'-position is hydrogen, and R^s at the other 1'-position is not hydrogen as described herein. In some embodiments, R^s at both 1'-positions are hydrogen. In some embodiments, R^s at one 1'-position is hydrogen, and the other 1'-position is connected to an internucleotidic linkage. In some embodiments, R^{1s} is –F. In some embodiments, R^{1s} is –Cl. In some embodiments, R^{1s} is –Br. In some embodiments, R^{1s} is –I. In some embodiments, R^{1s} is –CN. In some embodiments, R^{1s} is –N_3. In some embodiments, R^{1s} is –NO. In some embodiments, R^{1s} is –NO_2. In some embodiments, R^{1s} is –L–R'. In some embodiments, R^{1s} is –R'. In some embodiments, R^{1s} is –L–OR'. In some embodiments, R^{1s} is –OR'. In some embodiments, R^{1s} is –L–SR'. In some embodiments, R^{1s} is –SR'. In some embodiments, R^{1s} is –L–N(R')$_2$. In some embodiments, R^{1s} is –N(R')$_2$. In some embodiments, R^{1s} is –OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{1s} is –OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{1s} is –OH. In some embodiments, R^{1s} is –OMe. In some embodiments, R^{1s} is –MOE. In some embodiments, R^{1s} is hydrogen. In some embodiments, one R^{1s} at a 1'-position is hydrogen, and the other R^{1s} at the other 1'-position is not hydrogen as described herein. In some embodiments, R^{1s} at both 1'-positions are hydrogen. In some embodiments, R^{1s} is –O–L–OR'. In some embodiments, R^{1s} is –O–L–OR', wherein L is optionally substituted C_{1-6} alkylene, and R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{1s} is –O–(optionally substituted C_{1-6} alkylene)–OR'. In some embodiments, R^{1s} is –O–(optionally substituted C_{1-6} alkylene)–OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{1s} is –OCH_2CH_2OMe.

[001304] In some embodiments, R^{2s} is R^s wherein R^s is as described in the present disclosure. In some embodiments, if there are two R^{2s} at the 2'-position, one R^{2s} is –H and the other is not. In some embodiments, R^{2s} is at 2'-position (BA is at 1'-position). In some embodiments, R^{2s} is –H. In some embodiments, R^{2s} is –F. In some embodiments, R^{2s} is –Cl. In some embodiments, R^{2s} is –Br. In some embodiments, R^{2s} is –I. In some embodiments, R^{2s} is –CN. In some embodiments, R^{2s} is –N_3. In some embodiments, R^{2s} is –NO. In some embodiments, R^{2s} is –NO_2. In some embodiments, R^{2s} is –L–R'. In some embodiments, R^{2s} is –R'. In some embodiments, R^{2s} is –L–OR'. In some embodiments, R^{2s} is –OR'. In some embodiments, R^{2s} is –L–SR'. In some embodiments, R^{2s} is –SR'. In some embodiments, R^{2s} is L–L–N(R')$_2$. In some embodiments, R^{2s} is –N(R')$_2$. In some embodiments, R^{2s} is –OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{2s} is –OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{2s} is –OMe. In some embodiments, R^{2s} is –MOE. In

some embodiments, R^{2s} is hydrogen. In some embodiments, R^s at one 2'-position is hydrogen, and R^s at the other 2'-position is not hydrogen as described herein. In some embodiments, R^s at both 2'-positions are hydrogen. In some embodiments, R^s at one 2'-position is hydrogen, and the other 2'-position is connected to an internucleotidic linkage. In some embodiments, R^{2s} is −F. In some embodiments, R^{2s} is −Cl. In some embodiments, R^{2s} is −Br. In some embodiments, R^{2s} is −I. In some embodiments, R^{2s} is −CN. In some embodiments, R^{2s} is $-N_3$. In some embodiments, R^{2s} is −NO. In some embodiments, R^{2s} is $-NO_2$. In some embodiments, R^{2s} is −L−R'. In some embodiments, R^{2s} is −R'. In some embodiments, R^{2s} is −L−OR'. In some embodiments, R^{2s} is −OR'. In some embodiments, R^{2s} is −L−SR'. In some embodiments, R^{2s} is −SR'. In some embodiments, R^{2s} is $-L-N(R')_2$. In some embodiments, R^{2s} is $-N(R')_2$. In some embodiments, R^{2s} is −OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{2s} is −OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{2s} is −OH. In some embodiments, R^{2s} is −OMe. In some embodiments, R^{2s} is −MOE. In some embodiments, R^{2s} is hydrogen. In some embodiments, one R^{2s} at a 2'-position is hydrogen, and the other R^{2s} at the other 2'-position is not hydrogen as described herein. In some embodiments, R^{2s} at both 2'-positions are hydrogen. In some embodiments, R^{2s} is −O−L−OR'. In some embodiments, R^{2s} is −O−L−OR', wherein L is optionally substituted C_{1-6} alkylene, and R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{2s} is −O−(optionally substituted C_{1-6} alkylene)−OR'. In some embodiments, R^{2s} is −O−(optionally substituted C_{1-6} alkylene)−OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{2s} is $-OCH_2CH_2OMe$.

[001305] In some embodiments, R^{2s} comprises a guanidine moiety. In some embodiments, R^{2s} comprises  . In some embodiments, R^{2s} is $-L-W^z$, wherein W^z is selected from  ,  ,  ,  ,  ,  ,  ,  , and  , wherein R'' is R' and n is 0-15. In some embodiments, R' and R'' are

independently  ,  ,  ,  , or  . In some embodiments, L is $-O-CH_2CH_2-$. In some embodiments, n is 0-3. In some embodiments, each R^s is independently $-H$, $-OCH_3$, $-F$, $-CN$, $-CH_3$, $-NO_2$, $-CF_3$, or $-OCF_3$. In some embodiments, R' and R" are the same. In some embodiments, R' and R" are different.

[001306] In some embodiments, R^{3s} is R^s wherein R^s is as described in the present disclosure. In some embodiments, R^{3s} is at 3'-position (BA is at 1'-position). In some embodiments, R^{3s} is $-H$. In some embodiments, R^{3s} is $-F$. In some embodiments, R^{3s} is $-Cl$. In some embodiments, R^{3s} is $-Br$. In some embodiments, R^{3s} is $-I$. In some embodiments, R^{3s} is $-CN$. In some embodiments, R^{3s} is $-N_3$. In some embodiments, R^{3s} is $-NO$. In some embodiments, R^{3s} is $-NO_2$. In some embodiments, R^{3s} is $-L-R'$. In some embodiments, R^{3s} is $-R'$. In some embodiments, R^{3s} is $-L-OR'$. In some embodiments, R^{3s} is $-OR'$. In some embodiments, R^{3s} is $-L-SR'$. In some embodiments, R^{3s} is $-SR'$. In some embodiments, R^{3s} is $-L-N(R')_2$. In some embodiments, R^{3s} is $-N(R')_2$. In some embodiments, R^{3s} is $-OR'$, wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{3s} is $-OR'$, wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{3s} is $-OMe$. In some embodiments, R^{3s} is $-MOE$. In some embodiments, R^{3s} is hydrogen. In some embodiments, R^s at one 3'-position is hydrogen, and R^s at the other 3'-position is not hydrogen as described herein. In some embodiments, R^s at both 3'-positions are hydrogen. In some embodiments, R^s at one 3'-position is hydrogen, and the other 3'-position is connected to an internucleotidic linkage. In some embodiments, R^{3s} is $-F$. In some embodiments, R^{3s} is $-Cl$. In some embodiments, R^{3s} is $-Br$. In some embodiments, R^{3s} is $-I$. In some embodiments, R^{3s} is $-CN$. In some embodiments, R^{3s} is $-N_3$. In some embodiments, R^{3s} is $-NO$. In some embodiments, R^{3s} is $-NO_2$. In some embodiments, R^{3s} is $-L-R'$. In some embodiments, R^{3s} is $-R'$. In some embodiments, R^{3s} is $-L-OR'$. In some embodiments, R^{3s} is $-OR'$. In some embodiments, R^{3s} is $-L-SR'$. In some embodiments, R^{3s} is $-SR'$. In some embodiments, R^{3s} is $L-L-N(R')_2$. In some embodiments, R^{3s} is $-N(R')_2$. In some embodiments, R^{3s} is $-OR'$, wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{3s} is $-OR'$, wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{3s} is $-OH$. In some embodiments, R^{3s} is $-OMe$. In some embodiments, R^{3s} is $-MOE$. In some embodiments, R^{3s} is hydrogen.

[001307] In some embodiments, R^{4s} is R^s wherein R^s is as described in the present disclosure. In some embodiments, R^{4s} is at 4'-position (BA is at 1'-position). In some embodiments, R^{4s} is $-H$. In some embodiments, R^{4s} is $-F$. In some embodiments, R^{4s} is $-Cl$. In some embodiments, R^{4s} is $-Br$. In some embodiments, R^{4s} is $-I$. In some embodiments, R^{4s} is $-CN$. In some embodiments, R^{4s} is $-N_3$. In

some embodiments, R^{4s} is –NO. In some embodiments, R^{4s} is $–NO_2$. In some embodiments, R^{4s} is –L–R'. In some embodiments, R^{4s} is –R'. In some embodiments, R^{4s} is –L–OR'. In some embodiments, R^{4s} is –OR'. In some embodiments, R^{4s} is –L–SR'. In some embodiments, R^{4s} is –SR'. In some embodiments, R^{4s} is $–L–N(R')_2$. In some embodiments, R^{4s} is $–N(R')_2$. In some embodiments, R^{4s} is –OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{4s} is –OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{4s} is –OMe. In some embodiments, R^{4s} is –MOE. In some embodiments, R^{4s} is hydrogen. In some embodiments, R^s at one 4'-position is hydrogen, and R^s at the other 4'-position is not hydrogen as described herein. In some embodiments, R^s at both 4'-positions are hydrogen. In some embodiments, R^s at one 4'-position is hydrogen, and the other 4'-position is connected to an internucleotidic linkage. In some embodiments, R^{4s} is –F. In some embodiments, R^{4s} is –Cl. In some embodiments, R^{4s} is –Br. In some embodiments, R^{4s} is –I. In some embodiments, R^{4s} is –CN. In some embodiments, R^{4s} is $–N_3$. In some embodiments, R^{4s} is –NO. In some embodiments, R^{4s} is $–NO_2$. In some embodiments, R^{4s} is –L–R'. In some embodiments, R^{4s} is –R'. In some embodiments, R^{4s} is –L–OR'. In some embodiments, R^{4s} is –OR'. In some embodiments, R^{4s} is –L–SR'. In some embodiments, R^{4s} is –SR'. In some embodiments, R^{4s} is $L–L–N(R')_2$. In some embodiments, R^{4s} is $–N(R')_2$. In some embodiments, R^{4s} is –OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{4s} is –OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{4s} is –OH. In some embodiments, R^{4s} is –OMe. In some embodiments, R^{4s} is –MOE. In some embodiments, R^{4s} is hydrogen.

[001308] In some embodiments, R^{5s} is R^s wherein R^s is as described in the present disclosure. In some embodiments, R^{5s} is R' wherein R' is as described in the present disclosure. In some embodiments, R^{5s} is –H. In some embodiments, two or more R^{5s} are connected to the same carbon atom, and at least one is not –H. In some embodiments, R^{5s} is not –H. In some embodiments, R^{5s} is –F. In some embodiments, R^{5s} is –Cl. In some embodiments, R^{5s} is –Br. In some embodiments, R^{5s} is –I. In some embodiments, R^{5s} is –CN. In some embodiments, R^{5s} is $–N_3$. In some embodiments, R^{5s} is –NO. In some embodiments, R^{5s} is $–NO_2$. In some embodiments, R^{5s} is –L–R'. In some embodiments, R^{5s} is –R'. In some embodiments, R^{5s} is –L–OR'. In some embodiments, R^{5s} is –OR'. In some embodiments, R^{5s} is –L–SR'. In some embodiments, R^{5s} is –SR'. In some embodiments, R^{5s} is $L–L–N(R')_2$. In some embodiments, R^{5s} is $–N(R')_2$. In some embodiments, R^{5s} is –OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{5s} is –OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{5s} is –OH. In some embodiments, R^{5s} is –OMe. In some embodiments, R^{5s} is –MOE. In some embodiments, R^{5s} is hydrogen.

[001309] In some embodiments, R^{5s} is optionally substituted C_{1-6} aliphatic as described in the present disclosure, e.g., C_{1-6} aliphatic embodiments described for R or other variables. In some

embodiments, R^{5s} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{5s} is optionally substituted methyl, wherein each substituent, if any, independently comprises no more than one carbon atoms. In some embodiments, R^{5s} is optionally substituted methyl, wherein each substituent, if any, independently is halogen. In some embodiments, R^{5s} is methyl. In some embodiments, R^{5s} is ethyl.

[001310] In some embodiments, R^{5s} is a protected hydroxyl group suitable for oligonucleotide synthesis. In some embodiments, R^{5s} is $-OR'$, wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{5s} is DMTrO−. Example protecting groups are widely known for use in accordance with the present disclosure. For additional examples, see Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, 2nd ed.; Wiley: New York, 1991, and US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, and/or WO 2017/210647, protecting groups of each of which are hereby incorporated by reference.

[001311] In some embodiments, two or more of R^{1s}, R^{2s}, R^{3s}, R^{4s}, and R^{5s} are R and can be taken together with intervening atom(s) to form a ring as described in the present disclosure. In some embodiments, R^{2s} and R^{4s} are R taken together to form a ring, and a sugar moiety can be a bicyclic sugar moiety, e.g., a LNA sugar moiety.

[001312] In some embodiments, L^s is L as described in the present disclosure.

[001313] In some embodiments, L^s is $-C(R^{5s})_2-$, wherein each R^{5s} is independently as described in the present disclosure. In some embodiments, one of R^{5s} is H and the other is not H. In some embodiments, none of R^{5s} is H. In some embodiments, L^s is $-CHR^{5s}-$, wherein each R^{5s} is independently as described in the present disclosure. In some embodiments, the carbon atom of $-C(R^{5s})_2-$ is stereorandom. In some embodiments, it is of R configuration. In some embodiments, it is of S configuration. In some embodiments, $-C(R^{5s})_2-$ is 5'-C, optionally substituted, of a sugar moiety. In some embodiments, the C of $-C(R^{5s})_2-$ is of R configuration. In some embodiments, the C of $-C(R^{5s})_2-$ is of S configuration. As described in the present disclosure, in some embodiments, R^{5s} is optionally substituted C_{1-6} aliphatic; in some embodiments, R^{5s} is methyl.

[001314] In some embodiments, provided compounds comprise one or more bivalent or multivalent optionally substituted rings, e.g., Ring A, Cy^L, those formed by two or more R groups (R and (combinations of) variables that can be R) taken together, etc. In some embodiments, a ring is a cycloaliphatic, aryl, heteroaryl, or heterocyclyl group as described for R but bivalent or multivalent. As appreciated by those skilled in the art, ring moieties described for one variable, e.g., Ring A, can also be applicable to other variables, e.g., Cy^L, if requirements of the other variables, e.g., number of heteroatoms, valence, etc., are satisfied. Example rings are extensively described in the present disclosure.

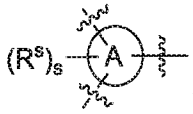
[001315] In some embodiments, a ring, e.g., in Ring A, R, etc. which is optionally substituted, is a 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[001316] In some embodiments, a ring can be of any size within its range, e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20-membered.

[001317] In some embodiments, a ring is monocyclic. In some embodiments, a ring is saturated and monocyclic. In some embodiments, a ring is monocyclic and partially saturated. In some embodiments, a ring is monocyclic and aromatic.

[001318] In some embodiments, a ring is bicyclic. In some embodiments, a ring is polycyclic. In some embodiments, a bicyclic or polycyclic ring comprises two or more monocyclic ring moieties, each of which can be saturated, partially saturated, or aromatic, and each which can contain no or 1-10 heteroatoms. In some embodiments, a bicyclic or polycyclic ring comprises a saturated monocyclic ring. In some embodiments, a bicyclic or polycyclic ring comprises a saturated monocyclic ring containing no heteroatoms. In some embodiments, a bicyclic or polycyclic ring comprises a saturated monocyclic ring comprising one or more heteroatoms. In some embodiments, a bicyclic or polycyclic ring comprises a partially saturated monocyclic ring. In some embodiments, a bicyclic or polycyclic ring comprises a partially saturated monocyclic ring containing no heteroatoms. In some embodiments, a bicyclic or polycyclic ring comprises a partially saturated monocyclic ring comprising one or more heteroatoms. In some embodiments, a bicyclic or polycyclic ring comprises an aromatic monocyclic ring. In some embodiments, a bicyclic or polycyclic ring comprises an aromatic monocyclic ring containing no heteroatoms. In some embodiments, a bicyclic or polycyclic ring comprises an aromatic monocyclic ring comprising one or more heteroatoms. In some embodiments, a bicyclic or polycyclic ring comprises a saturated ring and a partially saturated ring, each of which independently contains one or more heteroatoms. In some embodiments, a bicyclic ring comprises a saturated ring and a partially saturated ring, each of which independently comprises no, or one or more heteroatoms. In some embodiments, a bicyclic ring comprises an aromatic ring and a partially saturated ring, each of which independently comprises no, or one or more heteroatoms. In some embodiments, a polycyclic ring comprises a saturated ring and a partially saturated ring, each of which independently comprises no, or one or more heteroatoms. In some embodiments, a polycyclic ring comprises an aromatic ring and a partially saturated ring, each of which independently comprises no, or one or more heteroatoms. In some embodiments, a polycyclic ring comprises an aromatic ring and a saturated ring, each of which independently comprises no, or one or more heteroatoms. In some embodiments, a polycyclic ring comprises an aromatic ring, a saturated ring, and a partially saturated ring, each of which independently comprises no, or one or more heteroatoms. In some embodiments, a ring comprises at least one

heteroatom. In some embodiments, a ring comprises at least one nitrogen atom. In some embodiments, a ring comprises at least one oxygen atom. In some embodiments, a ring comprises at least one sulfur atom.

[001319] As appreciated by those skilled in the art in accordance with the present disclosure, a ring is typically optionally substituted. In some embodiments, a ring is unsubstituted. In some embodiments, a ring is substituted. In some embodiments, a ring is substituted on one or more of its carbon atoms. In some embodiments, a ring is substituted on one or more of its heteroatoms. In some embodiments, a ring is substituted on one or more of its carbon atoms, and one or more of its heteroatoms. In some embodiments, two or more substituents can be located on the same ring atom. In some embodiments, all available ring atoms are substituted. In some embodiments, not all available ring atoms are substituted. In some embodiments, in provided structures where rings are indicated to be connected to other structures (e.g., Ring A in ), "optionally substituted" is to mean that, besides those structures already connected, remaining substitutable ring positions, if any, are optionally substituted.

[001320] In some embodiments, a ring is a bivalent or multivalent C_{3-30} cycloaliphatic ring. In some embodiments, a ring is a bivalent or multivalent C_{3-20} cycloaliphatic ring. In some embodiments, a ring is a bivalent or multivalent C_{3-10} cycloaliphatic ring. In some embodiments, a ring is a bivalent or multivalent 3-30 membered saturated or partially unsaturated carbocyclic ring. In some embodiments, a ring is a bivalent or multivalent 3-7 membered saturated or partially unsaturated carbocyclic ring. In some embodiments, a ring is a bivalent or multivalent 3-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, a ring is a bivalent or multivalent 4-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, a ring is a bivalent or multivalent 5-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, a ring is a bivalent or multivalent 6-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, a ring is a bivalent or multivalent 7-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, a ring is a bivalent or multivalent cyclohexyl ring. In some embodiments, a ring is a bivalent or multivalent cyclopentyl ring. In some embodiments, a ring is a bivalent or multivalent cyclobutyl ring. In some embodiments, a ring is a bivalent or multivalent cyclopropyl ring.

[001321] In some embodiments, a ring is a bivalent or multivalent C_{6-30} aryl ring. In some embodiments, a ring is a bivalent or multivalent phenyl ring.

[001322] In some embodiments, a ring is a bivalent or multivalent 8-10 membered bicyclic saturated, partially unsaturated or aryl ring. In some embodiments, a ring is a bivalent or multivalent 8-10 membered bicyclic saturated ring. In some embodiments, a ring is a bivalent or multivalent 8-10

membered bicyclic partially unsaturated ring. In some embodiments, a ring is a bivalent or multivalent 8-10 membered bicyclic aryl ring. In some embodiments, a ring is a bivalent or multivalent naphthyl ring.

[001323] In some embodiments, a ring is a bivalent or multivalent 5-30 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, a ring is a bivalent or multivalent 5-30 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 5-30 membered heteroaryl ring having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, a ring is a bivalent or multivalent 5-30 membered heteroaryl ring having 1-5 heteroatoms independently selected from oxygen, nitrogen, and sulfur.

[001324] In some embodiments, a ring is a bivalent or multivalent 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, sulfur, and oxygen.

[001325] In some embodiments, a ring is a bivalent or multivalent 5-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur. In some embodiments, a ring is a bivalent or multivalent 6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001326] In certain embodiments, a ring is a bivalent or multivalent 8–10 membered bicyclic heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 5,6–fused heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 5,6–fused heteroaryl ring having 1–5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, a ring is a bivalent or multivalent 6,6–fused heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001327] In some embodiments, a ring is a bivalent or multivalent 3-30 membered heterocyclic ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, a ring is a bivalent or multivalent 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, a ring is a bivalent or multivalent 5–7 membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, a ring is a bivalent or multivalent 5–6 membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, a ring is a bivalent or multivalent 5-membered partially unsaturated monocyclic ring

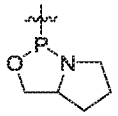
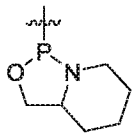
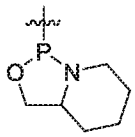
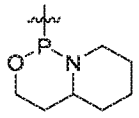
having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, a ring is a bivalent or multivalent 6-membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, a ring is a bivalent or multivalent 7-membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 3-membered heterocyclic ring having one heteroatom selected from nitrogen, oxygen or sulfur. In some embodiments, a ring is a bivalent or multivalent 4-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 5-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 6-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 7-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001328] In some embodiments, a ring is a bivalent or multivalent 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001329] In some embodiments, a ring is a bivalent or multivalent 5,6–fused heteroaryl ring having 1–5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, a ring is a bivalent or multivalent 6,6–fused heteroaryl ring having 1–5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001330] In some embodiments, a ring formed by two or more groups taken together, which is typically optionally substituted, is a monocyclic saturated 5-7 membered ring having no additional heteroatoms in addition to intervening heteroatoms, if any. In some embodiments, a ring formed by two or more groups taken together is a monocyclic saturated 5-membered ring having no additional heteroatoms in addition to intervening heteroatoms, if any. In some embodiments, a ring formed by two or more groups taken together is a monocyclic saturated 6-membered ring having no additional heteroatoms in addition to intervening heteroatoms, if any. In some embodiments, a ring formed by two or more groups taken together is a monocyclic saturated 7-membered ring having no additional heteroatoms in addition to intervening heteroatoms, if any.

[001331] In some embodiments, a ring formed by two or more groups taken together is a bicyclic, saturated, partially unsaturated, or aryl 5-30 membered ring having, in addition to the intervening heteroatoms, if any, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, a ring formed by two or more groups taken together is a bicyclic,

saturated, partially unsaturated, or aryl 5-30 membered ring having, in addition to the intervening heteroatoms, if any, 0-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, a ring formed by two or more groups taken together is a bicyclic and saturated 8-10 membered bicyclic ring having no additional heteroatoms in addition to intervening heteroatoms, if any. In some embodiments, a ring formed by two or more groups taken together is a bicyclic and saturated 8-membered bicyclic ring having no additional heteroatoms in addition to intervening heteroatoms, if any. In some embodiments, a ring formed by two or more groups taken together is a bicyclic and saturated 9-membered bicyclic ring having no additional heteroatoms in addition to intervening heteroatoms, if any. In some embodiments, a ring formed by two or more groups taken together is a bicyclic and saturated 10-membered bicyclic ring having no additional heteroatoms in addition to intervening heteroatoms, if any. In some embodiments, a ring formed by two or more groups taken together is bicyclic and comprises a 5-membered ring fused to a 5-membered ring. In some embodiments, a ring formed by two or more groups taken together is bicyclic and comprises a 5-membered ring fused to a 6-membered ring. In some embodiments, the 5-membered ring comprises one or more intervening nitrogen, phosphorus and oxygen atoms as ring atoms. In some embodiments, a ring formed by two or more groups taken together comprises a ring system having the backbone structure of  ,  ,  , or  .

[001332] In some embodiments, a ring formed by two or more groups taken together is a polycyclic, saturated, partially unsaturated, or aryl 3-30 membered ring having, in addition to the intervening heteroatoms, if any, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, a ring formed by two or more groups taken together is a polycyclic, saturated, partially unsaturated, or aryl 3-30 membered ring having, in addition to the intervening heteroatoms, if any, 0-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur.

[001333] In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 5-10 membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 5-9 membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is

monocyclic, bicyclic or polycyclic and comprises a 5-8 membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 5-7 membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 5-6 membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms.

[001334] In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 5-membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 6-membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 7-membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 8-membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 9-membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 10-membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms.

[001335] In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 5-membered ring whose ring atoms consist of carbon atoms and the intervening nitrogen, phosphorus and oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 6-membered ring whose ring atoms consist of carbon atoms and the intervening nitrogen, phosphorus and oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 7-membered ring whose ring atoms consist of carbon atoms and the intervening nitrogen, phosphorus and oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 8-membered ring whose ring atoms consist of carbon atoms and the intervening nitrogen, phosphorus and oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or

polycyclic and comprises a 9-membered ring whose ring atoms consist of carbon atoms and the intervening nitrogen, phosphorus and oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 10-membered ring whose ring atoms consist of carbon atoms and the intervening nitrogen, phosphorus and oxygen atoms.

[001336] In some embodiments, rings described herein are unsubstituted. In some embodiments, rings described herein are substituted. In some embodiments, substituents are selected from those described in example compounds provided in the present disclosure.

[001337] In some embodiments, each BA is independently an optionally substituted group selected from C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and C_{3-30} heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus, boron and silicon;

each Ring A is independently an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon; and

each L^P independently has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form there, wherein each variable is independently as described in the present disclosure.

[001338] In some embodiments, each BA is independently an optionally substituted C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein the heteroaryl comprises one or more heteroatoms selected from oxygen and nitrogen;

each Ring A is independently an optionally substituted 5-10 membered monocyclic or bicyclic saturated ring having 0-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein the ring comprises at least one oxygen atom; and

each L^P independently has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or salt form thereof, wherein each variable is independently as described in the present disclosure.

[001339] In some embodiments, each BA is independently an optionally substituted A, T, C, G, or U, or an optionally substituted tautomer of A, T, C, G, or U;

each Ring A is independently an optionally substituted 5-7 membered monocyclic or bicyclic saturated ring having one or more oxygen atoms; and

each L^P independently has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or salt form thereof, wherein each variable is independently as described in the present disclosure.

[001340] In some embodiments, each BA is independently an optionally substituted or protected

nucleobase selected from adenine, cytosine, guanosine, thymine, and uracil;

each Ring A is independently an optionally substituted 5-7 membered monocyclic or bicyclic saturated ring having one or more oxygen atoms; and

each L^P independently has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or salt form thereof, wherein each variable is independently as described in the present disclosure.

[001341] In some embodiments, R^{5s}–L^5– is $-CH_2OH$. In some embodiments, R^{5s}–L^5– is $-CH(R^{5s})-OH$, wherein R^{5s} is as described in the present disclosure.

[001342] In some embodiments, BA is an optionally substituted group selected from C_{3-30} cycloaliphatic, C_{6-30} aryl, C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{3-30} heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, a natural nucleobase moiety, and a modified nucleobase moiety. In some embodiments, BA is an optionally substituted group selected from C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{3-30} heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, a natural nucleobase moiety, and a modified nucleobase moiety. In some embodiments, BA is an optionally substituted group selected from C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, a natural nucleobase moiety, and a modified nucleobase moiety. In some embodiments, BA is optionally substituted C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, BA is optionally substituted natural nucleobases and tautomers thereof. In some embodiments, BA is protected natural nucleobases and tautomers thereof. Various nucleobase protecting groups for oligonucleotide synthesis are known and can be utilized in accordance with the present disclosure. In some embodiments, BA is an optionally substituted nucleobase selected from adenine, cytosine, guanosine, thymine, and uracil, and tautomers thereof. In some embodiments, BA is an optionally protected nucleobase selected from adenine, cytosine, guanosine, thymine, and uracil, and tautomers thereof.

[001343] In some embodiments, BA is optionally substituted C_{3-30} cycloaliphatic. In some embodiments, BA is optionally substituted C_{6-30} aryl. In some embodiments, BA is optionally substituted C_{3-30} heterocyclyl. In some embodiments, BA is optionally substituted C_{5-30} heteroaryl. In some embodiments, BA is an optionally substituted natural base moiety. In some embodiments, BA is an optionally substituted modified base moiety. BA is an optionally substituted group selected from C_{3-30} cycloaliphatic, C_{6-30} aryl, C_{3-30} heterocyclyl, and C_{5-30} heteroaryl. In some embodiments, BA is an optionally substituted group selected from C_{3-30} cycloaliphatic, C_{6-30} aryl, C_{3-30} heterocyclyl, C_{5-30}

heteroaryl, and a natural nucleobase moiety.

[001344] In some embodiments, BA is connected through an aromatic ring. In some embodiments, BA is connected through a heteroatom. In some embodiments, BA is connected through a ring heteroatom of an aromatic ring. In some embodiments, BA is connected through a ring nitrogen atom of an aromatic ring.

[001345] In some embodiments, BA is a natural nucleobase moiety. In some embodiments, BA is an optionally substituted natural nucleobase moiety. In some embodiments, BA is a substituted natural nucleobase moiety. In some embodiments, BA is optionally substituted, or an optionally substituted tautomer of, A, T, C, U, or G. In some embodiments, BA is natural nucleobase A, T, C, U, or G. In some embodiments, BA is an optionally substituted group selected from natural nucleobases A, T, C, U, and G.

[001346] In some embodiments, BA is an optionally substituted purine base residue. In some embodiments, BA is a protected purine base residue. In some embodiments, BA is an optionally substituted adenine residue. In some embodiments, BA is a protected adenine residue. In some embodiments, BA is an optionally substituted guanine residue. In some embodiments, BA is a protected guanine residue. In some embodiments, BA is an optionally substituted cytosine residue. In some embodiments, BA is a protected cytosine residue. In some embodiments, BA is an optionally substituted thymine residue. In some embodiments, BA is a protected thymine residue. In some embodiments, BA is an optionally substituted uracil residue. In some embodiments, BA is a protected uracil residue. In some embodiments, BA is an optionally substituted 5-methylcytosine residue. In some embodiments, BA is a protected 5-methylcytosine residue.

[001347] In some embodiments, s is 0-20. In some embodiments, s is 1-20. In some embodiments, s is 1-5. In some embodiments, s is 1. In some embodiments, s is 2. In some embodiments, s is 3. In some embodiments, s is 4. In some embodiments, s is 5. In some embodiments, s is 6. In some embodiments, s is 7. In some embodiments, s is 8. In some embodiments, s is 9. In some embodiments, s is 10. In some embodiments, s is 11. In some embodiments, s is 12. In some embodiments, s is 13. In some embodiments, s is 14. In some embodiments, s is 15. In some embodiments, s is 16. In some embodiments, s is 17. In some embodiments, s is 18. In some embodiments, s is 19. In some embodiments, s is 20.

[001348] In some embodiments, L^P is an internucleotidic linkage. In some embodiments, L^P is an internucleotidic linkage of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof. In some embodiments, L^P is a natural phosphate linkage. In some embodiments, L^P is a non-negatively charged internucleotidic linkage. In some embodiments, L^P is a neutral internucleotidic linkage. In some embodiments, L^P is a negatively-charged internucleotidic linkage. In some embodiments, L^P is a phosphorothioate internucleotidic linkage. In

some embodiments, L^P is a chirally controlled internucleotidic linkage.

[001349] In some embodiments, z is 1-1000. In some embodiments, z+1 is an oligonucleotide length as described in the present disclosure. In some embodiments, z is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 to 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 300, 400, 500, 600, 700, 800, 900 or 1000. In some embodiments, z is 10-100. In some embodiments, z is 10-50. In some embodiments, z is 15-100. In some embodiments, z is 20-50. In some embodiments, z is no less than 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19. In some embodiments, z is no less than 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14. In some embodiments, z is no more than 50, 60, 70, 80, 90, 100, 150, or 200. In some embodiments, z is 5-50, 10-50, 14-50, 14-45, 14-40, 14-35, 14-30, 14-25, 14-100, 14-150, 14-200, 14-250, 14-300, 15-50, 15-45, 15-40, 15-35, 15-30, 15-25, 15-100, 15-150, 15-200, 15-250, 15-300, 16-50, 16-45, 16-40, 16-35, 16-30, 16-25, 16-100, 16-150, 16-200, 16-250, 16-300, 17-50, 17-45, 17-40, 17-35, 17-30, 17-25, 17-100, 17-150, 17-200, 17-250, 17-300, 18-50, 18-45, 18-40, 18-35, 18-30, 18-25, 18-100, 18-150, 18-200, 18-250, 18-300, 19-50, 19-45, 19-40, 19-35, 19-30, 19-25, 19-100, 19-150, 19-200, 19-250, or 19-300. In some embodiments, z is 10. In some embodiments, z is 11. In some embodiments, z is 12. In some embodiments, z is 13. In some embodiments, z is 14. In some embodiments, z is 15. In some embodiments, z is 16. In some embodiments, z is 17. In some embodiments, z is 18. In some embodiments, z is 19. In some embodiments, z is 20. In some embodiments, z is 21. In some embodiments, z is 22. In some embodiments, z is 23. In some embodiments, z is 24. In some embodiments, z is 25. In some embodiments, z is 26. In some embodiments, z is 27. In some embodiments, z is 28. In some embodiments, z is 29. In some embodiments, z is 30. In some embodiments, z is 31. In some embodiments, z is 32. In some embodiments, z is 33. In some embodiments, z is 34.

[001350] In some embodiments, L^{3E} is −L− or −L−L−. In some embodiments, L^{3E} is −L−. In some embodiments, L^{3E} is −L−L−. In some embodiments, L^{3E} is a covalent bond. In some embodiments, L^{3E} is a linker used in oligonucleotide synthesis. In some embodiments, L^{3E} is a linker used in solid phase oligonucleotide synthesis. Various types of linkers are known and can be utilized in accordance with the present disclosure. In some embodiments, a linker is a succinate linker (−O−C(O)−CH_2−CH_2−C(O)−). In some embodiments, a linker is an oxalyl linker (−O−C(O)−C(O)−). In some embodiments, L^{3E} is a succinyl-piperidine linker (SP) linker. In some embodiments, L^{3E} is a succinyl linker. In some embodiments, L^{3E} is a Q-linker. In some embodiments, L^{3E} is −O−.

[001351] In some embodiments, R^{3E} is −R', −L−R', −OR', or a solid support. In some embodiments, R^{3E} is −R' as described in the present disclosure. In some embodiments, R^{3E} is −R as described in the present disclosure. In some embodiments, R^{3E} is hydrogen. In some embodiments, R^{3E} is −L−R'. In some embodiments, R^{3E} is −OR'. In some embodiments, R^{3E} is a support for

oligonucleotide synthesis. In some embodiments, R^{3E} is a solid support. In some embodiments, a solid support is a CPG support. In some embodiments, a solid support is a polystyrene support. In some embodiments, R^{3E} is −H. In some embodiments, $-L^3-R^{3E}$ is −H. In some embodiments, R^{3E} is −OH. In some embodiments, $-L^3-R^{3E}$ is −OH. In some embodiments, R^{3E} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{3E} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{3E} is −OR'. In some embodiments, R^{3E} is −OH. In some embodiments, R^{3E} is −OR', wherein R' is not hydrogen. In some embodiments, R^{3E} is −OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{3E} is a 3'-end cap (e.g., those used in RNAi technologies).

[001352] In some embodiments, R^{3E} is a solid support. In some embodiments, R^{3E} is a solid support for oligonucleotide synthesis. Various types of solid support are known and can be utilized in accordance with the present disclosure. In some embodiments, a solid support is HCP. In some embodiments, a solid support is CPG.

[001353] In some embodiments, R' is −R, −C(O)R, −C(O)OR, or $-S(O)_2R$, wherein R is as described in the present disclosure. In some embodiments, R' is R, wherein R is as described in the present disclosure. In some embodiments, R' is −C(O)R, wherein R is as described in the present disclosure. In some embodiments, R' is −C(O)OR, wherein R is as described in the present disclosure. In some embodiments, R' is $-S(O)_2R$, wherein R is as described in the present disclosure. In some embodiments, R' is hydrogen. In some embodiments, R' is not hydrogen. In some embodiments, R' is R, wherein R is optionally substituted C_{1-20} aliphatic as described in the present disclosure. In some embodiments, R' is R, wherein R is optionally substituted C_{1-20} heteroaliphatic as described in the present disclosure. In some embodiments, R' is R, wherein R is optionally substituted C_{6-20} aryl as described in the present disclosure. In some embodiments, R' is R, wherein R is optionally substituted C_{6-20} arylaliphatic as described in the present disclosure. In some embodiments, R' is R, wherein R is optionally substituted C_{6-20} arylheteroaliphatic as described in the present disclosure. In some embodiments, R' is R, wherein R is optionally substituted 5-20 membered heteroaryl as described in the present disclosure. In some embodiments, R' is R, wherein R is optionally substituted 3-20 membered heterocyclyl as described in the present disclosure. In some embodiments, two or more R' are R, and are optionally and independently taken together to form an optionally substituted ring as described in the present disclosure.

[001354] In some embodiments, each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-30 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur,

phosphorus and silicon, and 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, or

two R groups are optionally and independently taken together to form a covalent bond, or:

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon; or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[001355] In some embodiments, each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-30 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, or

two R groups are optionally and independently taken together to form a covalent bond, or:

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[001356] In some embodiments, each R is independently –H, or an optionally substituted group selected from C_{1-20} aliphatic, C_{1-20} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-20} aryl, C_{6-20} arylaliphatic, C_{6-20} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-20 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-20 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, or

two R groups are optionally and independently taken together to form a covalent bond, or:

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-20 membered monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-20 membered monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[001357] In some embodiments, each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-30 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[001358] In some embodiments, each R is independently –H, or an optionally substituted group selected from C_{1-20} aliphatic, C_{1-20} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-20} aryl, C_{6-20} arylaliphatic, C_{6-20} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-20 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-20 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[001359] In some embodiments, R is hydrogen. In some embodiments, R is not hydrogen. In some embodiments, R is an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, a 5-30 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and a 3-30 membered heterocyclic ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[001360] In some embodiments, R is hydrogen or an optionally substituted group selected from C_{1-20} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from

nitrogen, oxygen, and sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001361] In some embodiments, R is optionally substituted C_{1-30} aliphatic. In some embodiments, R is optionally substituted C_{1-20} aliphatic. In some embodiments, R is optionally substituted C_{1-15} aliphatic. In some embodiments, R is optionally substituted C_{1-10} aliphatic. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted hexyl, pentyl, butyl, propyl, ethyl or methyl. In some embodiments, R is optionally substituted hexyl. In some embodiments, R is optionally substituted pentyl. In some embodiments, R is optionally substituted butyl. In some embodiments, R is optionally substituted propyl. In some embodiments, R is optionally substituted ethyl. In some embodiments, R is optionally substituted methyl. In some embodiments, R is hexyl. In some embodiments, R is pentyl. In some embodiments, R is butyl. In some embodiments, R is propyl. In some embodiments, R is ethyl. In some embodiments, R is methyl. In some embodiments, R is isopropyl. In some embodiments, R is n-propyl. In some embodiments, R is tert-butyl. In some embodiments, R is sec-butyl. In some embodiments, R is n-butyl. In some embodiments, R is $-(CH_2)_2CN$.

[001362] In some embodiments, R is optionally substituted C_{3-30} cycloaliphatic. In some embodiments, R is optionally substituted C_{3-20} cycloaliphatic. In some embodiments, R is optionally substituted C_{3-10} cycloaliphatic. In some embodiments, R is optionally substituted cyclohexyl. In some embodiments, R is cyclohexyl. In some embodiments, R is optionally substituted cyclopentyl. In some embodiments, R is cyclopentyl. In some embodiments, R is optionally substituted cyclobutyl. In some embodiments, R is cyclobutyl. In some embodiments, R is optionally substituted cyclopropyl. In some embodiments, R is cyclopropyl.

[001363] In some embodiments, R is an optionally substituted 3-30 membered saturated or partially unsaturated carbocyclic ring. In some embodiments, R is an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring. In some embodiments, R is an optionally substituted 3-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, R is an optionally substituted 4-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, R is an optionally substituted 5-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, R is an optionally substituted 6-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, R is an optionally substituted 7-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, R is optionally substituted cycloheptyl. In some embodiments, R is cycloheptyl. In some embodiments, R is optionally substituted cyclohexyl. In some

embodiments, R is cyclohexyl. In some embodiments, R is optionally substituted cyclopentyl. In some embodiments, R is cyclopentyl. In some embodiments, R is optionally substituted cyclobutyl. In some embodiments, R is cyclobutyl. In some embodiments, R is optionally substituted cyclopropyl. In some embodiments, R is cyclopropyl.

[001364] In some embodiments, when R is or comprises a ring structure, e.g., cycloaliphatic, cycloheteroaliphatic, aryl, heteroaryl, etc., the ring structure can be monocyclic, bicyclic or polycyclic. In some embodiments, R is or comprises a monocyclic structure. In some embodiments, R is or comprises a bicyclic structure. In some embodiments, R is or comprises a polycyclic structure.

[001365] In some embodiments, R is optionally substituted C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is optionally substituted C_{1-20} heteroaliphatic having 1-10 heteroatoms. In some embodiments, R is optionally substituted C_{1-20} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus or silicon, optionally including one or more oxidized forms of nitrogen, sulfur, phosphorus or selenium. In some embodiments, R is optionally substituted C_{1-30} heteroaliphatic comprising 1-10 groups independently selected from , –N=, ≡N, –S–, –S(O)–, –S(O)$_2$–, –O–, =O, , , and .

[001366] In some embodiments, R is optionally substituted C_{6-30} aryl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl. In some embodiments, R is substituted phenyl.

[001367] In some embodiments, R is an optionally substituted 8-10 membered bicyclic saturated, partially unsaturated or aryl ring. In some embodiments, R is an optionally substituted 8-10 membered bicyclic saturated ring. In some embodiments, R is an optionally substituted 8-10 membered bicyclic partially unsaturated ring. In some embodiments, R is an optionally substituted 8-10 membered bicyclic aryl ring. In some embodiments, R is optionally substituted naphthyl.

[001368] In some embodiments, R is optionally substituted 5-30 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is optionally substituted 5-30 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, R is optionally substituted 5-30 membered heteroaryl ring having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is optionally substituted 5-30 membered heteroaryl ring having 1-5 heteroatoms independently selected from oxygen, nitrogen, and sulfur.

[001369] In some embodiments, R is an optionally substituted 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is a substituted 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an unsubstituted 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, sulfur, and oxygen. In some embodiments, R is a substituted 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an unsubstituted 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, sulfur, and oxygen.

[001370] In some embodiments, R is an optionally substituted 5-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur. In some embodiments, R is an optionally substituted 6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001371] In some embodiments, R is an optionally substituted 5-membered monocyclic heteroaryl ring having one heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R is selected from optionally substituted pyrrolyl, furanyl, or thienyl.

[001372] In some embodiments, R is an optionally substituted 5-membered heteroaryl ring having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 5-membered heteroaryl ring having one nitrogen atom, and an additional heteroatom selected from sulfur or oxygen. Example R groups include but are not limited to optionally substituted pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl or isoxazolyl.

[001373] In some embodiments, R is an optionally substituted 5-membered heteroaryl ring having three heteroatoms independently selected from nitrogen, oxygen, and sulfur. Example R groups include but are not limited to optionally substituted triazolyl, oxadiazolyl or thiadiazolyl.

[001374] In some embodiments, R is an optionally substituted 5-membered heteroaryl ring having four heteroatoms independently selected from nitrogen, oxygen, and sulfur. Example R groups include but are not limited to optionally substituted tetrazolyl, oxatriazolyl and thiatriazolyl.

[001375] In some embodiments, R is an optionally substituted 6-membered heteroaryl ring having 1–4 nitrogen atoms. In some embodiments, R is an optionally substituted 6-membered heteroaryl ring having 1–3 nitrogen atoms. In other embodiments, R is an optionally substituted 6-membered heteroaryl ring having 1–2 nitrogen atoms. In some embodiments, R is an optionally substituted 6-membered heteroaryl ring having four nitrogen atoms. In some embodiments, R is an optionally substituted 6-

membered heteroaryl ring having three nitrogen atoms. In some embodiments, R is an optionally substituted 6-membered heteroaryl ring having two nitrogen atoms. In certain embodiments, R is an optionally substituted 6-membered heteroaryl ring having one nitrogen atom. Example R groups include but are not limited to optionally substituted pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, or tetrazinyl.

[001376] In certain embodiments, R is an optionally substituted 8–10 membered bicyclic heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In other embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted indolyl. In some embodiments, R is an optionally substituted azabicyclo[3.2.1]octanyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted azaindolyl. In some embodiments, R is an optionally substituted benzimidazolyl. In some embodiments, R is an optionally substituted benzothiazolyl. In some embodiments, R is an optionally substituted benzoxazolyl. In some embodiments, R is an optionally substituted indazolyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001377] In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having three heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having four heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having five heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001378] In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having one heteroatom independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is

optionally substituted indolyl. In some embodiments, R is optionally substituted benzofuranyl. In some embodiments, R is optionally substituted benzo[b]thienyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted azaindolyl. In some embodiments, R is optionally substituted benzimidazolyl. In some embodiments, R is optionally substituted benzothiazolyl. In some embodiments, R is optionally substituted benzoxazolyl. In some embodiments, R is an optionally substituted indazolyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having three heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted oxazolopyridiyl, thiazolopyridinyl or imidazopyridinyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having four heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted purinyl, oxazolopyrimidinyl, thiazolopyrimidinyl, oxazolopyrazinyl, thiazolopyrazinyl, imidazopyrazinyl, oxazolopyridazinyl, thiazolopyridazinyl or imidazopyridazinyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having five heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001379] In some embodiments, R is optionally substituted 1,4-dihydropyrrolo[3,2-b]pyrrolyl, 4H-furo[3,2-b]pyrrolyl, 4H-thieno[3,2-b]pyrrolyl, furo[3,2-b]furanyl, thieno[3,2-b]furanyl, thieno[3,2-b]thienyl, 1H-pyrrolo[1,2-a]imidazolyl, pyrrolo[2,1-b]oxazolyl or pyrrolo[2,1-b]thiazolyl. In some embodiments, R is optionally substituted dihydropyrroloimidazolyl, 1H-furoimidazolyl, 1H-thienoimidazolyl, furooxazolyl, furoisoxazolyl, 4H-pyrrolooxazolyl, 4H-pyrroloisoxazolyl, thienooxazolyl, thienoisoxazolyl, 4H-pyrrolothiazolyl, furothiazolyl, thienothiazolyl, 1H-imidazoimidazolyl, imidazooxazolyl or imidazo[5,1-b]thiazolyl.

[001380] In certain embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having 1–2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In other embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted quinolinyl. In some embodiments, R is an optionally substituted isoquinolinyl. In some embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted quinazoline or a quinoxaline.

[001381] In some embodiments, R is 3-30 membered heterocyclic ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is 3-30 membered heterocyclic ring having 1-10 heteroatoms independently selected from oxygen,

nitrogen, and sulfur. In some embodiments, R is 3-30 membered heterocyclic ring having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is 3-30 membered heterocyclic ring having 1-5 heteroatoms independently selected from oxygen, nitrogen, and sulfur.

[001382] In some embodiments, R is an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is a substituted 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an unsubstituted 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 5–7 membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 5–6 membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 5-membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 6-membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 7-membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted 3-membered heterocyclic ring having one heteroatom selected from nitrogen, oxygen or sulfur. In some embodiments, R is optionally substituted 4-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted 5-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted 6-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted 7-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001383] In some embodiments, R is an optionally substituted 3-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 4-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 6-membered saturated or partially

unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 7-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001384] In some embodiments, R is an optionally substituted 4-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is nitrogen. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is oxygen. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is sulfur. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having 2 oxygen atoms. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having 2 nitrogen atoms. In some embodiments, R is an optionally substituted 4-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is nitrogen. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is oxygen. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is sulfur. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having 2 oxygen atoms. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having 2 nitrogen atoms.

[001385] In some embodiments, R is an optionally substituted 5-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5-membered partially unsaturated

heterocyclic ring having 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom. In some embodiments, R is an optionally substituted 5-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is nitrogen. In some embodiments, R is an optionally substituted 5-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is oxygen. In some embodiments, R is an optionally substituted 5-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is sulfur. In some embodiments, R is an optionally substituted 5-membered partially unsaturated heterocyclic ring having 2 oxygen atoms. In some embodiments, R is an optionally substituted 5-membered partially unsaturated heterocyclic ring having 2 nitrogen atoms.

[001386] In some embodiments, R is an optionally substituted 6-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 6-membered partially unsaturated heterocyclic ring having 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 6-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom. In some embodiments, R is an optionally substituted 6-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is nitrogen. In some embodiments, R is an optionally substituted 6-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is oxygen. In some embodiments, R is an optionally substituted 6-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is sulfur. In some embodiments, R is an optionally substituted 6-membered partially unsaturated heterocyclic ring having 2 oxygen atoms. In some embodiments, R is an optionally substituted 6-membered partially unsaturated heterocyclic ring having 2 nitrogen atoms.

[001387] In certain embodiments, R is a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is optionally substituted oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepaneyl, aziridineyl, azetidineyl, pyrrolidinyl, piperidinyl, azepanyl, thiiranyl, thietanyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, thiepanyl, dioxolanyl, oxathiolanyl, oxazolidinyl, imidazolidinyl, thiazolidinyl, dithiolanyl, dioxanyl, morpholinyl, oxathianyl, piperazinyl, thiomorpholinyl, dithianyl, dioxepanyl, oxazepanyl, oxathiepanyl, dithiepanyl, diazepanyl, dihydrofuranonyl, tetrahydropyranonyl, oxepanonyl, pyrolidinonyl, piperidinonyl, azepanonyl, dihydrothiophenonyl, tetrahydrothiopyranonyl, thiepanonyl, oxazolidinonyl, oxazinanonyl, oxazepanonyl,

dioxolanonyl, dioxanonyl, dioxepanonyl, oxathiolinonyl, oxathianonyl, oxathiepanonyl, thiazolidinonyl, thiazinanonyl, thiazepanonyl, imidazolidinonyl, tetrahydropyrimidinonyl, diazepanonyl, imidazolidinedionyl, oxazolidinedionyl, thiazolidinedionyl, dioxolanedionyl, oxathiolanedionyl, piperazinedionyl, morpholinedionyl, thiomorpholinedionyl, tetrahydropyranyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrothiophenyl, or tetrahydrothiopyranyl.

[001388] In certain embodiments, R is an optionally substituted 5–6 membered partially unsaturated monocyclic ring having 1–2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted tetrahydropyridinyl, dihydrothiazolyl, dihydrooxazolyl, or oxazolinyl group.

[001389] In some embodiments, R is an optionally substituted 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted indolinyl. In some embodiments, R is optionally substituted isoindolinyl. In some embodiments, R is optionally substituted 1, 2, 3, 4-tetrahydroquinolinyl. In some embodiments, R is optionally substituted 1, 2, 3, 4-tetrahydroisoquinolinyl. In some embodiments, R is an optionally substituted azabicyclo[3.2.1]octanyl.

[001390] In some embodiments, R is an optionally substituted 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001391] In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted 1,4-dihydropyrrolo[3,2-b]pyrrolyl, 4H-furo[3,2-b]pyrrolyl, 4H-thieno[3,2-b]pyrrolyl, furo[3,2-b]furanyl, thieno[3,2-b]furanyl, thieno[3,2-b]thienyl, 1H-pyrrolo[1,2-a]imidazolyl, pyrrolo[2,1-b]oxazolyl or pyrrolo[2,1-b]thiazolyl. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having three heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted dihydropyrroloimidazolyl, 1H-furoimidazolyl, 1H-thienoimidazolyl, furooxazolyl, furoisoxazolyl, 4H-pyrrolooxazolyl, 4H-pyrroloisoxazolyl, thienooxazolyl, thienoisoxazolyl, 4H-pyrrolothiazolyl, furothiazolyl, thienothiazolyl, 1H-imidazoimidazolyl, imidazooxazolyl or imidazo[5,1-b]thiazolyl. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having four heteroatoms independently selected from

nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having five heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001392] In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In other embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having one heteroatom independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted indolyl. In some embodiments, R is optionally substituted benzofuranyl. In some embodiments, R is optionally substituted benzo[b]thienyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted azaindolyl. In some embodiments, R is optionally substituted benzimidazolyl. In some embodiments, R is optionally substituted benzothiazolyl. In some embodiments, R is optionally substituted benzoxazolyl. In some embodiments, R is an optionally substituted indazolyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having three heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted oxazolopyridiyl, thiazolopyridinyl or imidazopyridinyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having four heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted purinyl, oxazolopyrimidinyl, thiazolopyrimidinyl, oxazolopyrazinyl, thiazolopyrazinyl, imidazopyrazinyl, oxazolopyridazinyl, thiazolopyridazinyl or imidazopyridazinyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having five heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001393] In certain embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having 1–5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having 1–2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In other embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having one heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted quinolinyl. In some embodiments, R is optionally substituted isoquinolinyl. In some embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted quinazolinyl, phthalazinyl, quinoxalinyl or naphthyridinyl. In some embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having three heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted pyridopyrimidinyl,

pyridopyridazinyl, pyridopyrazinyl, or benzotriazinyl. In some embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having four heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted pyridotriazinyl, pteridinyl, pyrazinopyrazinyl, pyrazinopyridazinyl, pyridazinopyridazinyl, pyrimidopyridazinyl or pyrimidopyrimidinyl. In some embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having five heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001394] In some embodiments, R is optionally substituted C_{6-30} arylaliphatic. In some embodiments, R is optionally substituted C_{6-20} arylaliphatic. In some embodiments, R is optionally substituted C_{6-10} arylaliphatic. In some embodiments, an aryl moiety of the arylaliphatic has 6, 10, or 14 aryl carbon atoms. In some embodiments, an aryl moiety of the arylaliphatic has 6 aryl carbon atoms. In some embodiments, an aryl moiety of the arylaliphatic has 10 aryl carbon atoms. In some embodiments, an aryl moiety of the arylaliphatic has 14 aryl carbon atoms. In some embodiments, an aryl moiety is optionally substituted phenyl.

[001395] In some embodiments, R is optionally substituted C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is optionally substituted C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, R is optionally substituted C_{6-20} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is optionally substituted C_{6-20} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, R is optionally substituted C_{6-10} arylheteroaliphatic having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is optionally substituted C_{6-10} arylheteroaliphatic having 1-5 heteroatoms independently selected from oxygen, nitrogen, and sulfur.

[001396] In some embodiments, two R groups are optionally and independently taken together to form a covalent bond. In some embodiments, –C=O is formed. In some embodiments, –C=C– is formed. In some embodiments, —C≡C— is formed.

[001397] In some embodiments, two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-20 membered monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In

some embodiments, two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-10 membered monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-6 membered monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-3 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-5 membered monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-3 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[001398] In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-20 membered monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-10 membered monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-10 membered monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-6 membered monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-3 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-5 membered monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-3 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[001399] In some embodiments, heteroatoms in R groups, or in the structures formed by two or more R groups taken together, are selected from oxygen, nitrogen, and sulfur. In some embodiments, a formed ring is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20-membered. In some embodiments, a formed ring is saturated. In some embodiments, a formed ring is partially saturated. In some embodiments, a formed ring is aromatic. In some embodiments, a formed ring comprises a saturated, partially saturated, or aromatic ring moiety. In some embodiments, a formed ring comprises 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 aromatic ring atoms. In some embodiments, a formed contains no more than 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 aromatic ring atoms. In some embodiments, aromatic ring atoms are selected from carbon, nitrogen, oxygen and sulfur.

[001400] In some embodiments, a ring formed by two or more R groups (or two or more groups selected from R and variables that can be R) taken together is a C_{3-30} cycloaliphatic, C_{6-30} aryl, 5-30 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, or 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, ring as described for R, but bivalent or multivalent.

[001401] As appreciated by those skilled in the art, embodiments of R described in the present disclosure can also independently be embodiments for variables that can be R.

[001402] In some embodiments, a is 1-100. In some embodiments, a is 1-50. In some embodiments, a is 1-40. In some embodiments, a is 1-30. In some embodiments, a is 1-20. In some embodiments, a is 1-15. In some embodiments, a is 1-10. In some embodiments, a is 1-9. In some embodiments, a is 1-8. In some embodiments, a is 1-7. In some embodiments, a is 1-6. In some embodiments, a is 1-5. In some embodiments, a is 1-4. In some embodiments, a is 1-3. In some embodiments, a is 1-2. In some embodiments, a is 1. In some embodiments, a is 2. In some embodiments, a is 3. In some embodiments, a is 4. In some embodiments, a is 5. In some embodiments, a is 6. In some embodiments, a is 7. In some embodiments, a is 8. In some embodiments, a is 9. In some embodiments, a is 10. In some embodiments, a is more than 10.

[001403] In some embodiments, b is 1-100. In some embodiments, b is 1-50. In some embodiments, b is 1-40. In some embodiments, b is 1-30. In some embodiments, b is 1-20. In some embodiments, b is 1-15. In some embodiments, b is 1-10. In some embodiments, b is 1-9. In some embodiments, b is 1-8. In some embodiments, b is 1-7. In some embodiments, b is 1-6. In some embodiments, b is 1-5. In some embodiments, b is 1-4. In some embodiments, b is 1-3. In some embodiments, b is 1-2. In some embodiments, b is 1. In some embodiments, b is 2. In some embodiments, b is 3. In some embodiments, b is 4. In some embodiments, b is 5. In some embodiments, b is 6. In some embodiments, b is 7. In some embodiments, b is 8. In some embodiments, b is 9. In some embodiments, b is 10. In some embodiments, b is 1. In some embodiments, b is 2, 3, 4, 5, 6, 7, 8,

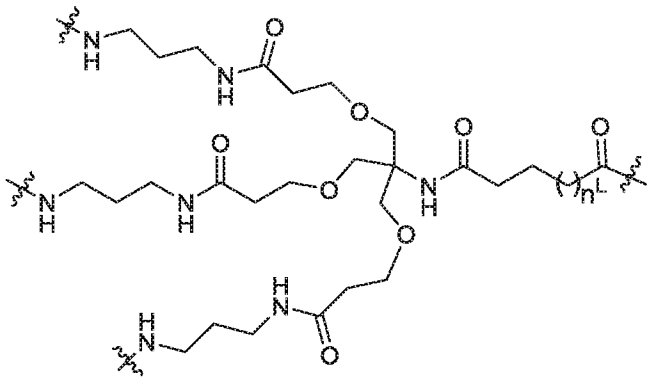
9, 10, 15, 20, or more.

[001404] In some embodiments, L^{LD} is L. In some embodiments, L^{LD} is bivalent L^{M}.

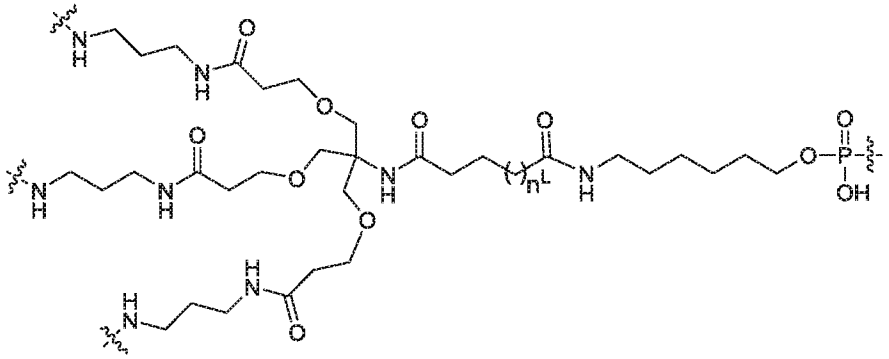
[001405] In some embodiments, L^{M} is $-L^{M1}-L^{M2}-L^{M3}-$ as described in the present disclosure. In some embodiments, L^{M} is L^{M1} as described in the present disclosure. In some embodiments, L^{M} is L^{M2} as described in the present disclosure. In some embodiments, L^{M} is L^{M3} as described in the present disclosure. In some embodiments, L^{M} is L as described in the present disclosure.

[001406] In some embodiments, L^{M1} is L. In some embodiments, L^{M2} is L. In some embodiments, L^{M3} is L. In some embodiments, L^{M1} is a covalent bond. In some embodiments, L^{M2} is a covalent bond. In some embodiments, L^{M3} is a covalent bond. In some embodiments, L^{M1} is L^{M2} as described in the present disclosure. In some embodiments, L^{M1} is L^{M3} as described in the present disclosure. In some embodiments, L^{M2} is L^{M1} as described in the present disclosure. In some embodiments, L^{M2} is L^{M3} as described in the present disclosure. In some embodiments, L^{M3} is L^{M1} as described in the present disclosure. In some embodiments, L^{M3} is L^{M2} as described in the present disclosure. In some embodiments, L^{M} is L^{M1} as described in the present disclosure. In some embodiments, L^{M} is L^{M2} as described in the present disclosure. In some embodiments, L^{M} is L^{M3} as described in the present disclosure. In some embodiments, L^{M} is L^{M1}–L^{M2}, wherein each of L^{M1} and L^{M2} is independently as described in the present disclosure. In some embodiments, L^{M} is L^{M1}–L^{M3}, wherein each of L^{M1} and L^{M3} is independently as described in the present disclosure. In some embodiments, L^{M} is L^{M2}–L^{M3}, wherein each of L^{M2} and L^{M3} is independently as described in the present disclosure. In some embodiments, L^{M} is L^{M1}–L^{M2}–L^{M3}, wherein each of L^{M1}, L^{M2} and L^{M3} is independently as described in the present disclosure.

[001407] In some embodiments, L^{M1} comprises one or more –N(R')– and one or more –C(O)–. In some embodiments, a linker or L^{M1} is or comprises

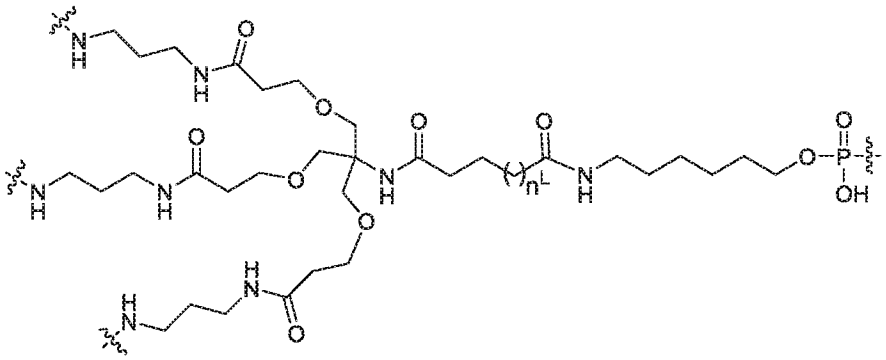


, wherein n^{L} is 1-8. In some embodiments, a



linker or $-L^{M1}-L^{M2}-L^{M3}-$ is ,

or a salt form thereof, wherein n^L is 1-8. In some embodiments, a linker or $-L^{M1}-L^{M2}-L^{M3}-$ is



,

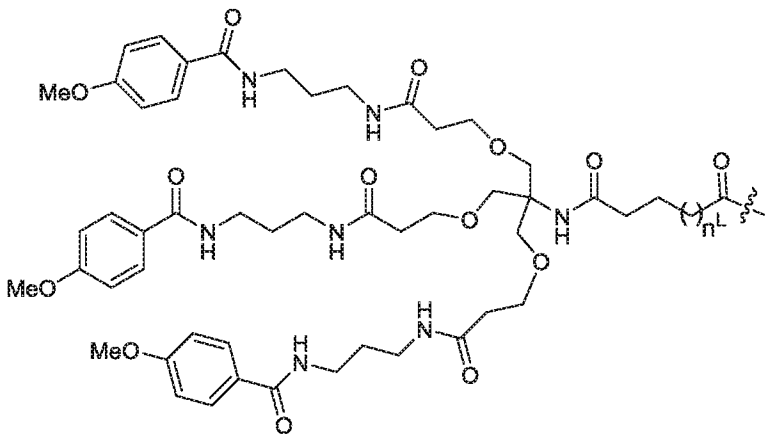
or a salt form thereof, wherein:

n^L is 1-8.

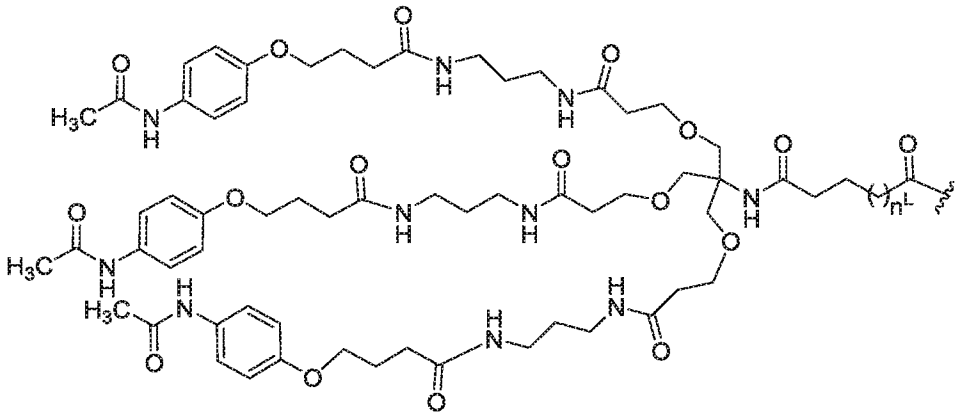
each amino group independently connects to a moiety; and

the P atom connects to the 5'-OH of the oligonucleotide.

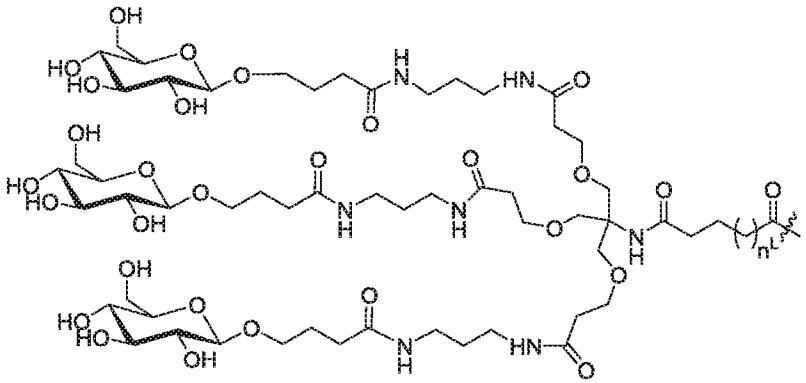
In some embodiments, the moiety and the linker, or $(R^D)b-L^{M1}-L^{M2}-L^{M3}-$, is or comprises



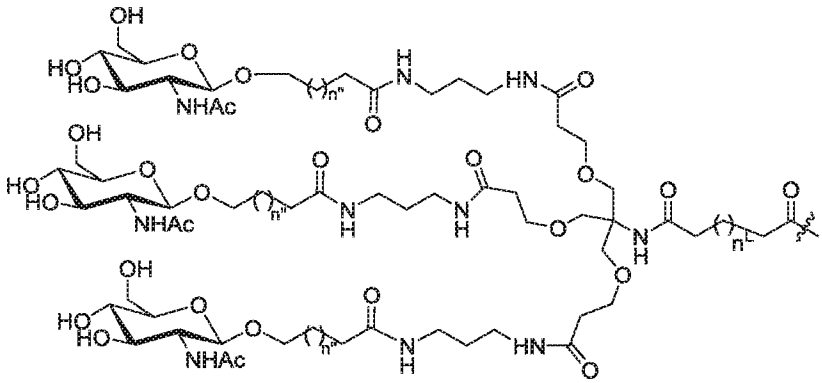
. In some embodiments, the moiety and the linker, or $(R^D)b-L^{M1}-L^{M2}-L^{M3}-$, is or comprises



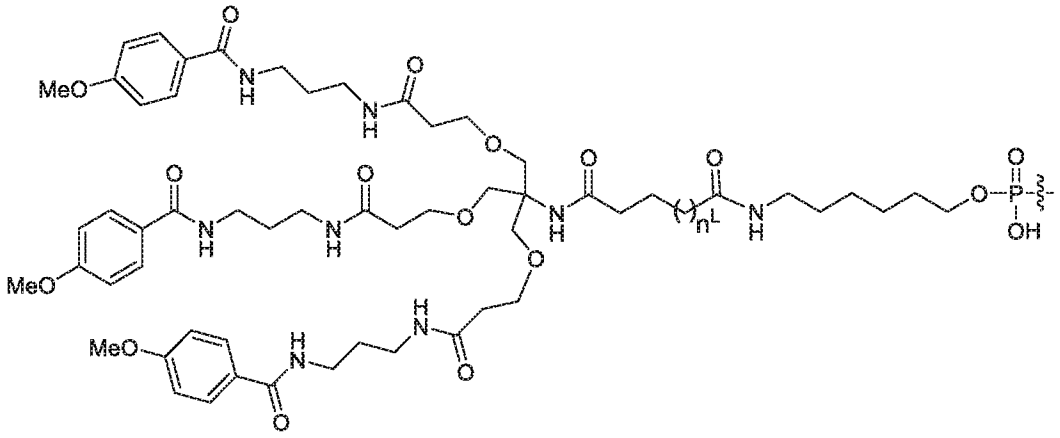
. In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



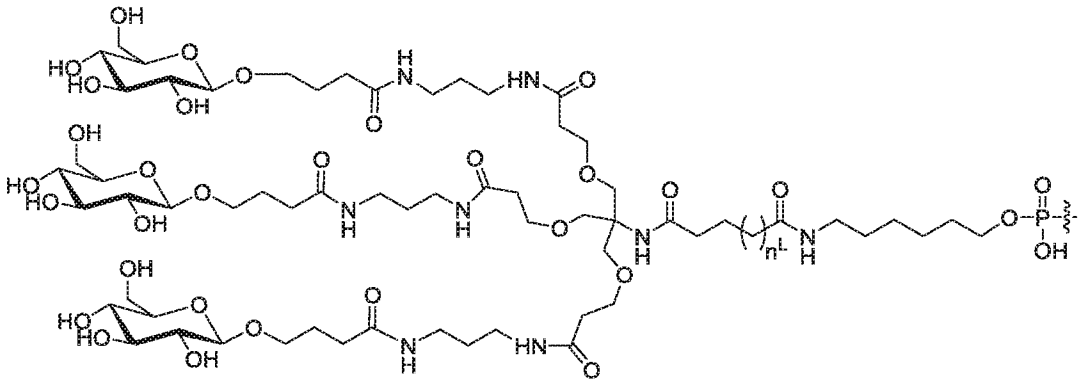
. In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



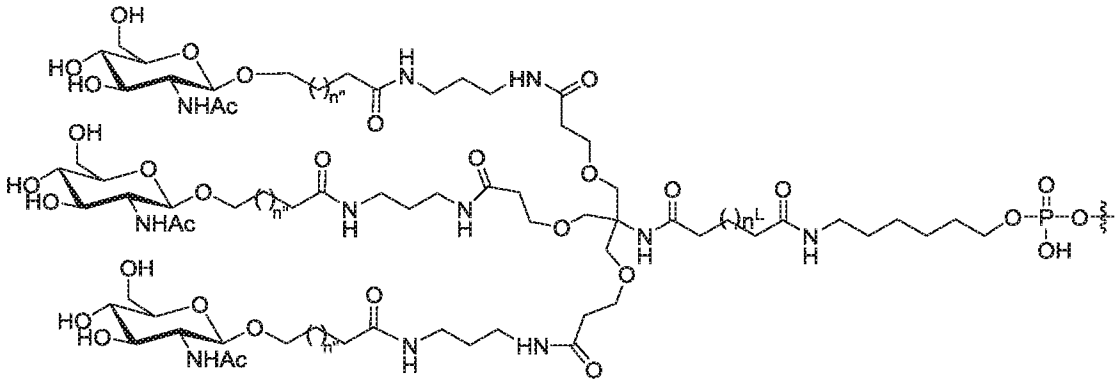
. In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



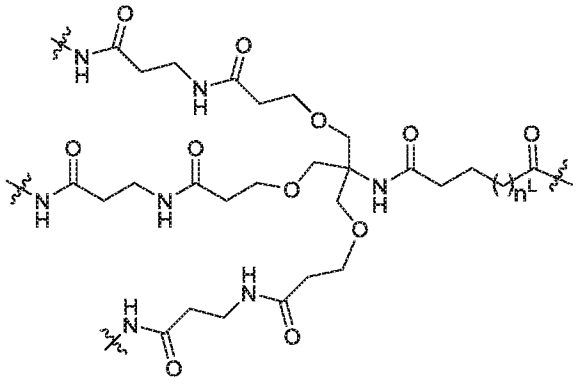
. In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



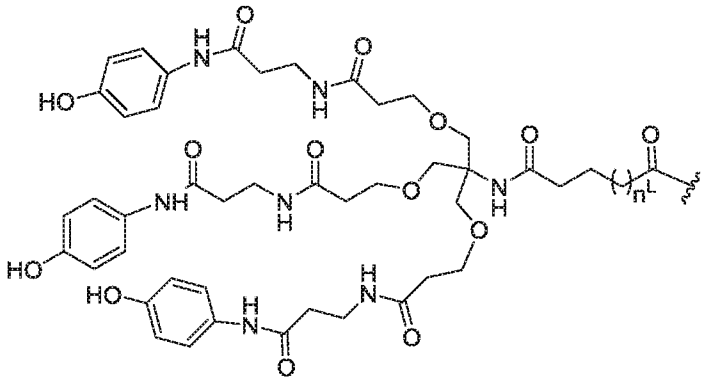
. In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



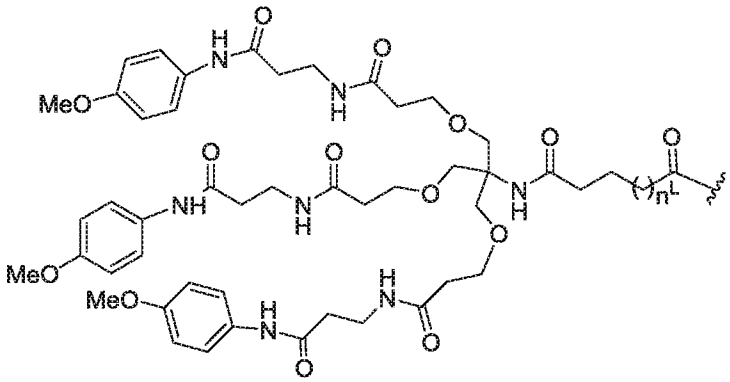
. In some



embodiments, the linker, or L^{M1}, is or comprises . In some embodiments, the moiety and linker, or $(R^D)b-L^{M1}-L^{M2}-L^{M3}-$, is or comprises:



. In some embodiments, the moiety and linker, or $(R^D)b-L^{M1}-L^{M2}-L^{M3}-$, is or comprises:



.

[001408] In some embodiments, n^L is 1-8. In some embodiments, n^L is 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments, n^L is 1. In some embodiments, n^L is 2. In some embodiments, n^L is 3. In some embodiments, n^L is 4. In some embodiments, n^L is 5. In some embodiments, n^L is 6. In some embodiments, n^L is 7. In some embodiments, n^L is 8.

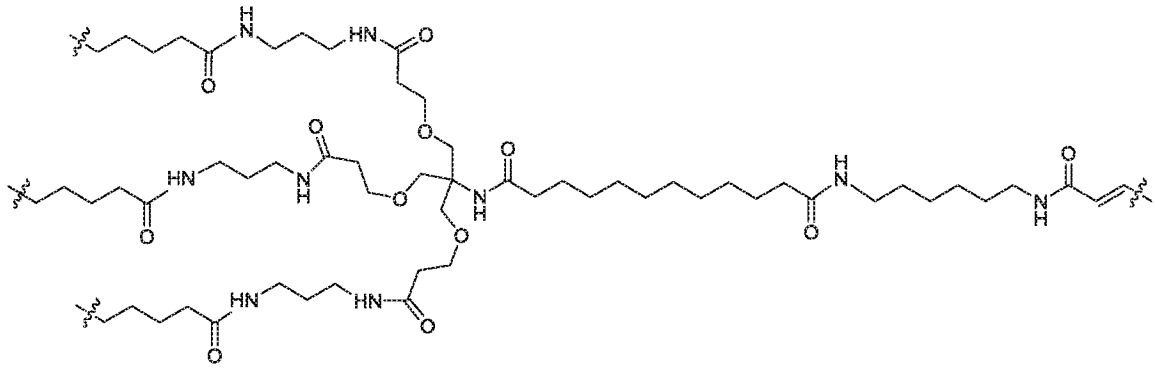
[001409] In some embodiments, at least one L^M is directly bound to a sugar unit of a provided oligonucleotide. In some embodiments, a L^M directly binds to a sugar unit incorporates a lipid moiety into an oligonucleotide. In some embodiments, a L^M directly binds to a sugar unit incorporates a carbohydrate moiety into an oligonucleotide. In some embodiments, a L^M directly binds to a sugar unit

incorporates a R^{LD} group into an oligonucleotide. In some embodiments, a L^M directly binds to a sugar unit incorporates a R^{CD} group into an oligonucleotide. In some embodiments, L^M is directed bound through 5'-OH of an oligonucleotide chain. In some embodiments, L^M is directed bound through 3'-OH of an oligonucleotide chain.

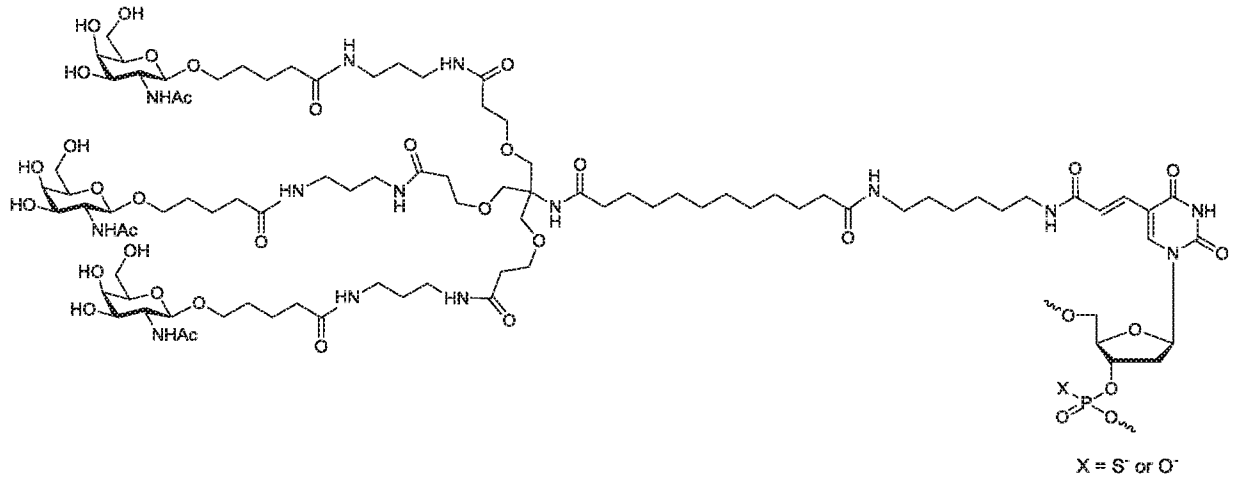
[001410] In some embodiments, at least one L^M is directly bound to an internucleotidic linkage unit of a provided oligonucleotide. In some embodiments, a L^M directly binds to an internucleotidic linkage unit incorporates a lipid moiety into an oligonucleotide. In some embodiments, a L^M directly binds to an internucleotidic linkage unit incorporates a carbohydrate moiety into an oligonucleotide. In some embodiments, a L^M directly binds to an internucleotidic linkage unit incorporates a R^{LD} group into an oligonucleotide. In some embodiments, a L^M directly binds to an internucleotidic linkage unit incorporates a R^{CD} group into an oligonucleotide.

[001411] In some embodiments, at least one L^M is directly bound to a nucleobase unit of a provided oligonucleotide. In some embodiments, a L^M directly binds to a nucleobase unit incorporates a lipid moiety into an oligonucleotide. In some embodiments, a L^M directly binds to a nucleobase unit incorporates a carbohydrate moiety into an oligonucleotide. In some embodiments, a L^M directly binds to a nucleobase unit incorporates a R^{LD} group into an oligonucleotide. In some embodiments, a L^M directly binds to a nucleobase unit incorporates a R^{CD} group into an oligonucleotide.

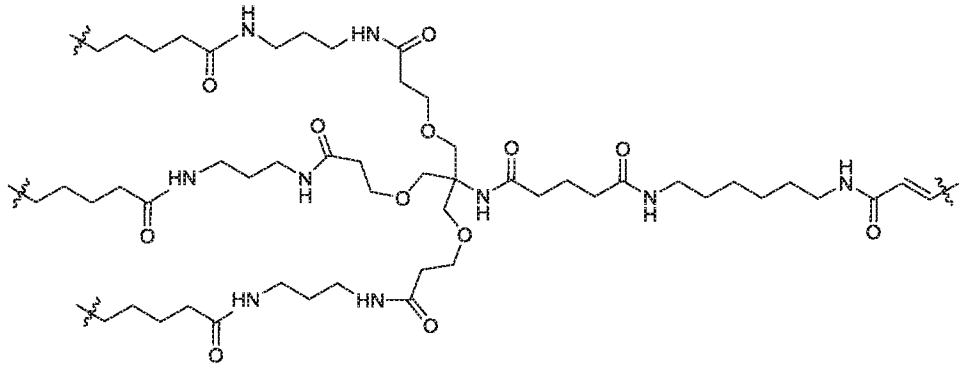
[001412] In some embodiments, L^M is bivalent. In some embodiments, L^M is multivalent. In some embodiments, L^M is



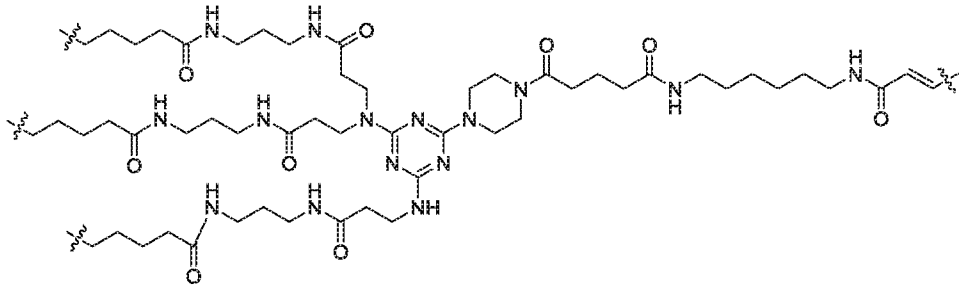
wherein L^M is directly bond to a nucleobase, for example, as in:

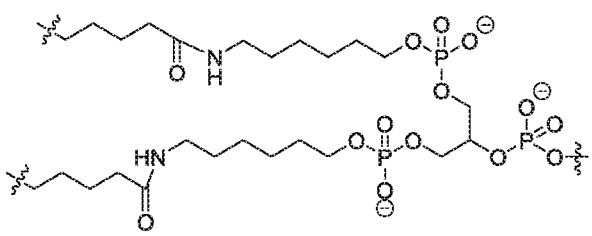


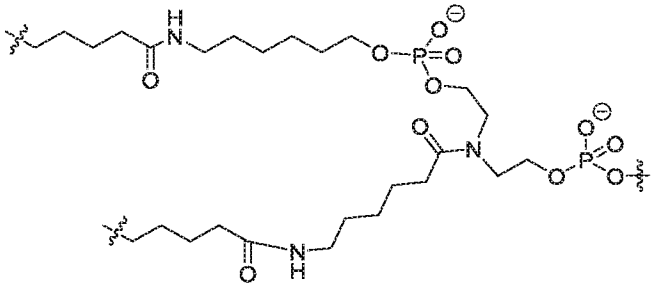
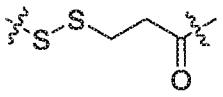
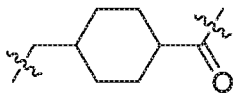
In some embodiments, L^M is



In some embodiments, L^M is



In some embodiments, L^M is  . In some embodiments,

L^M is  . In some embodiments, a linker moiety, e.g., L^M, L^{M1}, L^{M2}, L^{M3}, L, L^s, etc., is or comprises  . In some embodiments, a linker moiety, e.g., L^M, L^{M1}, L^{M2}, L^{M3}, L, L^s, etc., is or comprises  .

[001413] In some embodiments, R^D is a lipid moiety. In some embodiments, R^D is a targeting moiety. In some embodiments, R^D is a carbohydrate moiety. In some embodiments, R^D is a sulfonamide moiety. In some embodiments, R^D is an antibody or a fragment thereof. In some embodiments, R^D is R^{LD} as described in the present disclosure. In some embodiments, R^D is R^{CD} as described in the present disclosure. In some embodiments, R^D is R^{TD} as described in the present disclosure.

[001414] In some embodiments, a lipid moiety has the structure of R^{LD}. In some embodiments, R^{LD} is optionally substituted C_{10}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, or C_{25} to C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, C_{25}, C_{26}, C_{27}, C_{28}, C_{29}, C_{30}, C_{35}, C_{40}, C_{45}, C_{50}, C_{60}, C_{70}, or C_{80} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-80} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-80} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-70} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-70} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-60} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-60} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-50} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-50} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-40} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-40} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-30} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-30} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, or C_{25} to C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, C_{25}, C_{26}, C_{27}, C_{28}, C_{29}, C_{30}, C_{35}, C_{40}, C_{45}, C_{50}, C_{60}, C_{70}, or C_{80} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-80} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-80} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-70} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-70} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-60} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-60} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-50} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-50} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-40} aliphatic. In some

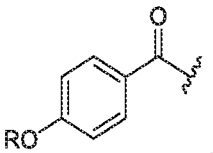
embodiments, R^{LD} is unsubstituted C_{20-40} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-30} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-30} aliphatic.

[001415] In some embodiments, R^{LD} is not hydrogen. In some embodiments, R^{LD} is a lipid moiety. In some embodiments, R^{LD} is a targeting moiety. In some embodiments, R^{LD} is a targeting moiety comprising a carbohydrate moiety. In some embodiments, R^{LD} is a GalNAc moiety.

[001416] In some embodiments, R^{TD} is R^{LD}, wherein R^{LD} is independently as described in the present disclosure. In some embodiments, R^{TD} is R^{CD}, wherein R^{CD} is independently as described in the present disclosure. In some embodiments, R^{TD} comprises a sulfonamide moiety. In some embodiments, a R^{TD} comprises a carbohydrate moiety. In some embodiments, a R^{TD} comprises a GalNAc moiety.

[001417] In some embodiments, R^{CD} is an optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus, boron and silicon, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, $-C(R')_2-$, –O–, –S–, –S–S–, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$, $-OP(O)(NR')O-$, $-OP(OR')O-$, $-OP(SR')O-$, $-OP(NR')O-$, $-OP(R')O-$, or $-OP(OR')[B(R')_3]O-$; and one or more carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, R^{CD} is an optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus, boron and silicon, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, $-C(R')_2-$, –O–, –S–, –S–S–, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$, $-OP(O)(NR')O-$, $-OP(OR')O-$, $-OP(SR')O-$, $-OP(NR')O-$, $-OP(R')O-$, or $-OP(OR')[B(R')_3]O-$; and one or more carbon atoms are independently replaced with a monosaccharide, disaccharide or polysaccharide moiety. In some embodiments, R^{CD} is an optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus, boron and silicon, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, $-C(R')_2-$, –O–, –S–, –S–S–,

–N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, $–S(O)_2–$, $–S(O)_2N(R')–$, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, $–P(OR')[B(R')_3]–$, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or $–OP(OR')[B(R')_3]O–$; and one or more carbon atoms are independently replaced with a GalNac moiety.

[001418] In some embodiments, each R^D is independently a chemical moiety as described in the present disclosure. In some embodiments, R^D is an additional chemical moiety. In some embodiments, R^D is targeting moiety. In some embodiments, R^D is or comprises a carbohydrate moiety. In some embodiments, R^D is or comprises a lipid moiety. In some embodiments, R^D is or comprises a ligand moiety for, e.g., cell receptors such as a sigma receptor, an asialoglycoprotein receptor, etc. In some embodiments, a ligand moiety is or comprises an anisamide moiety, which may be a ligand moiety for a sigma receptor. In some embodiments, a ligand moiety is or comprises a lipid. In some embodiments, a ligand moiety is or comprises a GalNAc moiety, which may be a ligand moiety for an asialoglycoprotein receptor. In some embodiments, R^D is selected from optionally substituted phenyl, 

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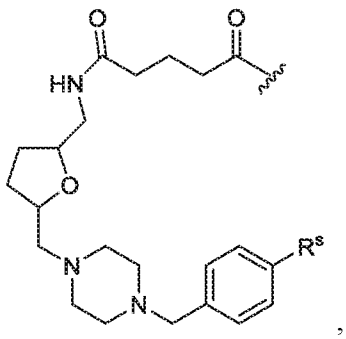

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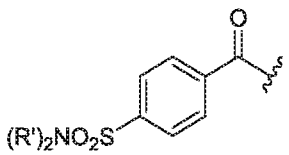

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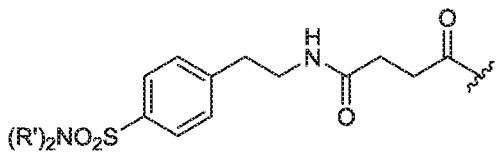

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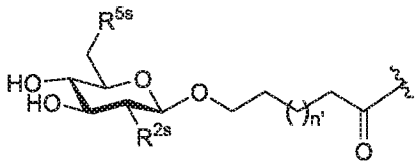

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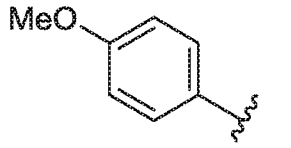
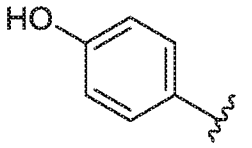
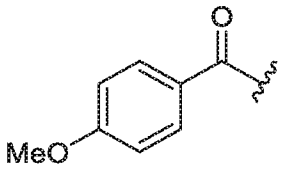
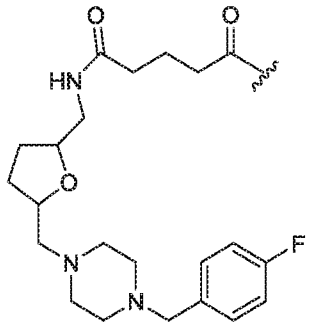
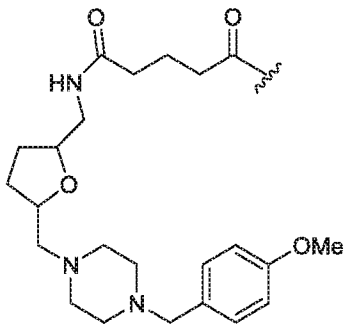
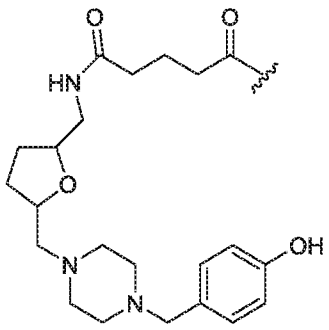
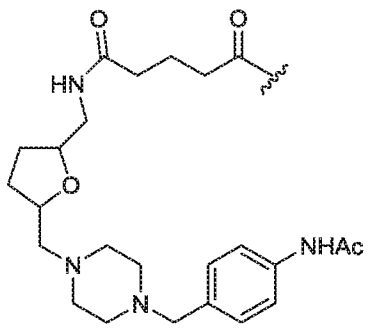
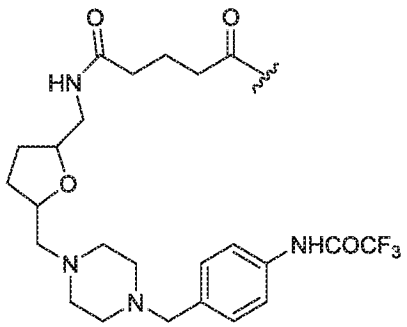
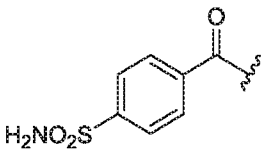
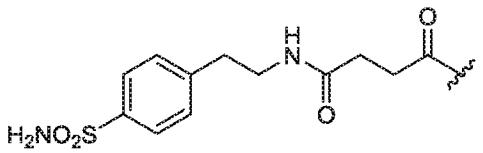
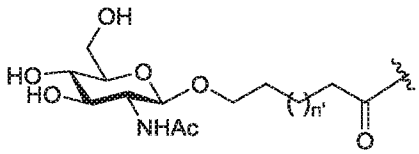
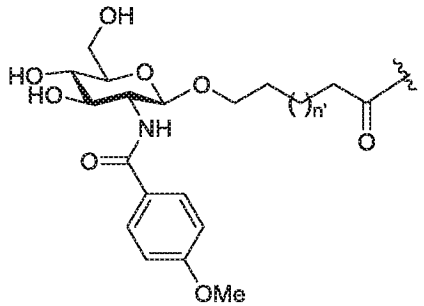
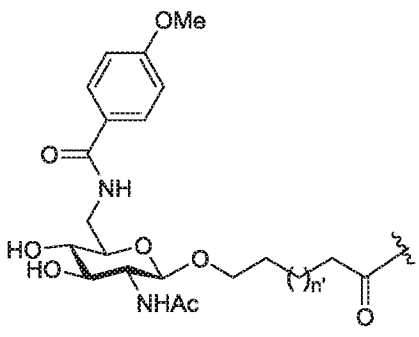
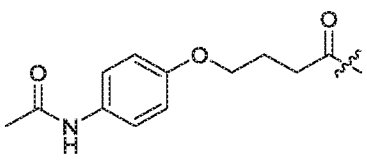
wherein n' is 0 or 1, and each other variable is independently as described in the present disclosure. In some embodiments, R^s is F. In some embodiments, R^s is OMe. In some embodiments, R^s is OH. In some embodiments, R^s is NHAc. In some embodiments, R^s is $NHCOCF_3$. In some embodiments, R' is H. In some embodiments, R is H. In some embodiments, R^{2s} is NHAc, and R^{5s} is OH. In some embodiments, R^{2s} is p-anisoyl, and R^{5s} is OH. In some embodiments, R^{2s} is NHAc and R^{5s} is p-anisoyl. In some embodiments, R^{2s} is OH, and R^{5s} is p-anisoyl. In some embodiments, R^D is selected from

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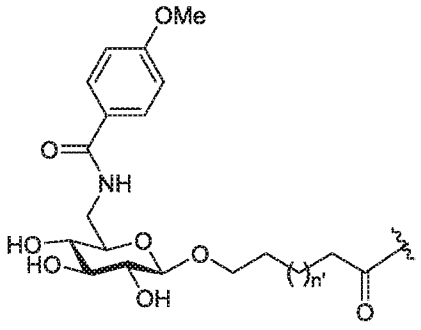
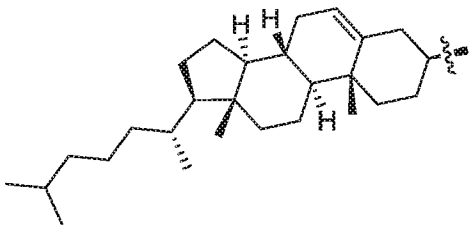
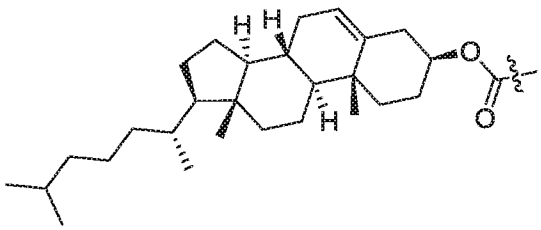


. Further embodiments of R^D includes additional chemical moiety embodiments, e.g., those described in the examples.

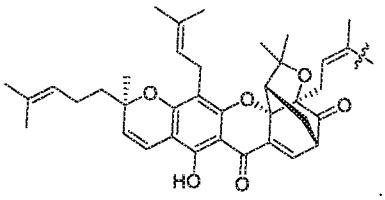
[001419] In some embodiments, R^D, R^{LD} or R^{TD} is or comprises



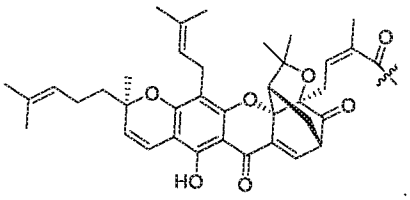
. In some embodiments, R^D, R^{LD} or R^{TD} is or comprises



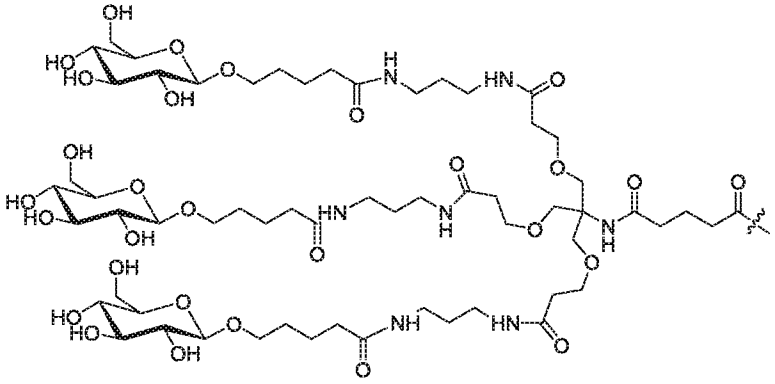
. In some embodiments, R^D, R^{LD} or R^{TD} is or comprises

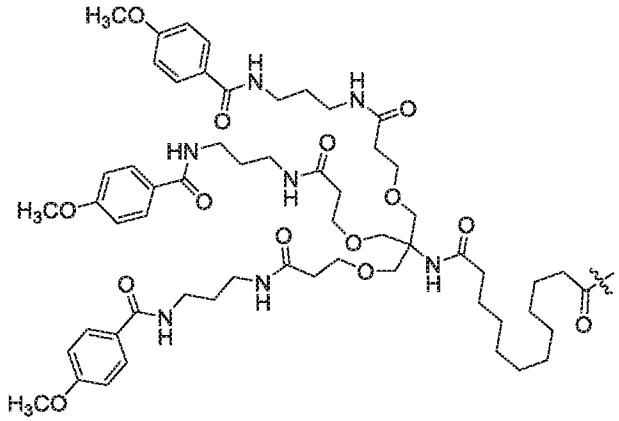
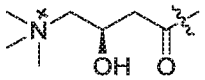
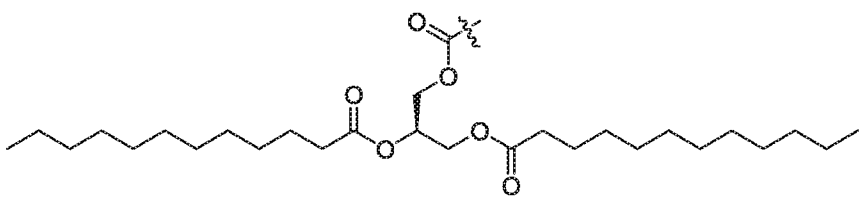


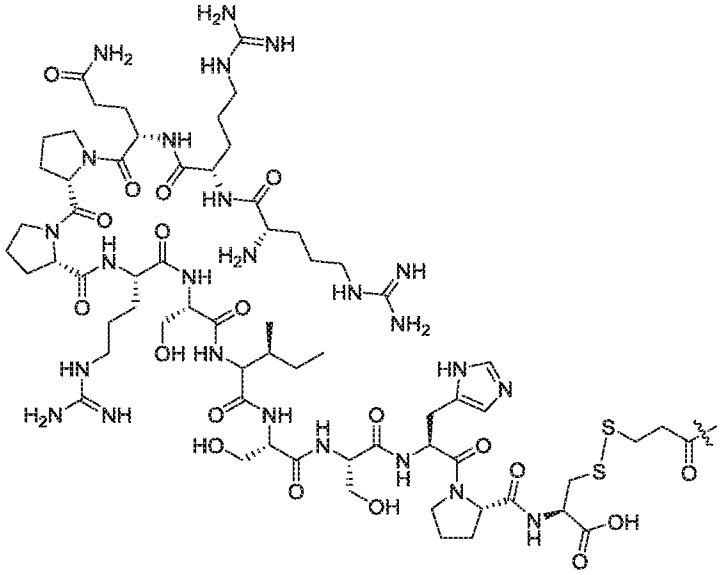
. In some embodiments, R^D, R^{LD} or R^{TD} is or comprises



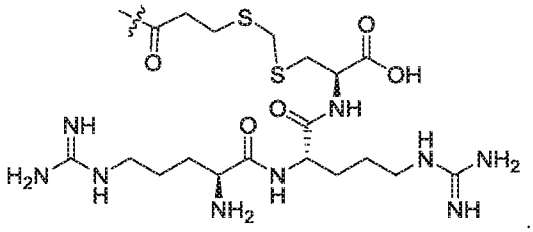
. In some embodiments, R^D, R^{LD}, R^{CD} or R^{TD} is or comprises



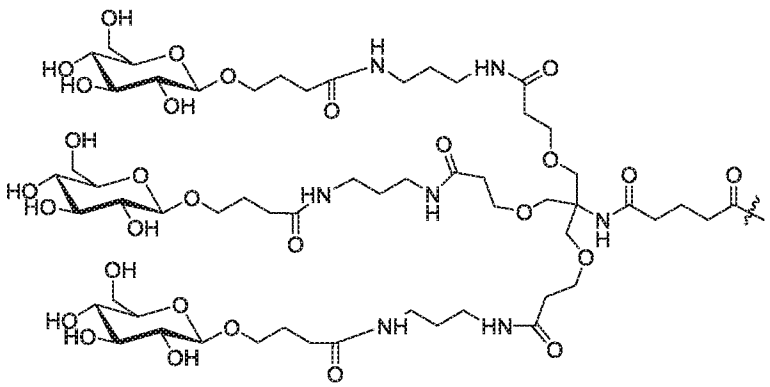
. In some embodiments, R^D, R^{LD}, or R^{TD} is or comprises  . In some embodiments, R^D, R^{LD}, R^{CD} or R^{TD} is or comprises $-N(R^1)_2$, wherein each R^1 is independently as described in the present disclosure. In some embodiments, R^D, R^{LD}, R^{CD} or R^{TD} is or comprises $-N(R^1)_3$, wherein each R^1 is independently as described in the present disclosure. In some embodiments, R^D, R^{LD}, R^{CD} or R^{TD} is or comprises one or more guanidine moieties. In some embodiments, R^D, R^{LD}, R^{CD} or R^{TD} is or comprises $-N=C(N(R^1)_2)$, wherein each R^1 is independently as described in the present disclosure. In some embodiments, R^D or R^{TD} is or comprises  . In some embodiments, R^D, R^{LD} or R^{TD} is or comprises  . In some



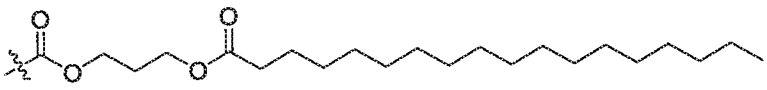
embodiments, R^D or R^{TD} is or comprises . In



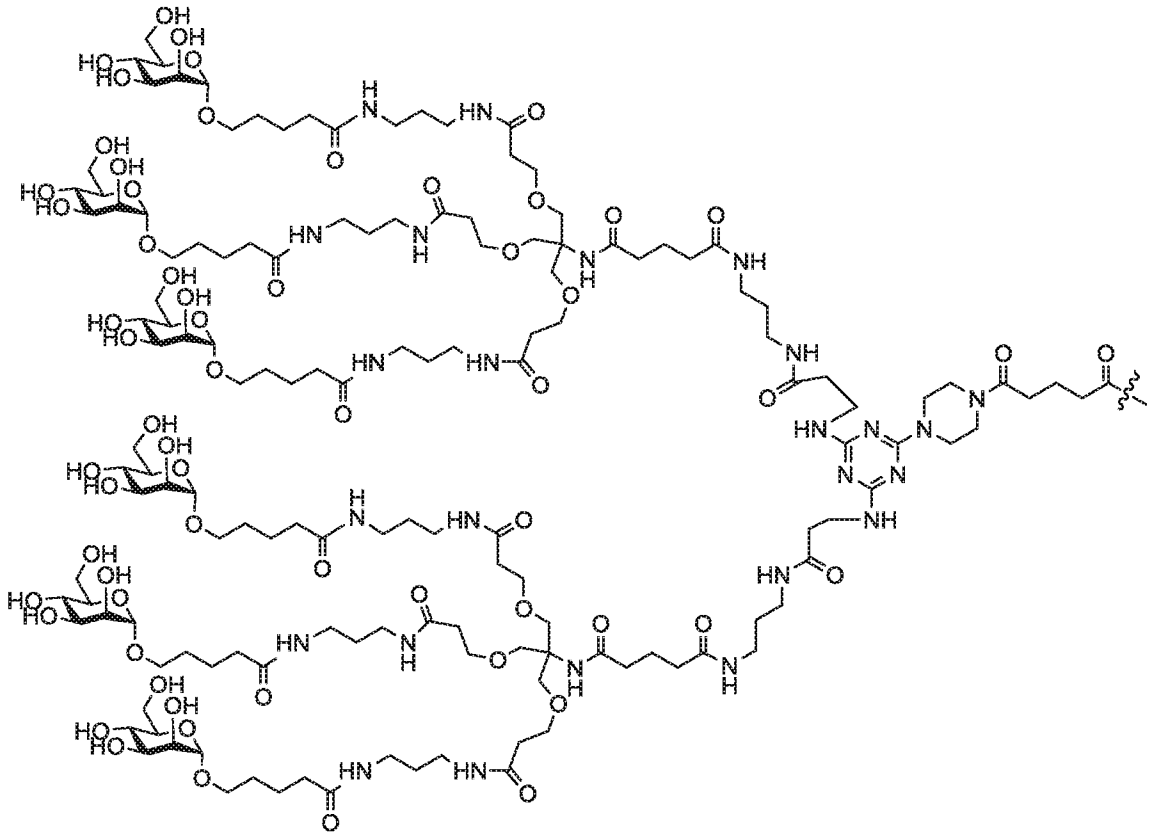
some embodiments, R^D or R^{TD} is or comprises . In some embodiments, R^D, R^{CD}, or R^{TD} is or comprises

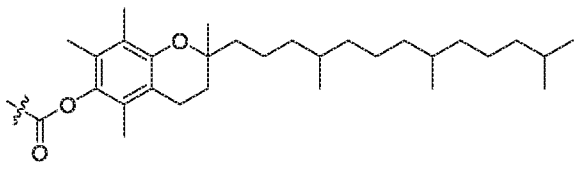
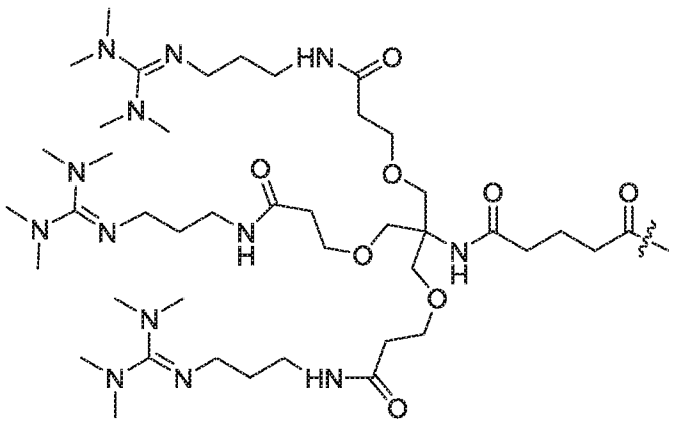


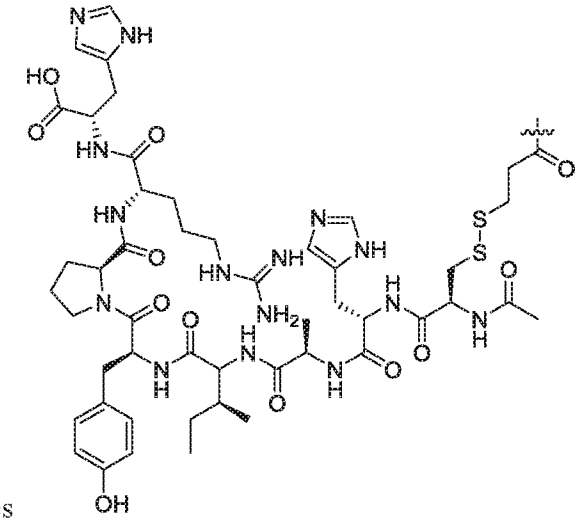
. In some embodiments, R^D, R^{LD}, or R^{TD} is or comprises



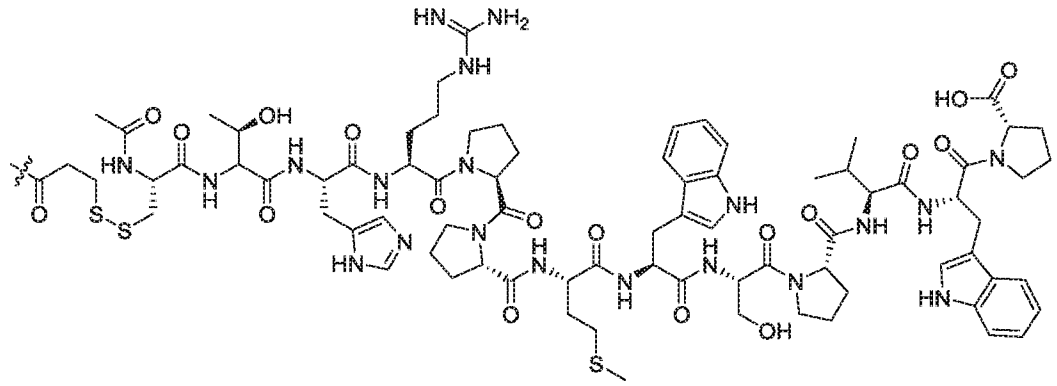
. In some embodiments, R^D, R^{CD}, or R^{TD} is or comprises



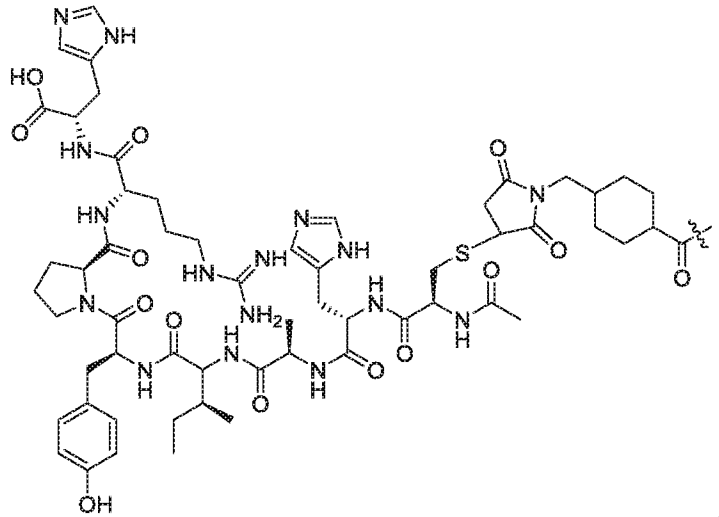
. In some embodiments, R^D, R^{LD}, or R^{TD} is or comprises  . In some embodiments, R^D or R^{TD} is or comprises  .



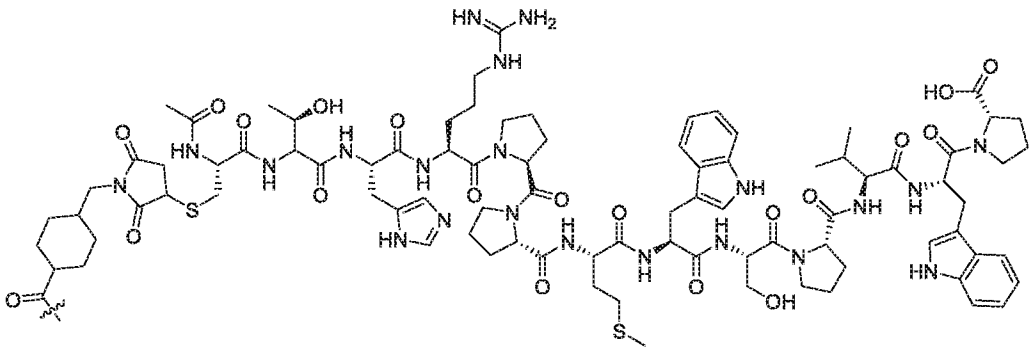
In some embodiments, R^D or R^{TD} is or comprises . In some embodiments, R^D or R^{TD} is or comprises



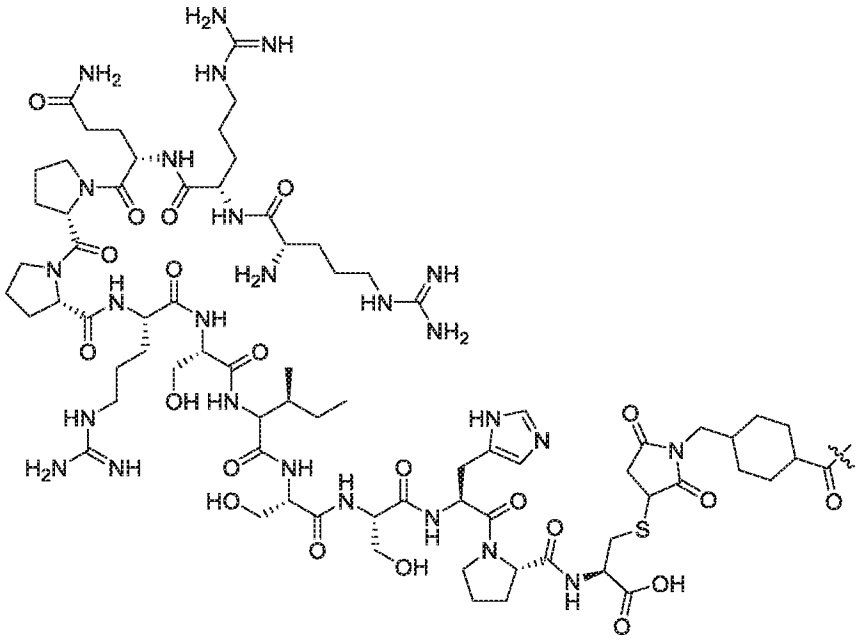
. In some embodiments, R^D or R^{TD} is or comprises



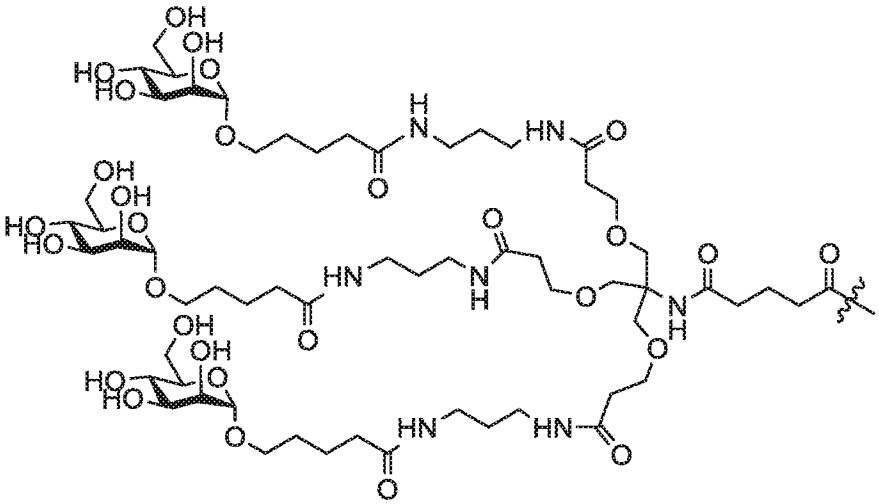
. In some embodiments, R^D or R^{TD} is or comprises



. In some embodiments, R^D or R^{TD} is or comprises



. In some embodiments, R^D, R^{CD}, or R^{TD} is or comprises



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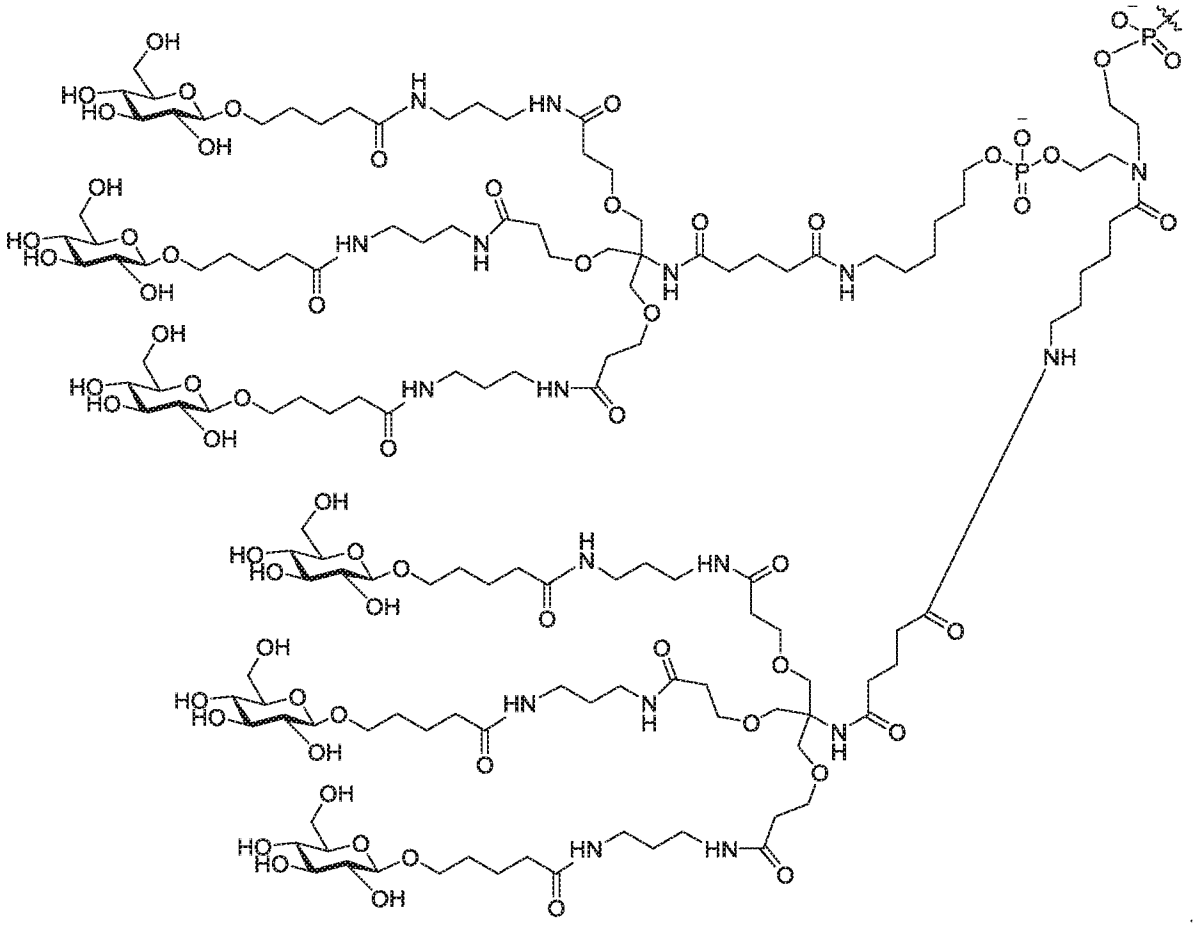
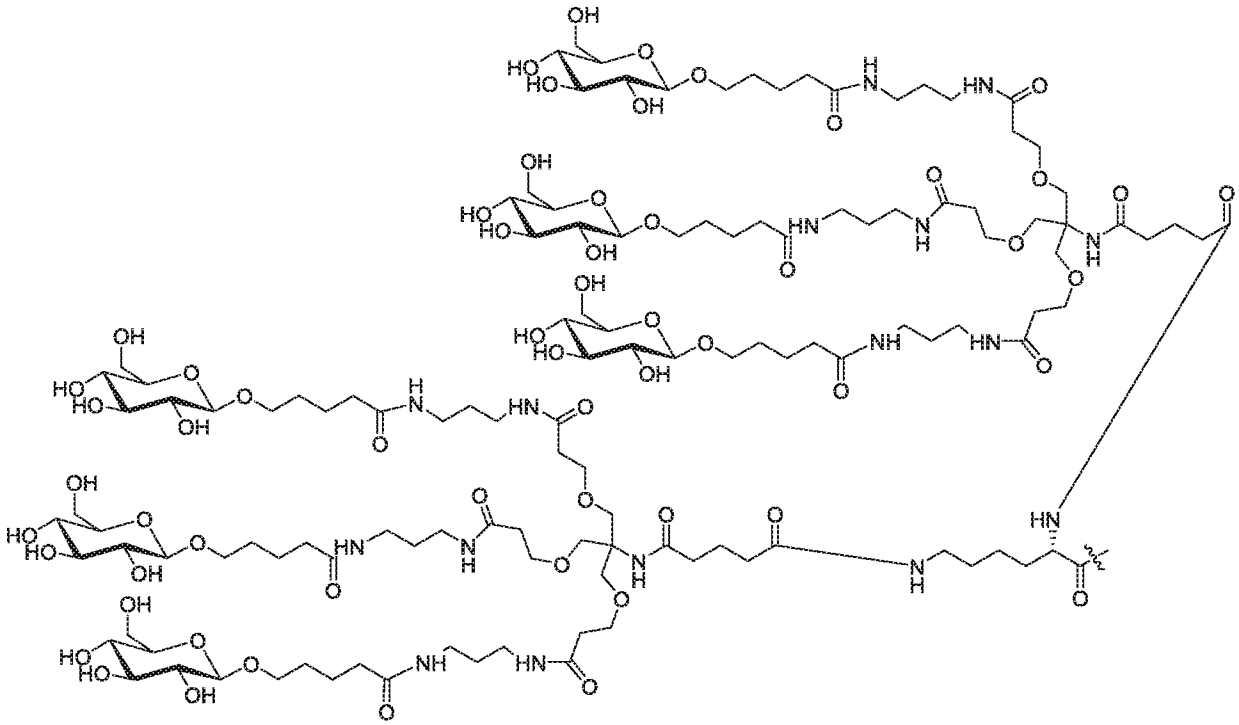
In some embodiments, R^D, R^{CD}, or R^{TD} is or comprises



. In some embodiments, R^{D}, R^{CD}, or R^{TD} is or comprises



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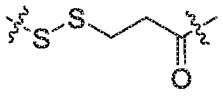
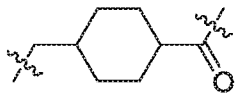
In some embodiments, R^D, R^{LD}, R^{CD} or R^{TD} comprises  . In some embodiments, R^D, R^{LD}, R^{CD} or R^{TD} comprises  .

[001420] In some embodiments, n' is 1. In some embodiments, n' is 0.

[001421] In some embodiments, n" is 1. In some embodiments, n" is 2.

In some embodiments, a moiety of the present disclosure, e.g., a heteroaliphatic, heteroaryl, heterocyclyl, a ring, etc., may contain one or more heteroatoms. In some embodiments, a heteroatom is any atom that is not carbon and is not hydrogen. In some embodiments, each heteroatom is independently selected from boron, nitrogen, oxygen, sulfur, silicon and phosphorus. In some embodiments, each heteroatom is independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus. In some embodiments, each heteroatom is independently selected from boron, nitrogen, oxygen, sulfur and phosphorus. In some embodiments, each heteroatom is independently selected from boron, nitrogen, oxygen, sulfur and silicon. In some embodiments, each heteroatom is independently selected from nitrogen, oxygen, and sulfur. In some embodiments, at least one heteroatom is nitrogen. In some embodiments, at least one heteroatom is oxygen. In some embodiments, at least one heteroatom is sulfur.

[001422] In some embodiments, y, t, n and m, e.g., in a stereochemistry pattern, each are independently 1-20 as described in the present disclosure. In some embodiments, y is 1. In some embodiments, y is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, y is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, y is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, y is 1. In some embodiments, y is 2. In some embodiments, y is 3. In some embodiments, y is 4. In some embodiments, y is 5. In some embodiments, y is 6. In some embodiments, y is 7. In some embodiments, y is 8. In some embodiments, y is 9. In some embodiments, y is 10.

[001423] In some embodiments, n is 1. In some embodiments, n is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, n is 1-10. In some embodiments, n is 1, 2, 3, 4, 5, 6, 7 or 8. In some embodiments, n is 1. In some embodiments, n is 2, 3, 4, 5, 6, 7 or 8. In some embodiments, n is 3, 4, 5, 6, 7 or 8. In some embodiments, n is 4, 5, 6, 7 or 8. In some embodiments, n is 5, 6, 7 or 8. In some embodiments, n is 6, 7 or 8. In some embodiments, n is 7 or 8. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is 5. In some embodiments, n is 6. In some embodiments, n is 7. In some embodiments, n is 8. In some embodiments, n is 9. In some embodiments, n is 10.

[001424] In some embodiments, m is 0-50. In some embodiments, m is 1-50. In some

embodiments, m is 1. In some embodiments, m is 2-50. In some embodiments, m is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, m is 2, 3, 4, 5, 6, 7 or 8. In some embodiments, m is 3, 4, 5, 6, 7 or 8. In some embodiments, m is 4, 5, 6, 7 or 8. In some embodiments, m is 5, 6, 7 or 8. In some embodiments, m is 6, 7 or 8. In some embodiments, m is 7 or 8. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4. In some embodiments, m is 5. In some embodiments, m is 6. In some embodiments, m is 7. In some embodiments, m is 8. In some embodiments, m is 9. In some embodiments, m is 10. In some embodiments, m is 11. In some embodiments, m is 12. In some embodiments, m is 13. In some embodiments, m is 14. In some embodiments, m is 15. In some embodiments, m is 16. In some embodiments, m is 17. In some embodiments, m is 18. In some embodiments, m is 19. In some embodiments, m is 20. In some embodiments, m is 21. In some embodiments, m is 22. In some embodiments, m is 23. In some embodiments, m is 24. In some embodiments, m is 25. In some embodiments, m is at least 2. In some embodiments, m is at least 3. In some embodiments, m is at least 4. In some embodiments, m is at least 5. In some embodiments, m is at least 6. In some embodiments, m is at least 7. In some embodiments, m is at least 8. In some embodiments, m is at least 9. In some embodiments, m is at least 10. In some embodiments, m is at least 11. In some embodiments, m is at least 12. In some embodiments, m is at least 13. In some embodiments, m is at least 14. In some embodiments, m is at least 15. In some embodiments, m is at least 16. In some embodiments, m is at least 17. In some embodiments, m is at least 18. In some embodiments, m is at least 19. In some embodiments, m is at least 20. In some embodiments, m is at least 21. In some embodiments, m is at least 22. In some embodiments, m is at least 23. In some embodiments, m is at least 24. In some embodiments, m is at least 25. In some embodiments, m is at least greater than 25.

[001425] In some embodiments, t is 1-20. In some embodiments, t is 1. In some embodiments, t is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, t is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, t is 1-5. In some embodiments, t is 2. In some embodiments, t is 3. In some embodiments, t is 4. In some embodiments, t is 5. In some embodiments, t is 6. In some embodiments, t is 7. In some embodiments, t is 8. In some embodiments, t is 9. In some embodiments, t is 10. In some embodiments, t is 11. In some embodiments, t is 12. In some embodiments, t is 13. In some embodiments, t is 14. In some embodiments, t is 15. In some embodiments, t is 16. In some embodiments, t is 17. In some embodiments, t is 18. In some embodiments, t is 19. In some embodiments, t is 20.

[001426] In some embodiments, each of t and m is independently at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, each of t and m is independently at least 3. In some

embodiments, each of t and m is independently at least 4. In some embodiments, each of t and m is independently at least 5. In some embodiments, each of t and m is independently at least 6. In some embodiments, each of t and m is independently at least 7. In some embodiments, each of t and m is independently at least 8. In some embodiments, each of t and m is independently at least 9. In some embodiments, each of t and m is independently at least 10.

[001427] As used in the present disclosure, in some embodiments, "one or more" is 1-200, 1-150, 1-100, 1-90, 1-80, 1-70, 1-60, 1-50, 1-40, 1-30, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some embodiments, "one or more" is one. In some embodiments, "one or more" is two. In some embodiments, "one or more" is three. In some embodiments, "one or more" is four. In some embodiments, "one or more" is five. In some embodiments, "one or more" is six. In some embodiments, "one or more" is seven. In some embodiments, "one or more" is eight. In some embodiments, "one or more" is nine. In some embodiments, "one or more" is ten. In some embodiments, "one or more" is at least one. In some embodiments, "one or more" is at least two. In some embodiments, "one or more" is at least three. In some embodiments, "one or more" is at least four. In some embodiments, "one or more" is at least five. In some embodiments, "one or more" is at least six. In some embodiments, "one or more" is at least seven. In some embodiments, "one or more" is at least eight. In some embodiments, "one or more" is at least nine. In some embodiments, "one or more" is at least ten. As used in the present disclosure, in some embodiments, "at least one" is 1-200, 1-150, 1- 100, 1-90, 1-80, 1-70, 1-60, 1-50, 1-40, 1-30, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some embodiments, "at least one" is one. In some embodiments, "at least one" is two. In some embodiments, "at least one" is three. In some embodiments, "at least one" is four. In some embodiments, "at least one" is five. In some embodiments, "at least one" is six. In some embodiments, "at least one" is seven. In some embodiments, "at least one" is eight. In some embodiments, "at least one" is nine. In some embodiments, "at least one" is ten.

[001428] In some embodiments, the present disclosure provides the following embodiments:

1. An oligonucleotide composition, comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

wherein:

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 chirally controlled internucleotidic linkages; and

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 non-negatively charged internucleotidic linkages.

2. The oligonucleotide composition of embodiment 1, wherein the oligonucleotide composition being characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

3. An oligonucleotide composition, comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

wherein:

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 chirally controlled internucleotidic linkages; and

the oligonucleotide composition being characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

4. The composition of any one of the preceding embodiments, wherein each chiral internucleotidic linkage of the oligonucleotides of the plurality is independently a chirally controlled internucleotidic linkage.

5. The composition of any one of the preceding embodiments, wherein each chiral modified internucleotidic linkage independently has a stereopurity of at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% at its chiral linkage phosphorus.

6. A composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

which composition is chirally controlled and it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same base sequence, pattern of backbone linkages and pattern of backbone phosphorus modifications, for oligonucleotides of the particular oligonucleotide type,

wherein:

the oligonucleotide composition is characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered in that level of inclusion of a nucleic acid sequence is increased relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

7. The composition of any one of the preceding embodiments, wherein the pattern of backbone chiral centers comprises at least one *S*p.

8. The composition of any one of the preceding embodiments, wherein the pattern of backbone chiral centers comprises at least one *R*p.

9. A composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages; and

3) pattern of backbone phosphorus modifications,

wherein:

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 non-negatively charged internucleotidic linkages;

the oligonucleotide composition is characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered in that level of inclusion of a nucleic acid sequence is increased relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

10. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage is independently an internucleotidic linkage at least 50% of which exists in its non-negatively charged form at pH 7.4.

11. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage is independently a neutral internucleotidic linkage, wherein at least 50% of the internucleotidic linkage exists in its neutral form at pH 7.4.

12. The composition of any one of the preceding embodiments, wherein the neutral form of each non-negatively charged internucleotidic linkage independently has a pKa no less than 8, 9, 10, 11, 12, 13, or 14.

13. The composition of any one of the preceding embodiments, wherein the neutral form of each non-negatively charged internucleotidic linkage, when the units which it connects are replaced with $-CH_3$, independently has a pKa no less than 8, 9, 10, 11, 12, 13, or 14.

14. The composition of any one of the preceding embodiments, wherein the reference condition is

absence of the composition.

15. The composition of any one of the preceding embodiments, wherein the reference condition is presence of a reference composition.

16. The composition of any one of the preceding embodiments, wherein the reference composition is an otherwise identical composition wherein the oligonucleotides of the plurality comprise no chirally controlled internucleotidic linkages.

17. The composition of any one of the preceding embodiments, wherein the reference composition is an otherwise identical composition wherein the oligonucleotides of the plurality comprise no non-negatively charged internucleotidic linkages.

18. The composition of any one of the preceding embodiments, wherein the pattern of backbone linkages comprises one or more backbone linkages selected from phosphodiester, phosphorothioate and phosphodithioate linkages.

19. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality each comprise one or more sugar modifications.

20. The composition of any one of the preceding embodiments, wherein the sugar modifications comprise one or more modifications selected from: 2'-O-methyl, 2'-MOE, 2'-F, morpholino and bicyclic sugar moieties.

21. The composition of any one of the preceding embodiments, wherein one or more sugar modifications are 2'-F modifications.

22. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality each comprise a 5'-end region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleoside units comprising a 2'-F modified sugar moiety.

23. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality each comprise a 3'-end region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleoside units comprising a 2'-F modified sugar moiety.

24. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality each comprise a middle region between the 5'-end region and the 3'-region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleotidic units comprising a phosphodiester linkage..

25. A composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages; and

3) pattern of backbone phosphorus modifications,

wherein:

oligonucleotides of the plurality comprise:

1) a 5'-end region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleoside units comprising a 2'-F modified sugar moiety;

2) a 3'-end region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleoside units comprising a 2'-F modified sugar moiety; and

3) a middle region between the 5'-end region and the 3'-region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleotidic units comprising a phosphodiester linkage.

26. The composition of embodiment 25, wherein the oligonucleotide composition is characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered in that level of inclusion of a nucleic acid sequence is increased relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

27. The composition of any one of the preceding embodiments, wherein the 5'-end region comprises 1 or more nucleoside units not comprising a 2'-F modified sugar moiety.

28. The composition of any one of the preceding embodiments, wherein the 3'-end region comprises 1 or more nucleoside units not comprising a 2'-F modified sugar moiety.

29. The composition of any one of the preceding embodiments, wherein the middle region comprises 1 or more nucleotidic units comprising no phosphodiester linkage.

30. The composition of any one of the preceding embodiments, wherein the first of the 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleoside units comprising a 2'-F modified sugar moiety and a modified internucleotidic linkage of the 5'-end is the first, second, third, fourth or fifth nucleoside unit of the oligonucleotide from the 5'-end, and the last of the 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleoside units comprising a 2'-F modified sugar moiety and a modified internucleotidic linkage of the 3'-end is the last, second last, third last, fourth last, or fifth last nucleoside unit of the oligonucleotide.

31. The composition of any one of the preceding embodiments, wherein the 5'-end region comprising 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive nucleoside units comprising a 2'-F modified sugar moiety.

32. The composition of any one of the preceding embodiments, wherein the 5'-end region comprising 5, 6, 7, 8, 9, 10 or more consecutive nucleoside units comprising a 2'-F modified sugar moiety.

33. The composition of any one of the preceding embodiments, wherein the 3'-end region comprising 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive nucleoside units comprising a 2'-F modified sugar moiety.

34. The composition of any one of the preceding embodiments, wherein the 3'-end region comprising 5, 6, 7, 8, 9, 10 or more consecutive nucleoside units comprising a 2'-F modified sugar moiety.

35. The composition of any one of the preceding embodiments, wherein each internucleotidic linkage between two nucleoside units comprising a 2'-F modified sugar moiety in the 5'-end region is

independently a modified internucleotidic linkage.

36. The composition of any one of the preceding embodiments, wherein each internucleotidic linkage between two nucleoside units comprising a 2'-F modified sugar moiety in the 3'-end region is independently a modified internucleotidic linkage.

37. The composition of embodiment 35 or 36, wherein each modified internucleotidic linkage is independently a chiral internucleotidic linkage.

38. The composition of embodiment 35 or 36, wherein each modified internucleotidic linkage is independently a chirally controlled internucleotidic linkage.

39. The composition of embodiment 35 or 36, wherein each modified internucleotidic linkage is a phosphorothioate internucleotidic linkage.

40. The composition of embodiment 35 or 36, wherein each modified internucleotidic linkage is a chirally controlled phosphorothioate internucleotidic linkage.

41. The composition of embodiment 35 or 36, wherein each modified internucleotidic linkage is a *Sp* chirally controlled phosphorothioate internucleotidic linkage.

42. The composition of any one of the preceding embodiments, wherein the middle region comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more natural phosphate linkages.

43. The composition of any one of the preceding embodiments, wherein the middle region comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more natural phosphate linkages each independently between a nucleoside unit comprising a 2'–OR^1 modified sugar moiety and a nucleoside unit comprising a 2'–F modified sugar moiety, or between two nucleoside units each independently comprising a 2'–OR^1 modified sugar moiety, wherein R^1 is optionally substituted C_{1-6} alkyl.

44. The composition of any one of the preceding embodiments, wherein the middle region comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more non-negatively charged internucleotidic linkages.

45. The composition of any one of the preceding embodiments, wherein the middle region comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more non-negatively charged internucleotidic linkages each independently between a nucleoside unit comprising a 2'–OR^1 modified sugar moiety and a nucleoside unit comprising a 2'–F modified sugar moiety, or between two nucleoside units each independently comprising a 2'–OR^1 modified sugar moiety, wherein R^1 is optionally substituted C_{1-6} alkyl.

46. The composition of embodiment 43 or 45, wherein 2'–OR^1 is 2'–OCH_3.

47. The composition of embodiment 43 or 45, wherein 2'–OR^1 is 2'–$OCH_2CH_2OCH_3$.

48. The composition of any one of the preceding embodiments, wherein the 5'-end region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 chiral modified internucleotidic linkages.

49. The composition of any one of the preceding embodiments, wherein the 5'-end region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive chiral modified internucleotidic linkages.

50. The composition of any one of the preceding embodiments, wherein each internucleotidic linkage in the 5'-end region is a chiral modified internucleotidic linkage.

51. The composition of any one of the preceding embodiments, wherein the 3'-end region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 chiral modified internucleotidic linkages.

52. The composition of any one of the preceding embodiments, wherein the 3'-end region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive chiral modified internucleotidic linkages.

53. The composition of any one of the preceding embodiments, wherein each internucleotidic linkage in the 3'-end region is a chiral modified internucleotidic linkage.

54. The composition of any one of the preceding embodiments, wherein the middle region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 chiral modified internucleotidic linkages.

55. The composition of any one of the preceding embodiments, wherein the middle region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive chiral modified internucleotidic linkages.

56. The composition of any one of embodiments 48-55, wherein each chiral modified internucleotidic linkage is independently a chirally controlled internucleotidic linkage.

57. The composition of any one of embodiments 48-55, wherein each chiral modified internucleotidic linkage is independently a chirally controlled internucleotidic linkage wherein its chirally controlled linkage phosphorus has a *Sp* configuration.

58. The composition of any one of embodiments 48-57, wherein each chiral modified internucleotidic linkage is independently a chirally controlled phosphorothioate internucleotidic linkage.

59. The composition of any one of the preceding embodiments, wherein the middle region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-negatively charged internucleotidic linkages.

60. The composition of any one of the preceding embodiments, wherein the middle region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 neutral internucleotidic linkages.

61. The composition of any one of the preceding embodiments, wherein a neutral internucleotidic linkage is a chiral internucleotidic linkage.

62. The composition of any one of the preceding embodiments, wherein a neutral internucleotidic linkage is a chirally controlled internucleotidic linkage independently of *Rp* or *Sp* at its linkage phosphorus.

63. The composition of any one of the preceding embodiments, wherein the base sequence comprises a sequence having no more than 5 mismatches from a 20 base long portion of the dystrophin gene or its complement.

64. The composition of any one of the preceding embodiments, wherein the length of the base sequence of the oligonucleotides of the plurality is no more than 50 bases.

65. The composition of any one of the preceding embodiments, wherein the pattern of backbone

chiral centers comprises at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 chirally controlled centers independently of *R*p or *S*p.

66. The composition of any one of the preceding embodiments, wherein the pattern of backbone chiral centers comprises at least 5 chirally controlled centers independently of *R*p or *S*p.

67. The composition of any one of the preceding embodiments, wherein the pattern of backbone chiral centers comprises at least 6 chirally controlled centers independently of *R*p or *S*p.

68. The composition of any one of the preceding embodiments, wherein the pattern of backbone chiral centers comprises at least 10 chirally controlled centers independently of *R*p or *S*p.

69. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the particular oligonucleotide type are capable of mediating skipping of one or more exons of the dystrophin gene.

70. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality are capable of mediating the skipping of exon 45, 51 or 53 of the dystrophin gene.

71. The composition of embodiment 70, wherein the oligonucleotides of the plurality are capable of mediating the skipping of exon 45 of the dystrophin gene.

72. The composition of embodiment 70, wherein the oligonucleotides of the plurality are capable of mediating the skipping of exon 51 of the dystrophin gene.

73. The composition of embodiment 70, wherein the oligonucleotides of the plurality are capable of mediating the skipping of exon 53 of the dystrophin gene.

74. The composition of any one of preceding embodiments, wherein the composition provides exon skipping of two or more exons.

75. The composition of embodiment 71, wherein the base sequence comprises a sequence having no more than 5 mismatches from a sequence of Table A1.

76. The composition of embodiment 71, wherein the base sequence comprises or is a sequence of Table A1.

77. The composition of embodiment 71, wherein the base sequence is a sequence of Table A1.

78. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality are oligonucleotides of an oligonucleotide selected from Table A1.

79. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more non-negatively charged internucleotidic linkages.

80. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more chirally controlled non-negatively charged internucleotidic linkages.

81. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive non-negatively charged internucleotidic linkages.

82. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive chirally controlled non-negatively charged internucleotidic linkages.

83. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure.

84. The composition of any one of the preceding embodiments, wherein a wing comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more non-negatively charged internucleotidic linkages.

85. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure, and wherein a wing comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more chirally controlled non-negatively charged internucleotidic linkages.

86. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure, and wherein a wing comprises 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive non-negatively charged internucleotidic linkages.

87. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure, and wherein a wing comprises 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive chirally controlled non-negatively charged internucleotidic linkages.

88. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise or consist of a wing-core-wing structure, and wherein only one wing comprise one or more non-negatively charged internucleotidic linkages.

89. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure, and wherein a core comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more non-negatively charged internucleotidic linkages.

90. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure, and wherein a core comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more chirally controlled non-negatively charged internucleotidic linkages.

91. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure, and wherein a core comprises 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive non-negatively charged internucleotidic linkages.

92. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure, and wherein a core comprises 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive chirally controlled non-negatively charged internucleotidic linkages.

93. The composition of any one of the preceding embodiments, wherein 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of internucleotidic linkages of a wing is independently a non-negatively charged internucleotidic linkage, a natural phosphate internucleotidic linkage or a *Rp*

chiral internucleotidic linkage.

94. The composition of any one of the preceding embodiments, wherein 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of internucleotidic linkages of a wing is independently a non-negatively charged internucleotidic linkage or a natural phosphate internucleotidic linkage.

95. The composition of any one of the preceding embodiments, wherein 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of internucleotidic linkages of a wing is independently a non-negatively charged internucleotidic linkage.

96. The composition of any one of embodiments 93-95, wherein the percentage is 50% or more.

97. The composition of any one of embodiments 93-95, wherein the percentage is 60% or more.

98. The composition of any one of embodiments 93-95, wherein the percentage is 75% or more.

99. The composition of any one of embodiments 93-95, wherein the percentage is 80% or more.

100. The composition of any one of embodiments 93-95, wherein the percentage is 90% or more.

101. The composition of any one of the preceding embodiments, wherein the oligonucleotides each comprise a non-negatively charged internucleotidic linkage and a natural phosphate internucleotidic linkage.

102. The composition of any one of the preceding embodiments, wherein the oligonucleotides each comprise a non-negatively charged internucleotidic linkage, a natural phosphate internucleotidic linkage and a *Rp* chiral internucleotidic linkage.

103. The composition of any one of the preceding embodiments, wherein a wing comprises a non-negatively charged internucleotidic linkage and a natural phosphate internucleotidic linkage.

104. The composition of any one of the preceding embodiments, wherein a wing comprises a non-negatively charged internucleotidic linkage, a natural phosphate internucleotidic linkage and a *Rp* chiral internucleotidic linkage.

105. The composition of any one of the preceding embodiments, wherein a core comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more non-negatively charged internucleotidic linkages.

106. The composition of any one of the preceding embodiments, wherein all non-negatively charged internucleotidic linkages of the same oligonucleotide have the same constitution.

107. The composition of any one of the preceding embodiments, wherein each of the non-negatively charged internucleotidic linkages independently has the structure of formula **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof.

108. The composition of any one of the preceding embodiments, wherein each of the non-negatively charged internucleotidic linkages independently has the structure of formula **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof.

109. The composition of any one of the preceding embodiments, wherein the pattern of backbone

linkages comprises at least one non-negatively charged internucleotidic linkage which is a neutral internucleotidic linkage.

110. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the particular type are structurally identical.

111. The composition of any one of the preceding claims, wherein each of the oligonucleotides comprises a chemical moiety conjugated to the oligonucleotide chain of the oligonucleotide optionally through a linker moiety, wherein the chemical moiety comprises a carbohydrate moiety, a peptide moiety, a receptor ligand moiety, or a moiety having the structure of $-N(R^1)_2$, $-N(R^1)_3$, or $-N=C(N(R^1)_2)_2$.

112. The composition of any one of the preceding claims, wherein each of the oligonucleotides comprises a chemical moiety conjugated to the oligonucleotide chain of the oligonucleotide optionally through a linker moiety, wherein the chemical moiety comprises a guanidine moiety.

113. The composition of any one of the preceding claims, wherein each of the oligonucleotides comprises a chemical moiety conjugated to the oligonucleotide chain of the oligonucleotide optionally through a linker moiety, wherein the chemical moiety comprises $-N=C(N(CH_3)_2)_2$.

114. The composition of any one of the preceding embodiments, wherein at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the oligonucleotides in the composition that have the same constitution as oligonucleotides of the particular oligonucleotide type are oligonucleotides of the particular oligonucleotide type.

115. The composition of any one of the preceding embodiments, wherein at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the oligonucleotides in the composition that have the base sequence, pattern of backbone linkages, and pattern of backbone phosphorus modifications of the particular oligonucleotide type are oligonucleotides of the particular oligonucleotide type.

116. The composition of any one of the preceding embodiments, wherein at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the oligonucleotides in the composition that have the base sequence of the particular oligonucleotide type are oligonucleotides of the particular oligonucleotide type.

117. The composition of any one of embodiments 114-116, wherein the percentage is at least 10%.

118. The composition of any one of embodiments 114-116, wherein the percentage is at least 50%.

119. The composition of any one of embodiments 114-116, wherein the percentage is at least 80%.

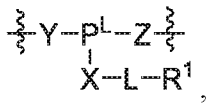
120. The composition of any one of embodiments 114-116, wherein the percentage is at least 90%.

121. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage is a phosphoramidate linkage.

122. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage comprises a guanidine moiety.

123. The composition of any one of the preceding embodiments, wherein a non-negatively charged

internucleotidic linkage has the structure of formula I:



I

or a salt form thereof, wherein:

P^L is P(=W), P, or P→$B(R')_3$;

W is O, N(–L–R^5), S or Se;

each of R^1 and R^5 is independently –H, –L–R', halogen, –CN, –NO_2, –L–$Si(R')_3$, –OR', –SR', or –$N(R')_2$;

each of X, Y and Z is independently –O–, –S–, –N(–L–R^5)–, or L;

each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, –C≡C–, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, –$C(R')_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –$S(O)_2$–, –$S(O)_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[$B(R')_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[$B(R')_3$]O–, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L;

each –Cy– is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Cy^L is independently an optionally substituted trivalent or tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each R' is independently –R, –C(O)R, –C(O)OR, or –$S(O)_2$R;

each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

two R groups are optionally and independently taken together to form a covalent bond, or

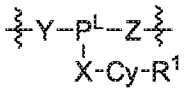
two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in

addition to the atom, 0-10 heteroatoms, or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

124. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula I or a salt form thereof.

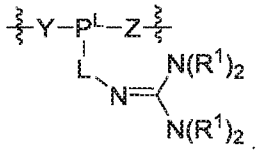
125. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula I-n-1 or a salt form thereof:



I-n-1

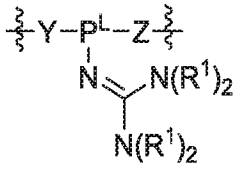
126. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula I-n-1 or a salt form thereof.

127. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula I-n-2 or a salt form thereof:



I-n-2

128. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula I-n-3 or a salt form thereof:



I-n-3

129. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula I-n-3 or a salt form thereof.

130. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula I-n-3 or a salt form thereof, wherein one R' from one $-N(R')_2$ and one R' from the other $-N(R')_2$ are taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

131. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **I-n-3** or a salt form thereof, wherein one R' from one $-N(R')_2$ and one R' from the other $-N(R')_2$ are taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

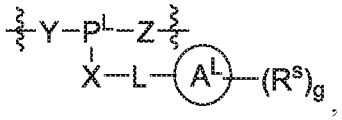
132. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **I-n-3** or a salt form thereof, wherein one R' from one $-N(R')_2$ and one R' from the other $-N(R')_2$ are taken together with their intervening atoms to form an optionally substituted 5- membered monocyclic ring having no more than two nitrogen atoms.

133. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **I-n-3** or a salt form thereof, wherein one R' from one $-N(R')_2$ and one R' from the other $-N(R')_2$ are taken together with their intervening atoms to form an optionally substituted 5- membered monocyclic ring having no more than two nitrogen atoms.

134. The composition of any one of embodiments 128-131, wherein the ring formed is a saturated ring.

135. The composition of any one of embodiments 128-131, wherein the ring formed is a partially unsaturated ring.

136. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II**:



II

or a salt form thereof, wherein:

P^L is P(=W), P, or P→B(R')$_3$;

W is O, N(–L–R^5), S or Se;

each of X, Y and Z is independently –O–, –S–, –N(–L–R^5)–, or L;

R^5 is –H, –L–R', halogen, –CN, $-NO_2$, –L–Si(R')$_3$, –OR', –SR', or $-N(R')_2$;

Ring A^L is an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms;

each R^s is independently –H, halogen, –CN, $-N_3$, –NO, $-NO_2$, –L–R', –L–Si(R)$_3$, –L–OR', –L–SR', –L–N(R')$_2$, –O–L–R', –O–L–Si(R)$_3$, –O–L–OR', –O–L–SR', or –O–L–N(R')$_2$;

g is 0-20;

each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched

group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L;

each –Cy– is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Cy^L is independently an optionally substituted trivalent or tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each R' is independently –R, –C(O)R, –C(O)OR, or –S(O)$_2$R;

each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

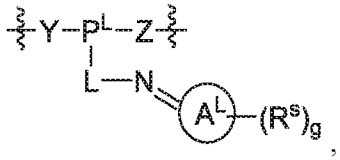
two R groups are optionally and independently taken together to form a covalent bond, or,

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms, or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

137. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **II**, or a salt form thereof.

138. The composition any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II-a-1**:

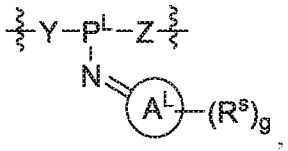


II-a-1

or a salt form thereof.

139. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **II-a-1**, or a salt form thereof.

140. The composition any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II-a-2**:

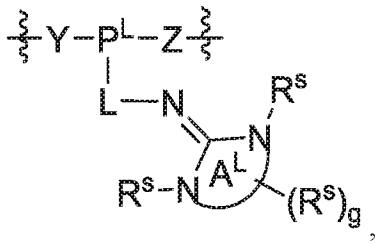


II-a-2

or a salt form thereof.

141. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **II-a-2**, or a salt form thereof.

142. The composition any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II-b-1**:

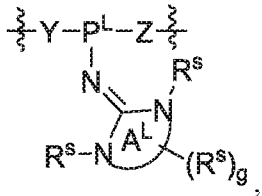


II-b-1

or a salt form thereof.

143. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **II-b-1**, or a salt form thereof.

144. The composition any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II-b-2**:

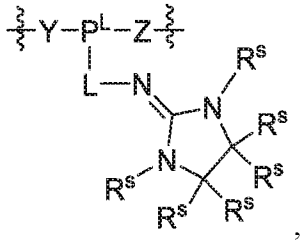


II-b-2

or a salt form thereof.

145. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **II-b-2**, or a salt form thereof.

146. The composition any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II-c-1**:

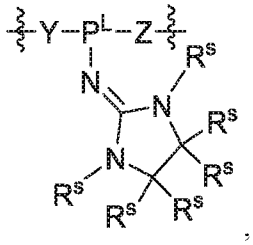


II-c-1

or a salt form thereof.

147. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **II-c-1**, or a salt form thereof.

148. The composition any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II-c-2**:

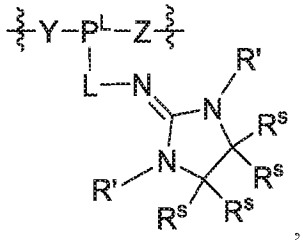


II-c-2

or a salt form thereof.

149. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **II-c-2**, or a salt form thereof.

150. The composition any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II-d-1**:

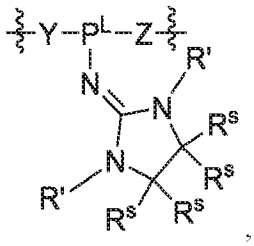


II-d-1

or a salt form thereof.

151. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **II-d-1**, or a salt form thereof.

152. The composition any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II-d-2**:



II-d-2

or a salt form thereof.

153. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **II-d-2**, or a salt form thereof.

154. The composition of any one of embodiments 136-153, wherein each non-negatively charged internucleotidic linkage has the same structure.

155. The composition of any one of the preceding embodiments, wherein, if applicable, each internucleotidic linkage in the oligonucleotides of the plurality that is not a non-negatively charged internucleotidic linkage independently has the structure of formula **I**.

156. The composition of any one of the preceding embodiments, wherein each internucleotidic linkage in the oligonucleotides of the plurality independently has the structure of formula **I**.

157. The composition of any one of the preceding embodiments, wherein one or more P^L is P(=W).

158. The composition of any one of the preceding embodiments, wherein each P^L is independently P(=W).

159. The composition of any one of the preceding embodiments, wherein one or more W is O.

160. The composition of any one of the preceding embodiments, wherein each W is O.

161. The composition of any one of the preceding embodiments, wherein one or more Y is O.

162. The composition of any one of the preceding embodiments, wherein each Y is O.

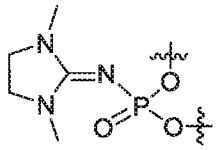
163. The composition of any one of the preceding embodiments, wherein one or more Z is O.

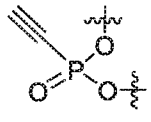
164. The composition of any one of the preceding embodiments, wherein each Z is O.

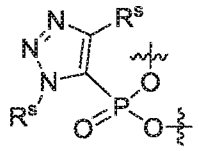
165. The composition of any one of the preceding embodiments, wherein one or more X is O.

166. The composition of any one of the preceding embodiments, wherein one or more X is S.

167. The composition of any one of the preceding embodiments, wherein a non-negatively charged

internucleotidic linkage has the structure of  .

168. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of  .

169. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of  .

170. The composition of any one of the preceding embodiments, wherein for each internucleotidic linkage of formula I or a salt fore thereof that is not a non-negatively charged internucleotidic linkage, X is independently O or S, and $-L^s-R^5$ is –H (natural phosphate linkage or phosphorothioate linkage, respectively).

171. The composition of any one of the preceding embodiments, wherein each phosphorothioate linkage, if any, in the oligonucleotides of the plurality is independently a chirally controlled internucleotidic linkage.

172. The composition of any one of the preceding embodiments, wherein at least one non-negatively charged internucleotidic linkage is a chirally controlled oligonucleotide composition.

173. The composition of any one of the preceding embodiments, wherein at least one non-negatively charged internucleotidic linkage is a chirally controlled oligonucleotide composition.

174. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality comprise a targeting moiety wherein the targeting moiety is independently connected to an oligonucleotide backbone through a linker.

175. The composition of embodiment 174, wherein the targeting moiety is a carbohydrate moiety.

176. The composition of embodiment 174 or 175, wherein the targeting moiety comprises or is a GalNAc moiety.

177. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality comprise a lipid moiety wherein the lipid moiety is independently connected to an oligonucleotide backbone through a linker.

178. The composition of any one of the preceding embodiments, wherein the oligonucleotide of the plurality comprise a pattern of backbone chiral centers of (Np/Op)t[(Rp)n(Sp)m]y,

(Np/Op)t[(Op)n(Sp)m]y, (Np/Op)t[(Op/Rp)n(Sp)m]y, (Sp)t[(Rp)n(Sp)m]y, (Sp)t[(Op)n(Sp)m]y, (Sp)t[(Op/Rp)n(Sp)m]y, [(Rp)n(Sp)m]y, [(Op)n(Sp)m]y, [(Op/Rp)n(Sp)m]y, (Rp)t(Np)n(Rp)m, (Rp)t(Sp)n(Rp)m, (Rp)t[(Np/Op)n]y(Rp)m, (Rp)t[(Sp/Np)n]y(Rp)m, (Rp)t[(Sp/Op)n]y(Rp)m, (Np/Op)t(Np)n(Np/Op)m, (Np/Op)t(Sp)n(Np/Op)m, (Np/Op)t[(Np/Op)n]y(Np/Op)m, (Np/Op)t[(Sp/Op)n]y(Np/Op)m, (Np/Op)t[(Sp/Op)n]y(Np/Op)m, (Rp/Op)t(Np)n(Rp/Op)m, (Rp/Op)t(Sp)n(Rp/Op)m, (Rp/Op)t[(Np/Op)n]y(Rp/Op)m, (Rp/Op)t[(Sp/Op)n]y(Rp/Op)m, or (Rp/Op)t[(Sp/Op)n]y(Rp/Op)m.

179. The composition of any one of the preceding embodiments, wherein the oligonucleotide of the plurality comprise a pattern of backbone chiral centers of (Sp)t[(Rp)n(Sp)m]y.

180. The composition of any one of the preceding embodiments, wherein y is 1.

181. The composition of any one of the preceding embodiments, wherein n is 1.

182. The composition of any one of the preceding embodiments, wherein t is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

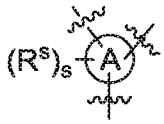
183. The composition of any one of the preceding embodiments, wherein t is 4, 5, 6, 7, 8, 9 or 10.

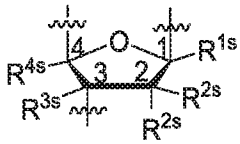
184. The composition of any one of the preceding embodiments, wherein m is 2, 3, 4, 5, 6, 7, 8, 9 or 10.

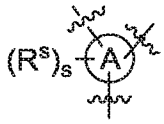
185. The composition of any one of the preceding embodiments, wherein m is 4, 5, 6, 7, 8, 9 or 10.

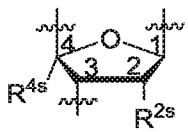
186. The composition of any one of the preceding embodiments, wherein oligonucleotides of the plurality has the structure of formula **O-I** or a salt thereof.

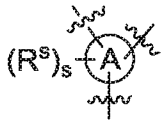
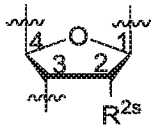
187. The composition of any one of the preceding embodiments, wherein L^P in formula O-I independently has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof.

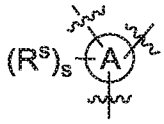
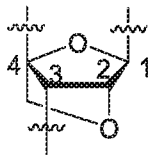
188. The composition of any one of the preceding embodiments, wherein a  is



189. The composition of any one of the preceding embodiments, wherein a  is



190. The composition of any one of the preceding embodiments, wherein a  is  .

191. The composition of any one of the preceding embodiments, wherein a  is optionally substituted  .

192. The composition of any one of the preceding embodiments, wherein L^S in formula O-I between L^P and Ring A is $-C(R^{5s})_2-$.

193. The composition of any one of the preceding embodiments, wherein L^S in formula O-I between L^P and Ring A is $-CH(R^{5s})-$.

194. The composition of any one of the preceding embodiments, wherein $-L^{3E}-R^{3E}$ in formula O-I IS $-OH$.

195. The composition of any one of the preceding embodiments, wherein oligonucleotides of the plurality has the structure of $A^c-[-L^{LD}-(R^{LD})_a]_b$, $A^c-[-L^M-(R^D)_a]_b$, $[(A^c)_a-L^M]_b-R^D$, $(A^c)_a-L^M-(A^c)_b$, or $(A^c)_a-L^M-(R^D)_b$, or a salt thereof.

196. The composition of embodiment 195, wherein $H-A^c$, $[H]_a-A^c$ or $[H]_b-A^c$ is an oligonucleotide of any one of embodiments 186-194.

197. The composition of any one of the preceding embodiments, wherein oligonucleotides of the plurality exist as salts, wherein one or more non-neutral internucleotidic linkages at the condition of the composition independently exist as a salt form.

198. The composition of any one of the preceding embodiments, wherein oligonucleotides of the plurality exist as salts, wherein one or more negatively-charged internucleotidic linkages at the condition of the composition independently exist as a salt form.

199. The composition of any one of the preceding embodiments, wherein oligonucleotides of the plurality exist as salts, wherein one or more negatively-charged internucleotidic linkages at the condition of the composition independently exist as a metal salt.

200. The composition of any one of the preceding embodiments, wherein oligonucleotides of the

plurality exist as salts, wherein each negatively-charged internucleotidic linkage at the condition of the composition independently exists as a metal salt.

201. The composition of any one of the preceding embodiments, wherein oligonucleotides of the plurality exist as salts, wherein each negatively-charged internucleotidic linkage at the condition of the composition independently exists as sodium salt.

202. The composition of any one of the preceding embodiments, wherein oligonucleotides of the plurality exist as salts, wherein each negatively-charged internucleotidic linkage is independently a natural phosphate linkage (the neutral form of which is −O−P(O)(OH)−O) or phosphorothioate internucleotidic linkage (the neutral form of which is −O−P(O)(SH)−O).

203. The composition of any one of the preceding embodiments, wherein each heteroatom in heteroaliphatic, heteroalkyl, heterocyclyl, or heteroaryl is independently boron, nitrogen, oxygen, silicon, sulfur, or phosphorus.

204. The composition of any one of the preceding embodiments, wherein each heteroatom in heteroaliphatic, heteroalkyl, heterocyclyl, or heteroaryl is independently nitrogen, oxygen, silicon, sulfur, or phosphorus.

205. The composition of any one of the preceding embodiments, wherein each heteroatom in heteroaliphatic, heteroalkyl, heterocyclyl, or heteroaryl is independently nitrogen, oxygen, or sulfur.

206. A pharmaceutical composition comprising an oligonucleotide composition of any one of the preceding embodiments and a pharmaceutically acceptable carrier.

207. A method for altering splicing of a target transcript, comprising administering an oligonucleotide composition of any one of the preceding embodiments.

208. The method of embodiment 207, wherein the splicing of the target transcript is altered relative to absence of the composition.

209. The method of any one of the preceding embodiments, wherein the alteration is that one or more exon is skipped at an increased level relative to absence of the composition.

210. The method of any one of the preceding embodiments, wherein the target transcript is pre-mRNA of dystrophin.

211. The method of any one of the preceding embodiments, wherein exon 51 of dystrophin is skipped at an increased level relative to absence of the composition.

212. The method of any one of embodiments 207-210, wherein exon 53 of dystrophin is skipped at an increased level relative to absence of the composition.

213. The method of any one of embodiments 207-210, wherein exon 45 of dystrophin is skipped at an increased level relative to absence of the composition.

214. The method of any one of the preceding embodiments, wherein two or more exons of dystrophin

is skipped at an increased level relative to absence of the composition

215. The method of any one of the preceding embodiments, wherein a protein encoded by the mRNA with the exon skipped provides one or more functions better than a protein encoded by the corresponding mRNA without the exon skipping.

216. A method for treating muscular dystrophy, Duchenne (Duchenne's) muscular dystrophy (DMD), or Becker (Becker's) muscular dystrophy (BMD), comprising administering to a subject susceptible thereto or suffering therefrom a composition of any one of the preceding embodiments.

217. A method for treating muscular dystrophy, Duchenne (Duchenne's) muscular dystrophy (DMD), or Becker (Becker's) muscular dystrophy (BMD), comprising (a) administering to a subject susceptible thereto or suffering therefrom a composition of any one of the preceding embodiments, and (b) administering to the subject additional treatment.

218. The method of embodiment 217, wherein the additional treatment is capable of preventing, treating, ameliorating or slowing the progress of muscular dystrophy, Duchenne (Duchenne's) muscular dystrophy (DMD), or Becker (Becker's) muscular dystrophy (BMD).

219. The method of any one of the preceding embodiments, wherein the additional treatment comprises administering a composition of any one of the preceding embodiments, wherein oligonucleotides of the composition have a different base sequence.

220. The method of any one of the preceding embodiments, wherein the additional treatment comprises administering a composition of any one of the preceding embodiments, wherein oligonucleotides of the composition have a different base sequence and target a different exon.

221. The composition of any of the preceding embodiments, wherein the transcript splicing system comprises a myoblast or myotubule.

222. The composition of any of the preceding embodiments, wherein the transcript splicing system comprises a myoblast cell.

223. The composition of any of the preceding embodiments, wherein the transcript splicing system comprises a myoblast cell, which is contacted with the composition after 0, 4 or 7 days of pre-differentiation.

224. A composition comprising a combination comprising: (a) a first composition of any of the preceding embodiments; (b) a second composition of any of the preceding embodiments; and, optionally (c) a third composition of any of the preceding embodiments, wherein the first, second and third compositions are different.

EXEMPLIFICATION

[001429] The foregoing has been a description of certain non–limiting embodiments of the disclosure. Accordingly, it is to be understood that embodiments of the disclosure herein described are merely illustrative of applications of principles of the disclosure. Reference herein to details of illustrated embodiments is not intended to limit the scope of any claims.

[001430] Various methods for preparing, and for assessing properties and/or activities of, oligonucleotides and oligonucleotide compositions are widely known in the art and may be utilized in accordance with the present disclosure, including but not limited to those described in US 9394333, US 9744183, US 9605019, US 9598458, US 2015/0211006, US 2017/0037399, WO 2017/015555, WO 2017/192664, WO 2017/015575, WO 2017/062862, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/223056, WO 2018/237194, and WO 2019/055951, the methods and reagents of each of which are incorporated herein by reference. In some embodiments, the present disclosure provides technologies for preparing oligonucleotides and compositions thereof, particularly chirally controlled oligonucleotides which comprise neutral backbones (e.g., n001, n002, n003, n004, n005, n006, n007, n008, n009, n010, etc.) and chirally controlled oligonucleotide compositions thereof, and technologies for assessing and using various oligonucleotides and compositions thereof. Among other things, Applicant describes herein example technologies for preparing, assessing and using provided oligonucleotides and oligonucleotide compositions.

[001431] Functions and advantage of certain embodiments of the present disclosure may be more fully understood from the examples described below. The following examples are intended to illustrate certain benefits of such embodiments.

Example 1. Example synthesis of oligonucleotide compositions

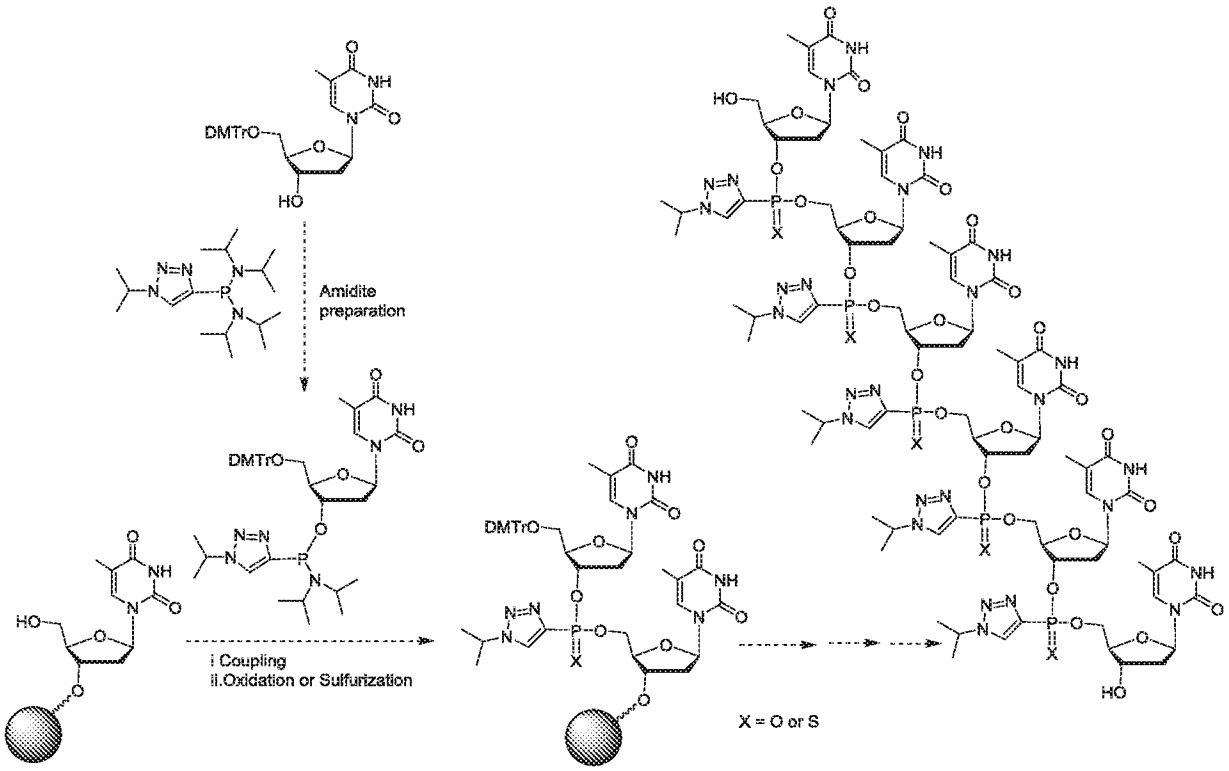
[001432] Technologies for preparing oligonucleotide and compositions thereof are widely known in the art. In some embodiments, oligonucleotides and oligonucleotide compositions of the present disclosure were prepared using technologies, e.g., reagents (e.g., solid supports, coupling reagents, cleavage reagents, phosphoramidites, etc.), chiral auxiliaries, solvents (e.g., for reactions, washing, etc.), cycles, reaction conditions (e.g., time, temperature, etc.), etc., described in one or more of US 9394333, US 9744183, US 9605019, US 9598458, US 2015/0211006, US 2017/0037399, WO 2017/015555, WO 2017/192664, WO 2017/015575, WO 2017/062862, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/223056, WO 2018/237194, and WO 2019/055951.

Example 2. Example synthesis of oligonucleotides comprising an internucleotidic linkage comprising

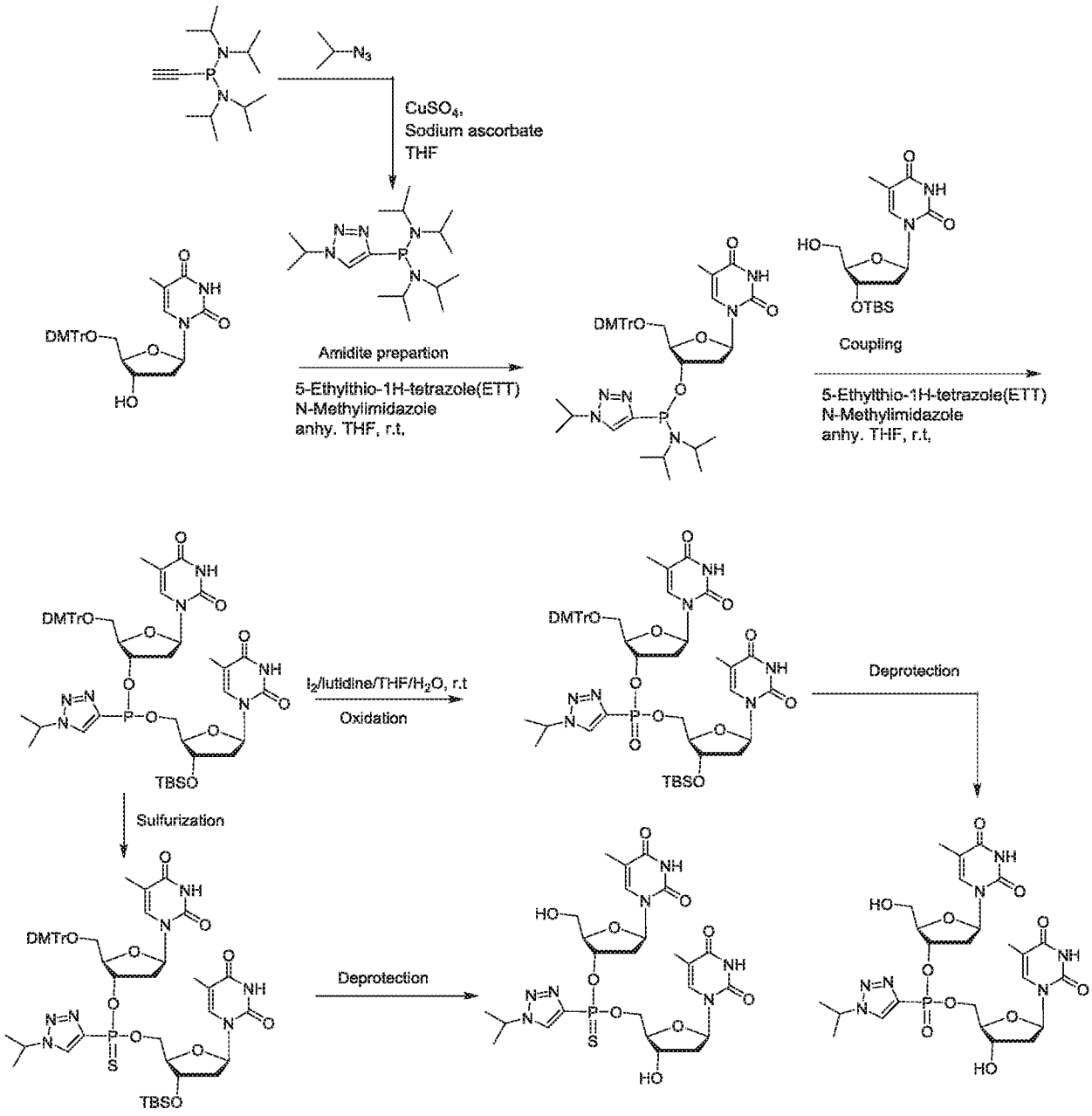
a triazole moiety or an alkyne moiety.

[001433] Various types of internucleotidic linkages can be prepared in accordance with the present disclosure. Described in this example is preparation of oligonucleotides comprising internucleotidic linkages comprising triazole moieties. As those skilled in the art appreciates, technology described herein can be readily utilized to conjugate various desirable moieties, e.g., those derived from GalNAc, lipids, peptides, ligands, etc. Among other things, such conjugation can be useful for delivery of oligonucleotides to various target systems (e.g., CNS, muscles, eye, etc.).

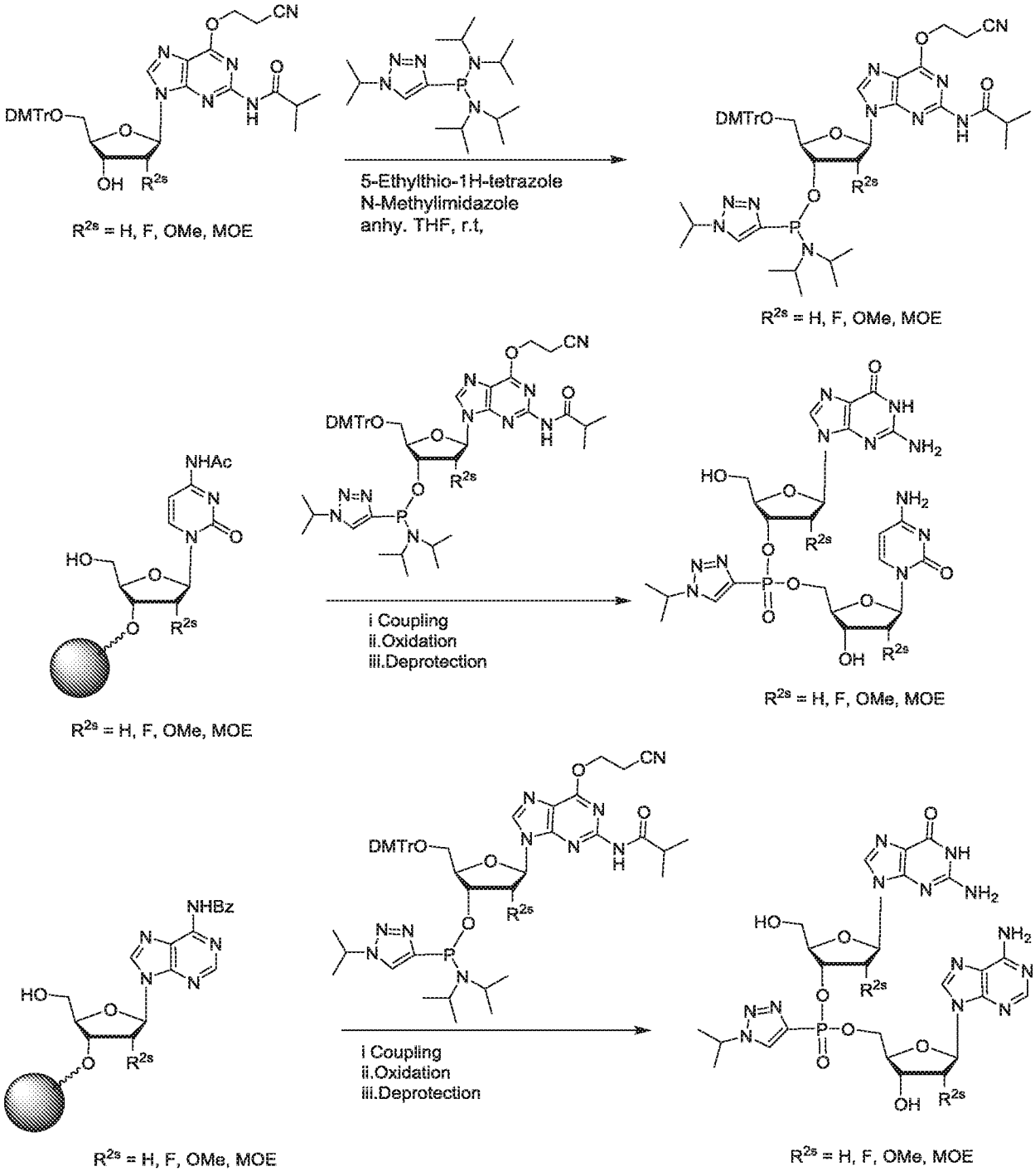
[001434] Example oligonucleotide comprising internucleotidic linkages comprising triazole moieties.

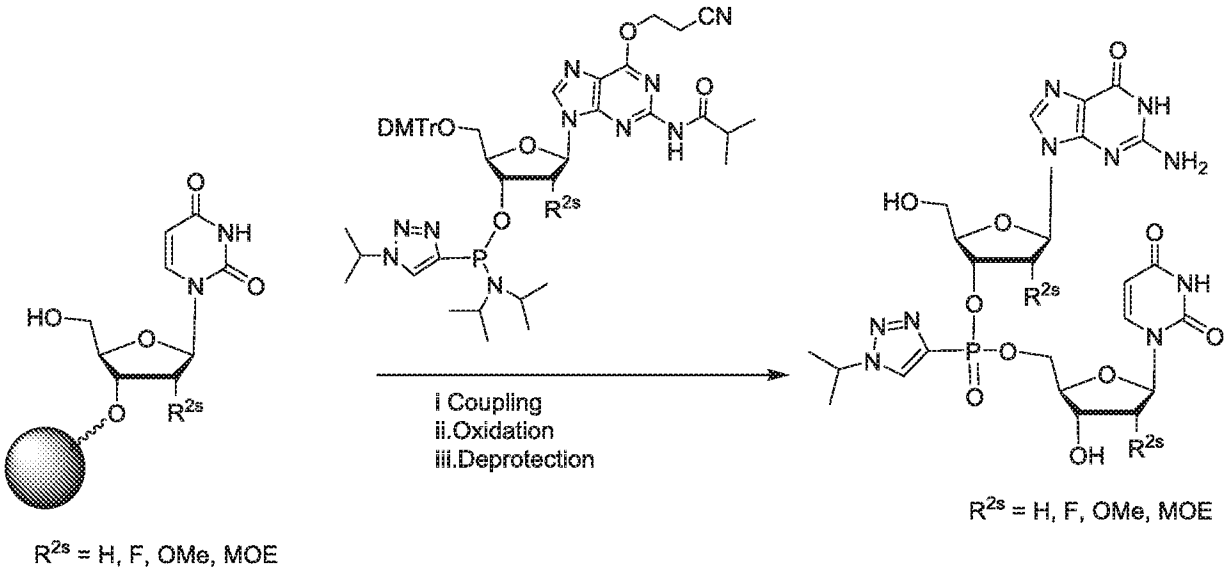


[001435] Synthesis scheme for dimer preparation in solution phase.

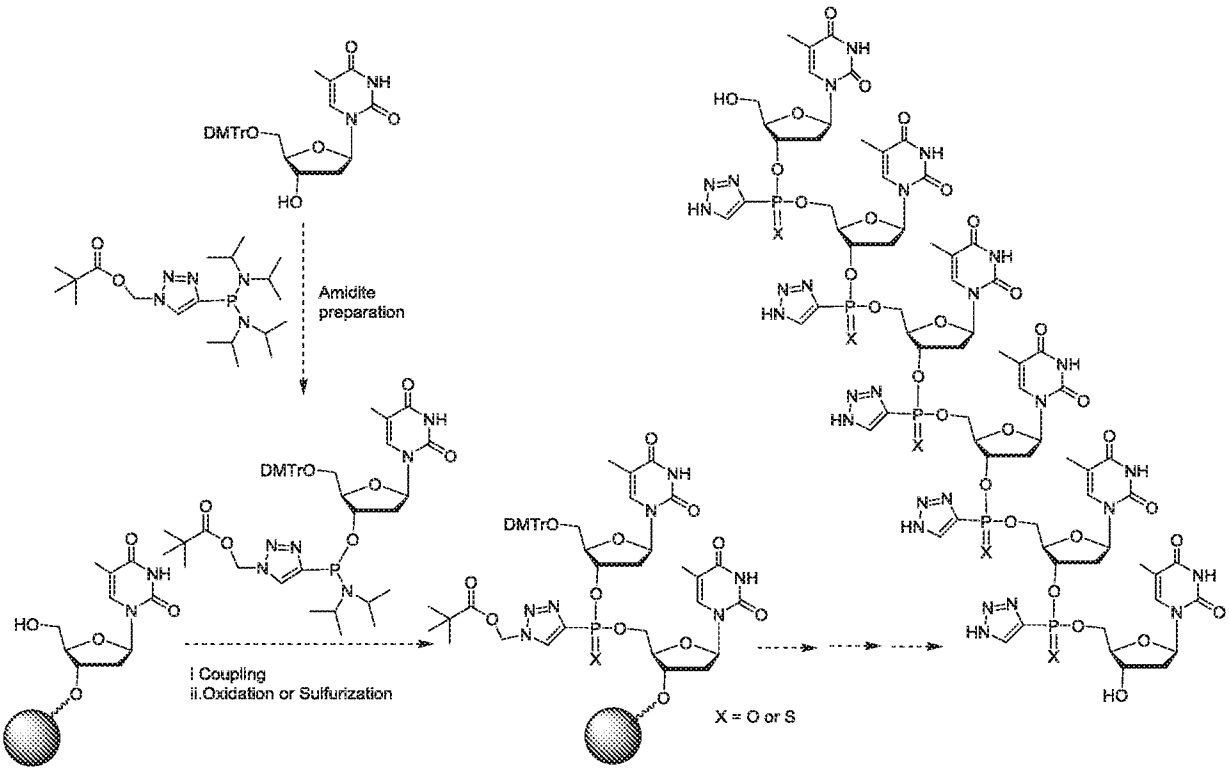


[001436] Synthesis scheme for dimer preparation on solid support.

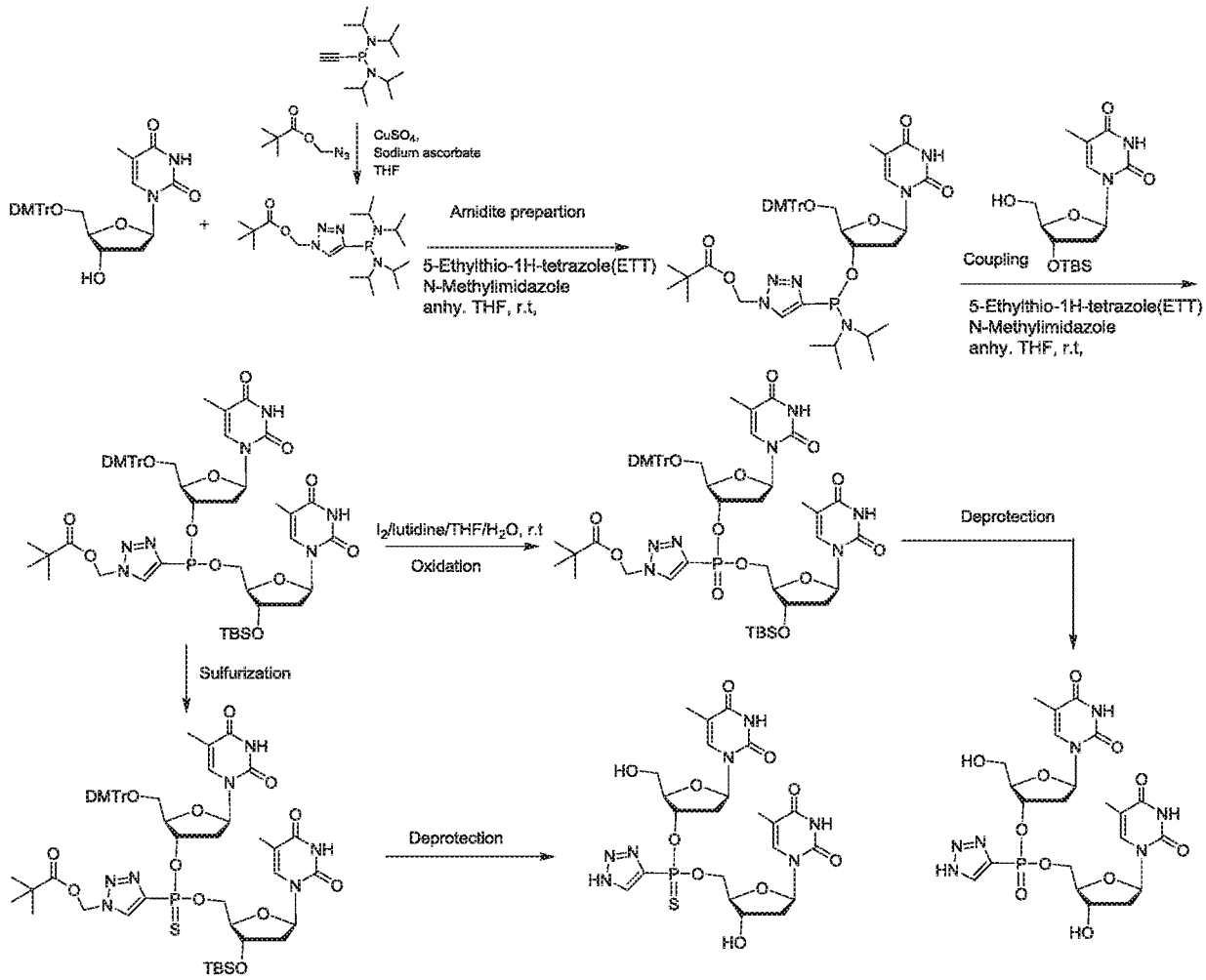

DMTrO
CN
OH
R2s
R2s = H, F, OMe, MOE
5-Ethylthio-1H-tetrazole
N-Methylimidazole
anhy. THF, r.t,
R2s = H, F, OMe, MOE
NHAc
HO
R2s = H, F, OMe, MOE
i Coupling
ii.Oxidation
iii.Deprotection
NH2
R2s = H, F, OMe, MOE
NHBz
R2s = H, F, OMe, MOE
i Coupling
ii.Oxidation
iii.Deprotection
R2s = H, F, OMe, MOE



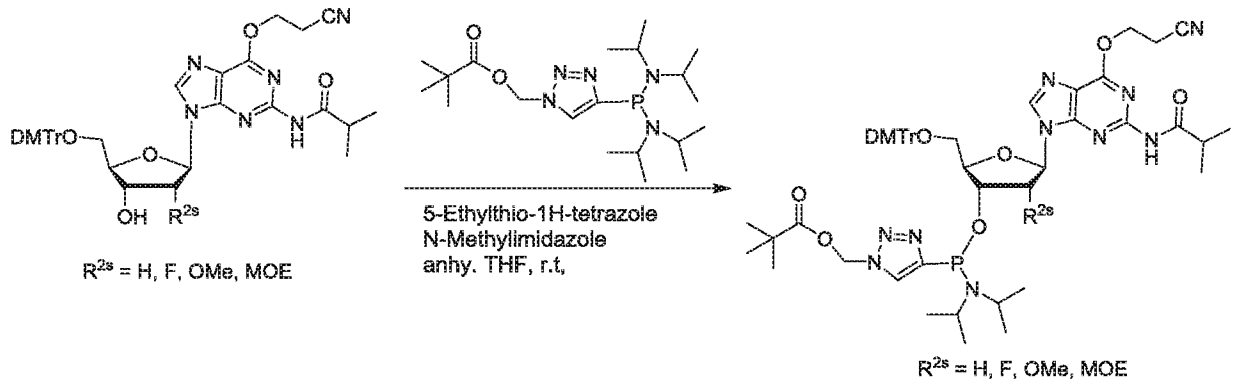
[001437] Triazole backbone oligonucleotides:



[001438] Synthesis scheme for dimer preparation in solution phase:

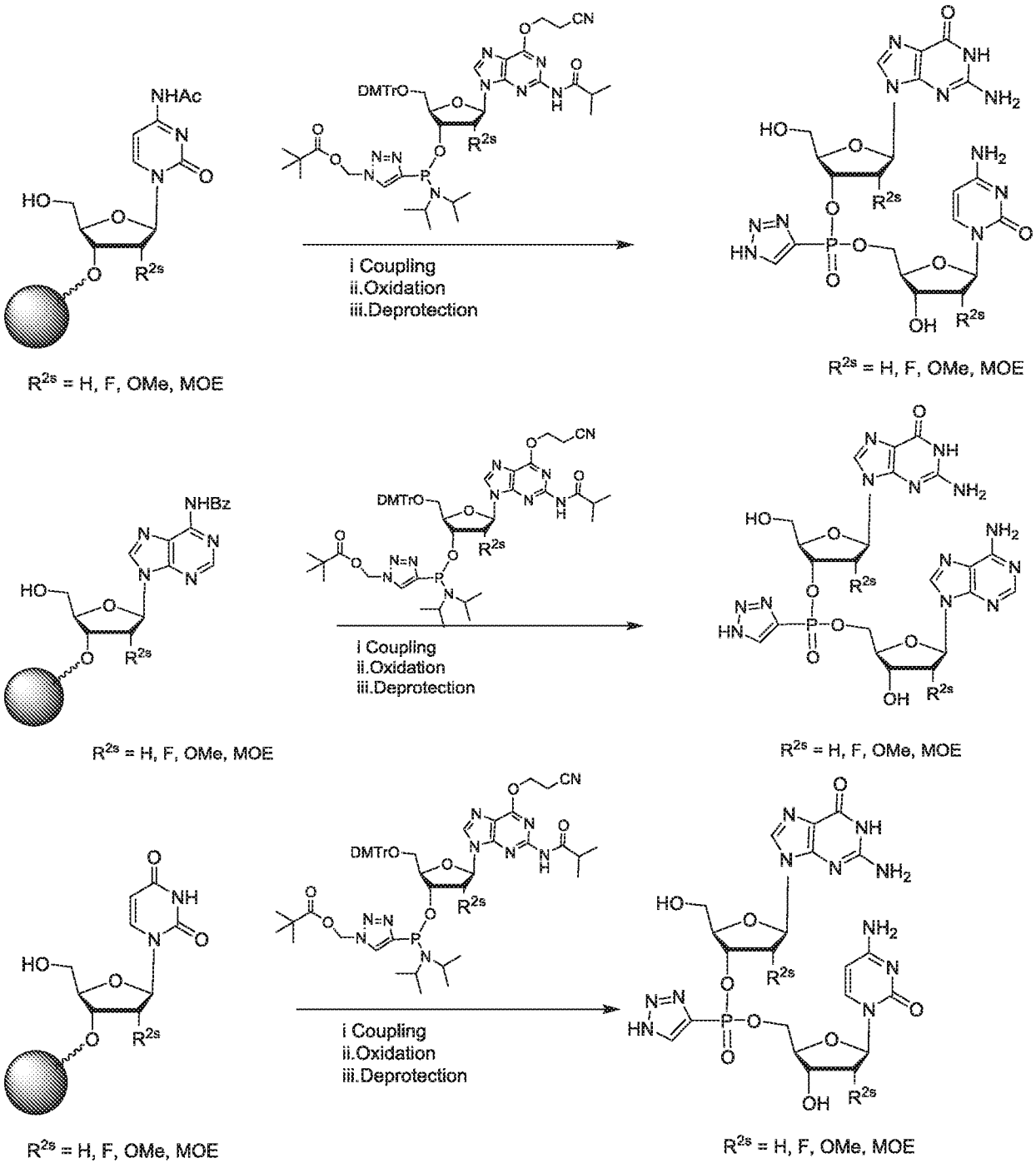


[001439] Synthesis scheme for dimer preparation on solid support:

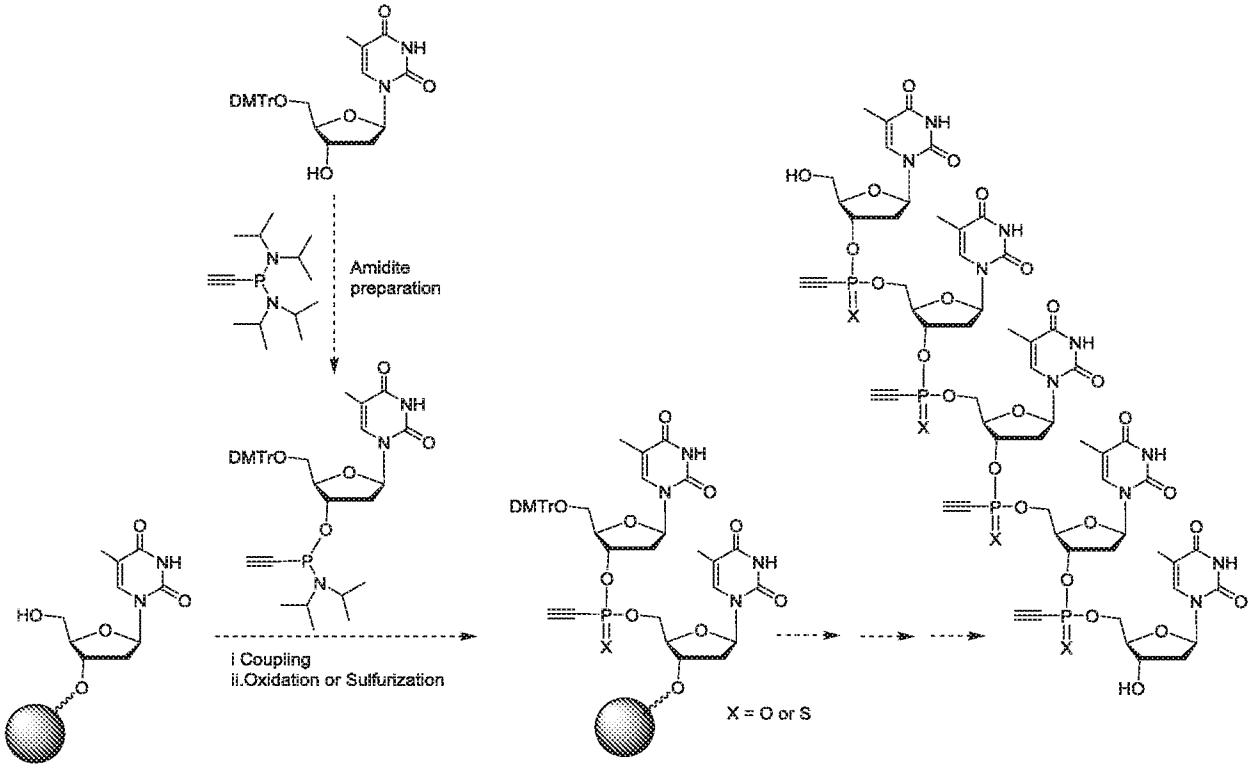


R^{2s} = H, F, OMe, MOE

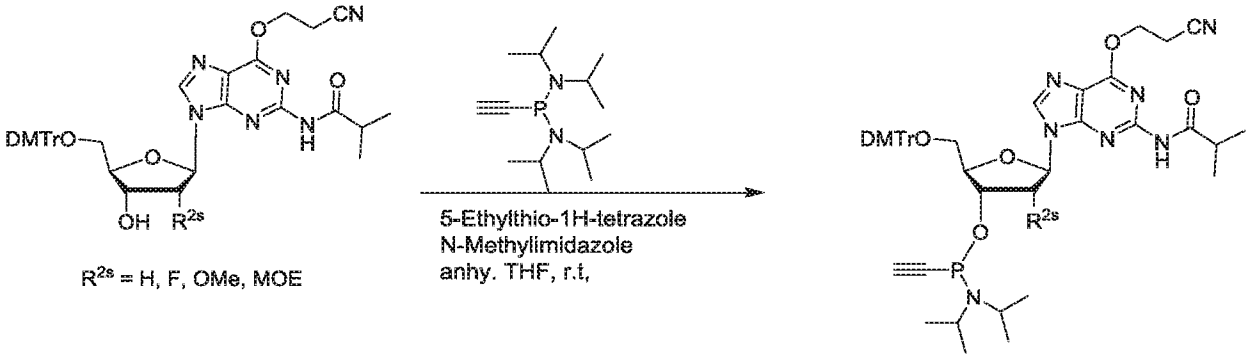
R^{2s} = H, F, OMe, MOE



[001440] Alkyne backbone oligonucleotides:

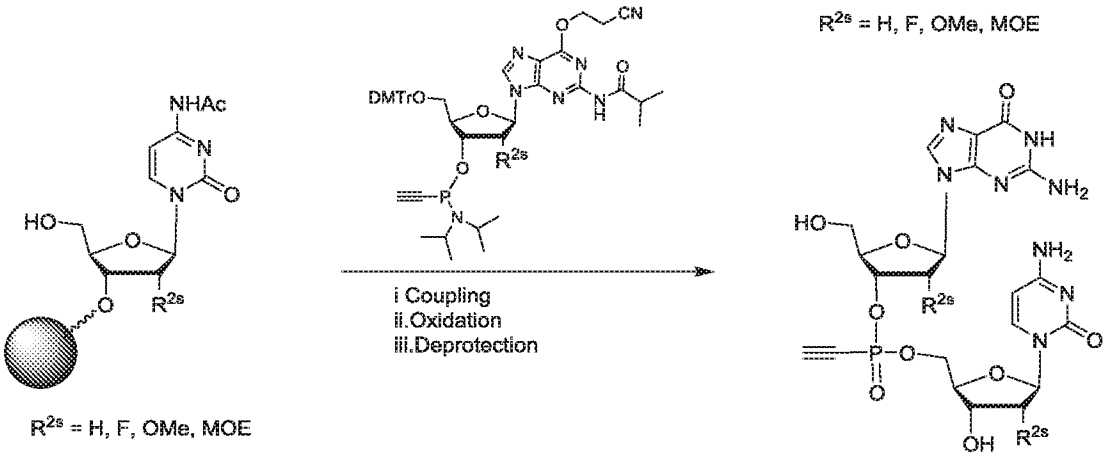


[001441] Synthesis scheme for dimer preparation on solid support:



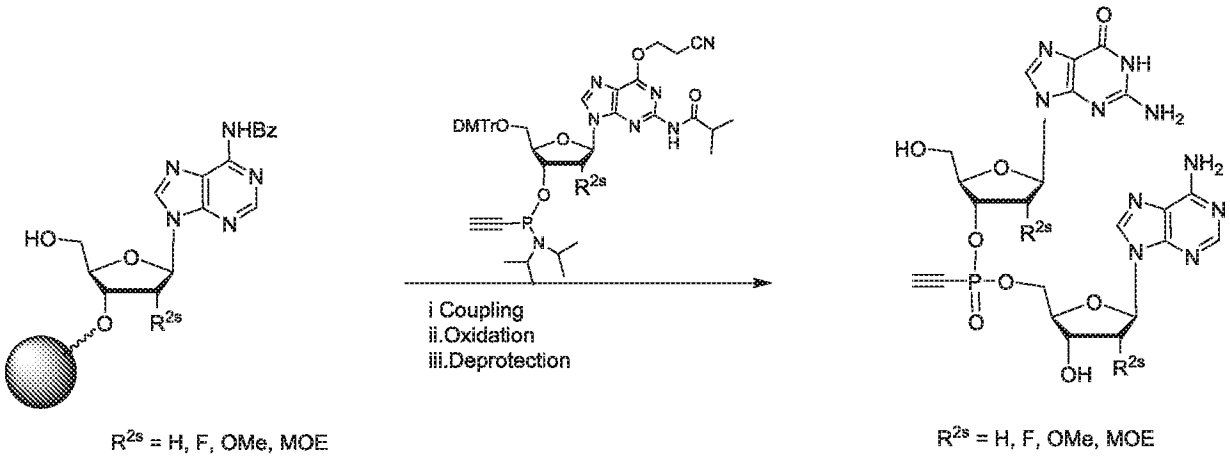
R^{2s} = H, F, OMe, MOE

R^{2s} = H, F, OMe, MOE



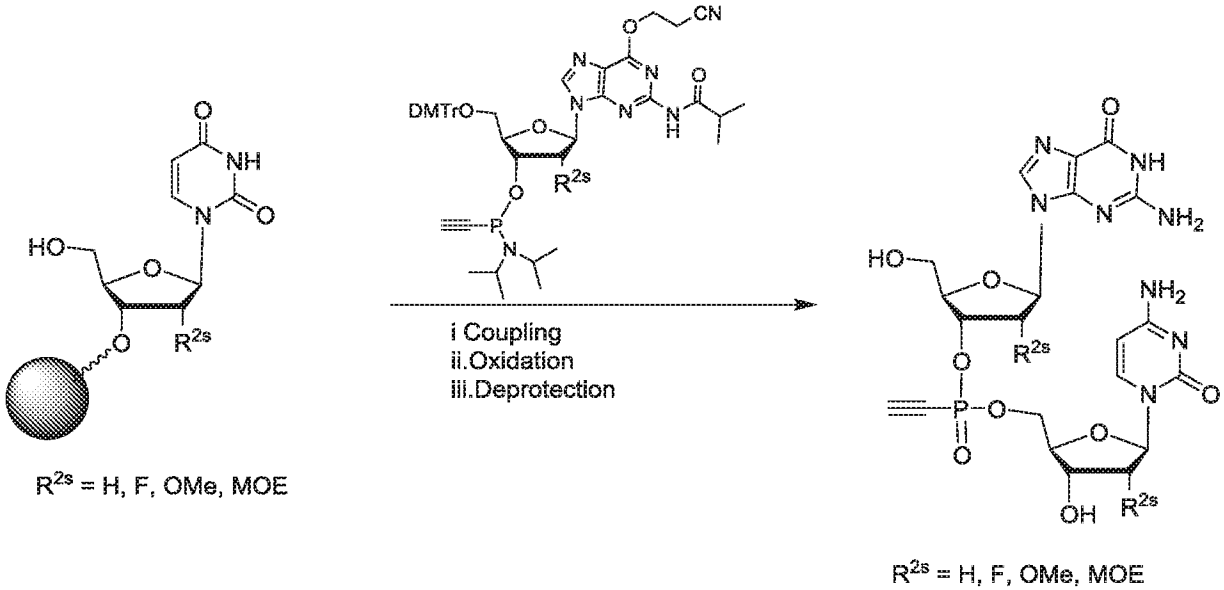
R^{2s} = H, F, OMe, MOE

R^{2s} = H, F, OMe, MOE



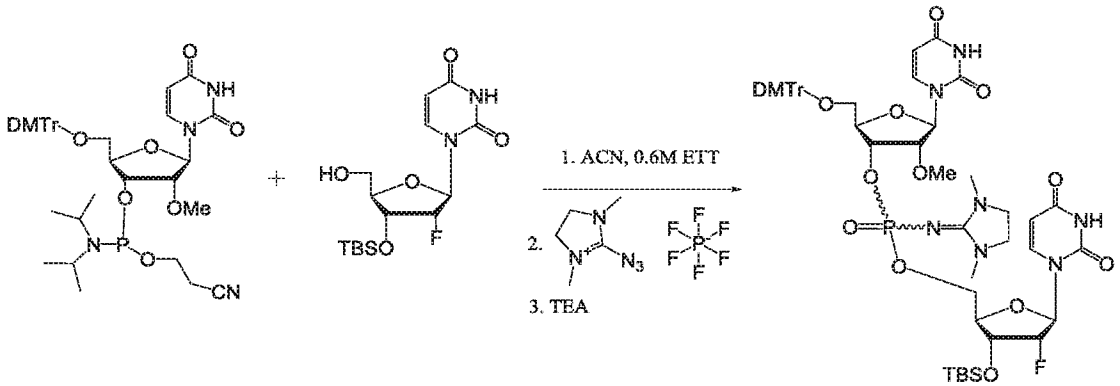
R^{2s} = H, F, OMe, MOE

R^{2s} = H, F, OMe, MOE



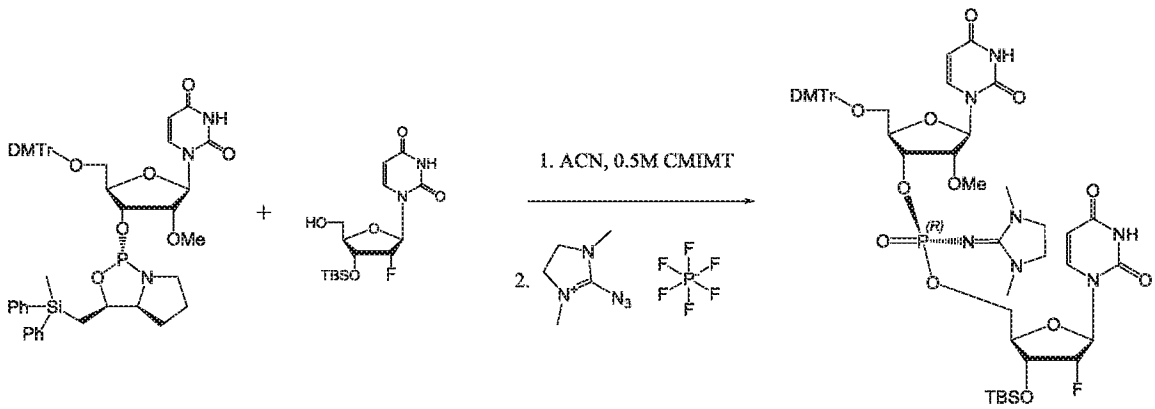
Example 3. Example synthesis of phosphoramidate internucleotidic linkages comprising a guanidine moiety

[001442] As illustrated herein, phosphoramidate internucleotidic linkages can be readily prepared from phosphite internucleotidic linkages, including stereopure phosphite internucleotidic linkages, in accordance with the present disclosure.



[001443] To a stirred solution of amidite (474 mg, 0.624 mmol, 1.5 equiv., pre-dried by co-evaporation with dry acetonitrile and under vacuum for a minimum of 12 h) and TBS protected alcohol (150 mg, 0.41 mmol, pre-dried by co-evaporation with dry acetonitrile and under vacuum for a minimum of 12 h) in dry acetonitrile (5.2 ml) was added 5-(ethylthio)-*1H*-tetrazole (ETT, 2.08 ml, 0.6M, 3 equiv.) under argon atmosphere at room temperature. The reaction mixture was stirred for 5 mins then monitored by LCMS and then a solution of 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (356 mg, 1.24 mmol, 3 equiv.) in acetonitrile (1 ml) was added. Once the reaction was completed (after ~ 5 mins, monitored by LCMS) then triethylamine (0.17 ml, 1.24 mmol, 3 equiv) was added and the reaction was monitored by LCMS. The reaction mixture was concentrated under reduced pressure and then

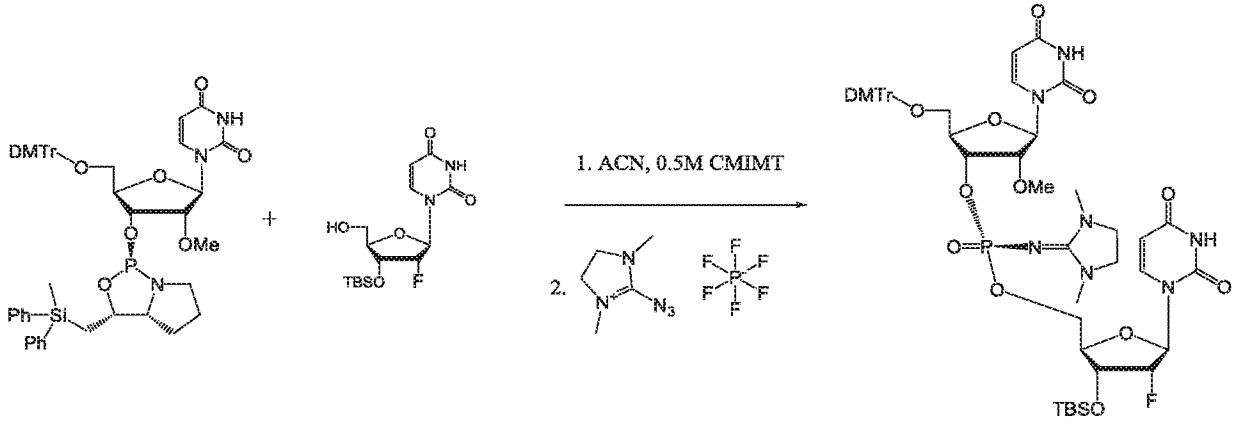
redissolved in dichloromethane (50 ml), washed with water (25 ml), saturated aq. sodium bicarbonate (25 ml), and brine (25 ml), and dried with magnesium sulfate. The solvent was removed under reduced pressure. The crude product was purified by silica gel column (80 g) using DCM (5% triethyl amine) and MeOH as eluent. Product-containing fractions were collected and the solvent was evaporated. The resulted product may contain Triethylamine trihydrochloride (TEA.HCl) salt. To remove the salt, the product was re-dissolved in DCM (50 ml) and washed with saturated aq. sodium bicarbonate (20 ml) and brine (20 ml) then dried with magnesium sulfate and the the solvent was evaporated. A pale yellow solid was obtained. Yield: 440 mg (89%). ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.34, -1.98. MS calculated for $C_{51}H_{65}FN_7O_{14}PSi$ $[M]^+$ 1078.17, Observed: 1078.57 $[M + H]^+$.



[001444] Synthesis of stereopure (Rp) dimer.

[001445] To a stirred solution of L-DPSE chiral amidite (1.87 g, 2.08 mmol, 1.5 equiv., pre-dried by co-evaporation with dry acetonitrile and under vacuum for a minimum of 12 h) and TBS protected alcohol (500 mg, 1.38 mmol, pre-dried by co-evaporation with dry acetonitrile and under vacuum for a minimum of 12 h) in dry acetonitrile (18 mL) was added 2-(1H-imidazol-1-yl) acetonitrile trifluoromethanesulfonate (CMIMT, 5.54 mL, 0.5M, 2 equiv.) under argon atmosphere at room temperature. The resulting reaction mixture was stirred for 5 mins then monitored by LCMS and then a solution of 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (1.18 g, 4.16 mmol, 3 equiv.) in acetonitrile (2 mL) was added. Once the reaction was completed (after ~ 5mins, monitored by LCMS), the reaction mixture was concentrated under reduced pressure and then redissolved in dichloromethane (70 mL), washed with water (40 mL), saturated aq. sodium bicarbonate (40 mL) and brine (40 mL), and dried with magnesium sulfate. The solvent was removed under reduced pressure. The crude product was purified by silica gel column (120 g) using DCM (5% triethyl amine) and MeOH as eluent. Product containing fractions were collected and the solvent was evaporated. The resulted product contained TEA.HCl salt. To remove the salt, the product was re-dissolved in DCM (50 mL) and washed with saturated aq. sodium bicarbonate (20 mL) and brine (20 mL) and then dried with magnesium sulfate and

the solvent was evaporated. A pale yellow foamy solid was obtained. Yield: 710 mg (47%). ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.38. MS calculated for $C_{51}H_{65}FN_7O_{14}PSi$ $[M]^+$ 1078.17, Observed: 1078.19.



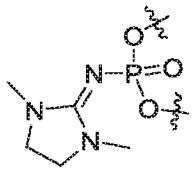
[001446] Synthesis of stereopure (Sp) dimer

[001447] The same procedure was followed as for the Rp dimer. In place of L-DPSE chiral amidite, D-DPSE chiral amidite was used. A pale yellow foamy solid was obtained. Yield: 890 mg (59%). ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.93. MS calculated for $C_{51}H_{65}FN_7O_{14}PSi$ $[M]^+$ 1078.17, Observed: 1078.00.

[001448] In an example ^{31}P NMR (internal standard of phosphoric acid at δ 0.0), the stereorandom preparation showed two peaks at -1.34 and -1.98, respectively; the stereopure Rp preparation showed a peak at -1.93, and the stereopure Sp preparation showed a peak at -1.38.

Example 4A. Preparation of oligonucleotides with internucleotidic linkages comprising neutral guanidinium group

[001449] In accordance with technologies described in the present disclosure, oligonucleotides with various neutral and/or cationic internucleotidic linkages (e.g., at physiological pH) can be prepared. Illustrated below are preparation of oligonucleotides comprising representative such internucleotidic linkages.

[001450] WV-11237 is an oligonucleotide comprising four internucleotidic linkages having the structure of  (n001) to introduce a neutral nature to the backbone and reduce the overall negative charges of the backbone. Expected molecular weight: 7113.4.

[001451] As an example, one preparation of WV-11237, including certain synthetic conditions and analytical results, is described below. Briefly, stereopure internucleotidic linkages were constructed using

L-DPSE amidites and typical DPSE coupling cycles comprising Detritylation-> Coupling-> Pre-Cap-> Thiolation-> Post-Cap. Cycles for the n001 internucleotidic linkages were modified and comprised Detritylation-> Coupling-> Dimethyl imidazolium treatment-> Post-cap. Compared to certain oxidation cycles, oxidation steps of oxidizing the P(III), e.g., with I_2-Pyridine (pyr)-water, was replaced with the dimethyl imidazolium treatment.

[001452] Certain conditions and/or results of an example preparation.

Synthetic scale: 127 μmol

Synthetic conditions (stereopure internucleotidic linkages)

Synthetic Steps	**Conditions**
Detritylation	3% DCA in Toluene; 300 cm/hr, 436 UV watch
Coupling	2.5 eq. of 0.2M chiral amidite, 67% of 0.6M CMIMT Recycle time: 10 min
Pre-Cap B	Reagent: 20:30:50::Acetic anhydride: Lutidine: Acetonitrile 1.5 CV, 3 min CT
Thiolation	Reagent: 0.2 M Xanthane Hydride 0.6 CV, 6 min CT
Capping (1:1 Cap A+Cap B)	0.4 CV, 0.8 min CT

Cap A = *N*-Methylimidazole in acetonitrile, 20/80, v/v (20%:80% = NMI:ACN (v/v))
Cap B = Acetic anhydride/2,6-Lutidine/Acetonitrile, 20/30/50, v/v/v , 20%:30%:50% = Ac_2O:2,6-Lutidine:ACN (v/v/v)

Synthetic conditions (stereorandom n001)

Synthetic Steps	**Conditions**
Detritylation	3% DCA in Toluene; 300 cm/hr, 436 UV watch
Coupling	2.5 eq. of 0.2M standard amidite, 67% of 0.6M ETT Recycle time: 8 min
Dimethyl imidazolium treatment:	2.30 CV, 5 min CT, 3.5 eq.
Capping (1:1 Cap A+Cap B)	0.4 CV, 0.8 min CT

Synthesis Process Parameters:

Synthesizer: AKTA Oligopilot 100

Solid Support: CPG 2'Fluoro-U, (85 umol/g)

Synthetic scale: 127 umol; 1.5 gm

Column diameter: 20 mm

Column volume: 6.3 mL

Stereopure Coupling reagents:

Monomer: 0.2M in MeCN (2'Fluoro-dA-L-DPSE, 2'Fluoro-dG-L-DPSE, 2'-OMe-A-L-DPSE); 0.2M in 20% isobutyronitrle/MeCN (2'Fluoro-dC-L-DPSE, 2'Fluoro-U-L-DPSE)

Deblocking: 3% Dichloroacetic acid (DCA) in Toluene

Activator: 0.6M CMIMT in MeCN

Sulfurization: 0.2M Xanthane Hydride in pyridine

Cap A: *N*-Methylimidazole in acetonitrile, 20/80, v/v (20% NMI in MeCN)
Cap B: Acetic anhydride/2,6-Lutidine/Acetonitrile, 20/30/50, v/v/v, (Acetic anhydride, Lutidine, MeCN (20:30:50))
Pre-Cap: Neat Cap B

Stereorandom Coupling reagents:

Monomer: 0.2M in MeCN (2'OMeA and 2'OMeG)

Deblocking: 3%DCA in Toluene

Activator: 0.6M ETT in MeCN

2-Azido-1,3-dimethylimidazolinium-hexafluorophosphate: 0.1M in MeCN

Cap A: 20% NMI in MeCN

Cap B: Acetic anhydride, Lutidine, MeCN

Deprotection Condition:

One pot deprotection by first treating the support with 5M Triethylamine trihydrofluoride (TEA.HF) in Dimethylsulfoxid (DMSO), H_2O, Triethylamine (pH 6.8). Incubation: 3 h, room temperature, 80 µL/µmol. Followed by addition of aqueous ammonia (200 µL/µmol). Incubation: 24 h, 35°C. The deprotected material was sterile filtered using 0.45 µm filters.

Yield: 72 O.D. / µmol

Recipe for 5X Solution of TEA.HF in DMSO/Water, 5/1, v/v:

Reagent	Solvents/Reagents	Volume (mL)	Total Volume (mL)
(5X) TEA.HF in DMSO/Water, 5/1, v/v	*DMSO*	55.0	100
	Water	11.0	
	Triethylamine (TEA)	9.0	
	Triethylamine trihydrofluoride (TEA.3HF)	25.0	

[001453] In an example crude UPLC chromatogram, there were four distinct peaks all having same desired molecular weight of 7113.2:

	RT	Area	% Area	Height
9	7.843	402732	16.75	212901
10	7.884	941388	39.14	327190
11	7.968	595232	24.75	275741
12	8.025	353090	14.68	150141

[001454] The example final QC UPLC chromatogram showed four distinct peaks all having the desired molecular weight of 7113.2 (% Purity 95.32). Crude LC-MS showed a single peak of desired molecular weight of 7113.2 (data not shown). The example final QC LC-MS showed a major peak with the desired molecular weight of 7113.1.

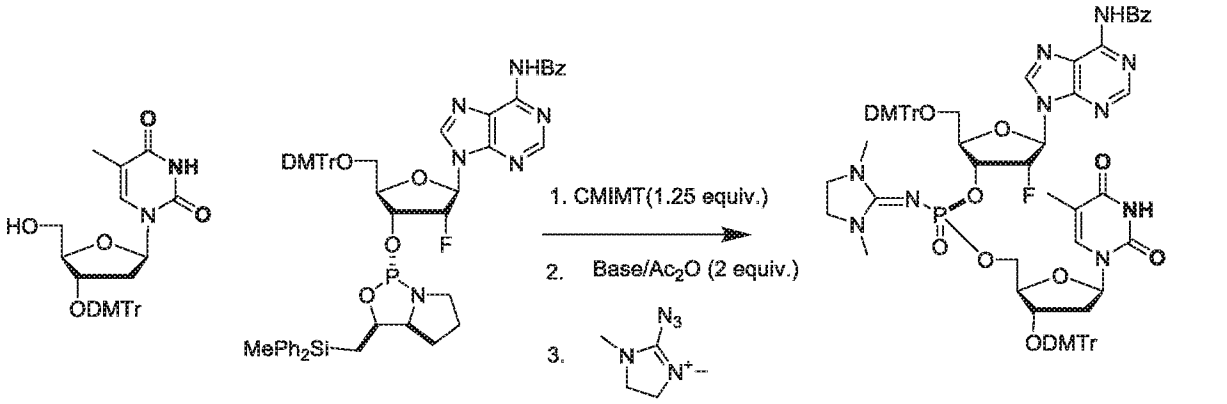
[001455] Other oligonucleotides may be prepared using similar cycle conditions or variants thereof depending on specific chemistries of each oligonucleotides. MS data of certain oligonucleotides are listed below:

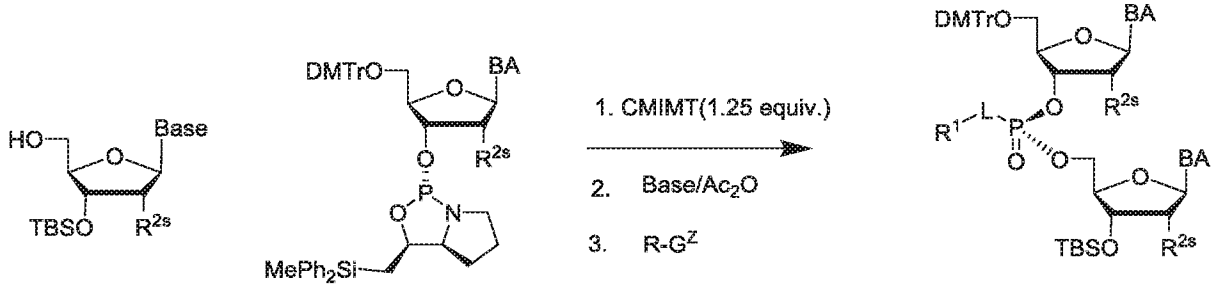
ID	Average	Observed	ID	Average	Observed
WV-11237	7113.40288	7113.1	WV-12504	8887.86402	8887.5
WV-11340	6967.19736	6967.4	WV-12505	7278.017	7278.2
WV-11341	6876.08178	6875.6	WV-12506	8944.9584	8945.2
WV-11342	6888.1173	6887.7	WV-12507	7335.11138	7334.4
WV-11343	7072.39402	7072.4	WV-12508	7155.95736	7156.3
WV-11344	6981.27844	6981.6	WV-12539	7171.78104	7171
WV-11345	6981.27844	6981.6	WV-12540	7171.78104	7171
WV-11346	6981.27844	6981.6	WV-12541	7457.21802	7457
WV-11347	6981.27844	6981.6	WV-12542	7219.97784	7219
WV-11532	6905.78632	6905	WV-12543	7235.97724	7236
WV-11533	7098.86298	7099	WV-12544	7112.86454	7113
WV-12116	7909.88196	7909.4	WV-12553	6872.0517	6872
WV-12117	7909.88196	7909.8	WV-12555	6876.08178	6875.8
WV-12118	7909.88196	7910.2	WV-12556	6888.1173	6887.8
WV-12119	7909.88196	7909.4	WV-12558	6876.08178	6875.6
WV-12120	7909.88196	7909.8	WV-12559	6888.1173	6887.7
WV-12121	7909.88196	7909.8	WV-12876	7204.43754	7204.4
WV-12123	7125.35748	7125	WV-12877	7113.32196	7113.5
WV-12124	6967.19736	6967	WV-12878	7125.35748	7125.4
WV-12125	6967.19736	6967	WV-12879	6919.00056	6919.1
WV-12126	6967.19736	6967	WV-12880	6923.03064	6923.2
WV-12127	7046.27742	7046	WV-12881	6935.06616	6935.3
WV-12128	7046.27742	7046	WV-12882	7094.4195	7094.1
WV-12129	7046.27742	7046	WV-12883	7410.73974	7411.1

Example 4B. Chirally controlled non-negatively charged internucleotidic linkages

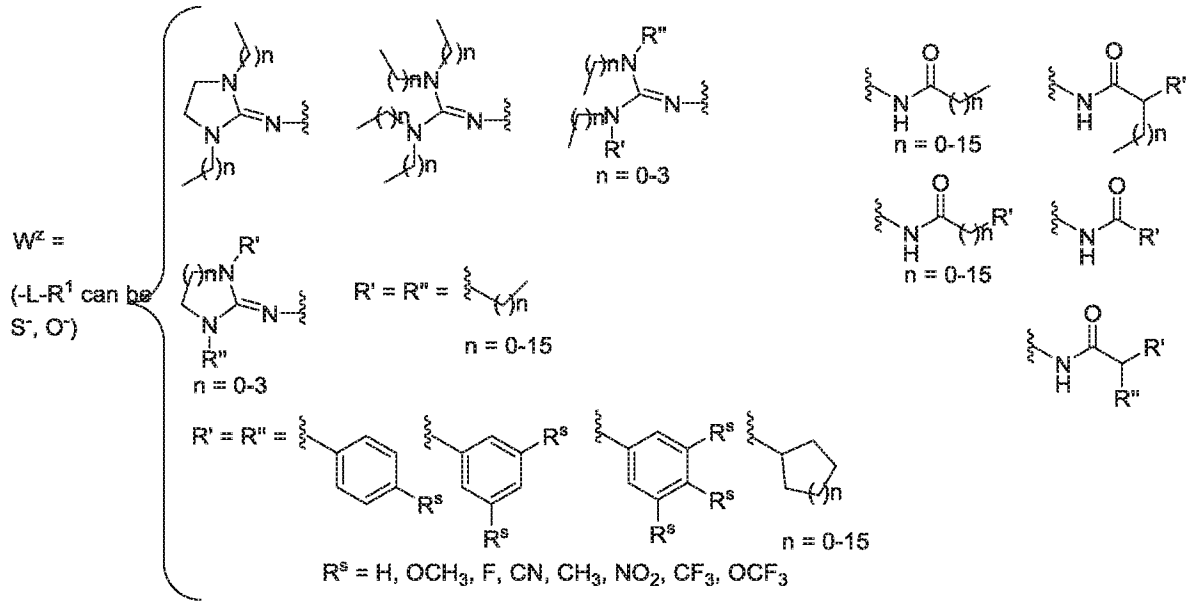
[001456] Dimer synthesis.

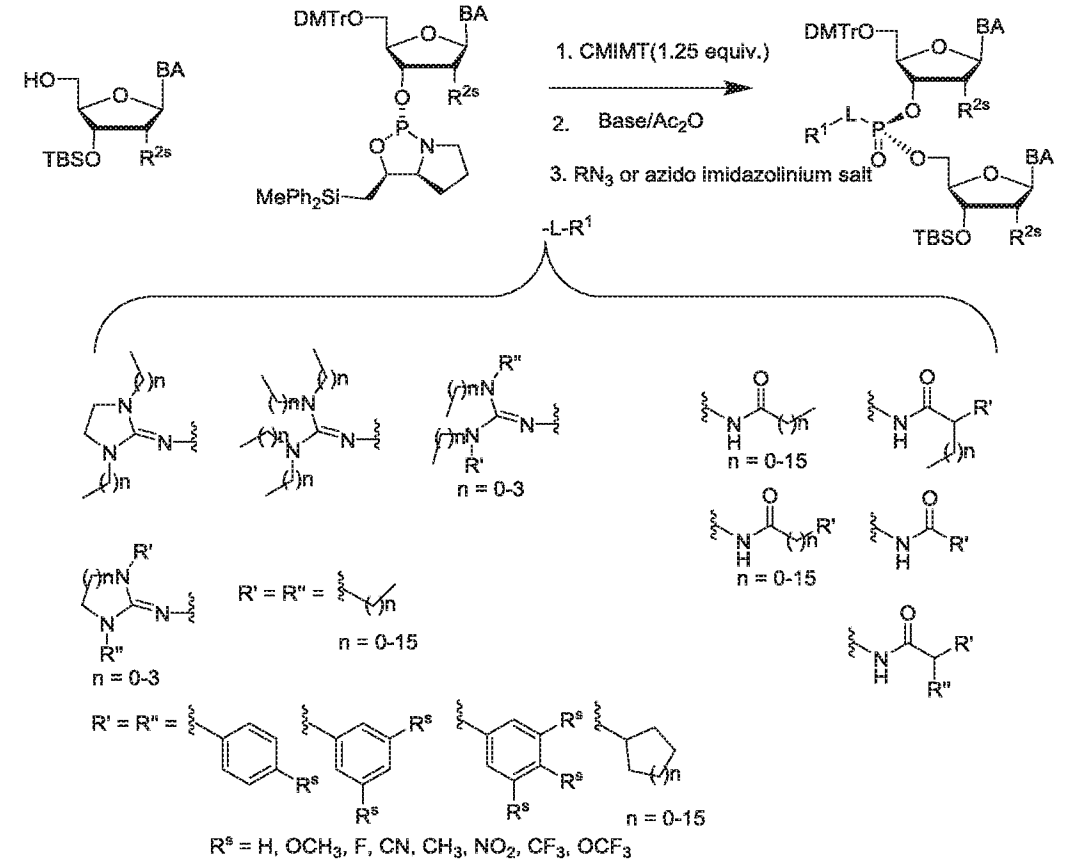
[001457] This procedure is to make stereopure dimer phosphate backbone followed by incorporating it to the selective sites of oligonucleotides (e.g., antisense oligonucleotide or ASO, single-stranded RNAi agent or ssRNA, etc.). A second approach is to synthesize molecules using an automated oligonucleotide synthesizer to introduce a non-negatively charged internucleotidic linkage, e.g., a neutral internucleotidic linkage, at a specific site or full oligonucleotide.

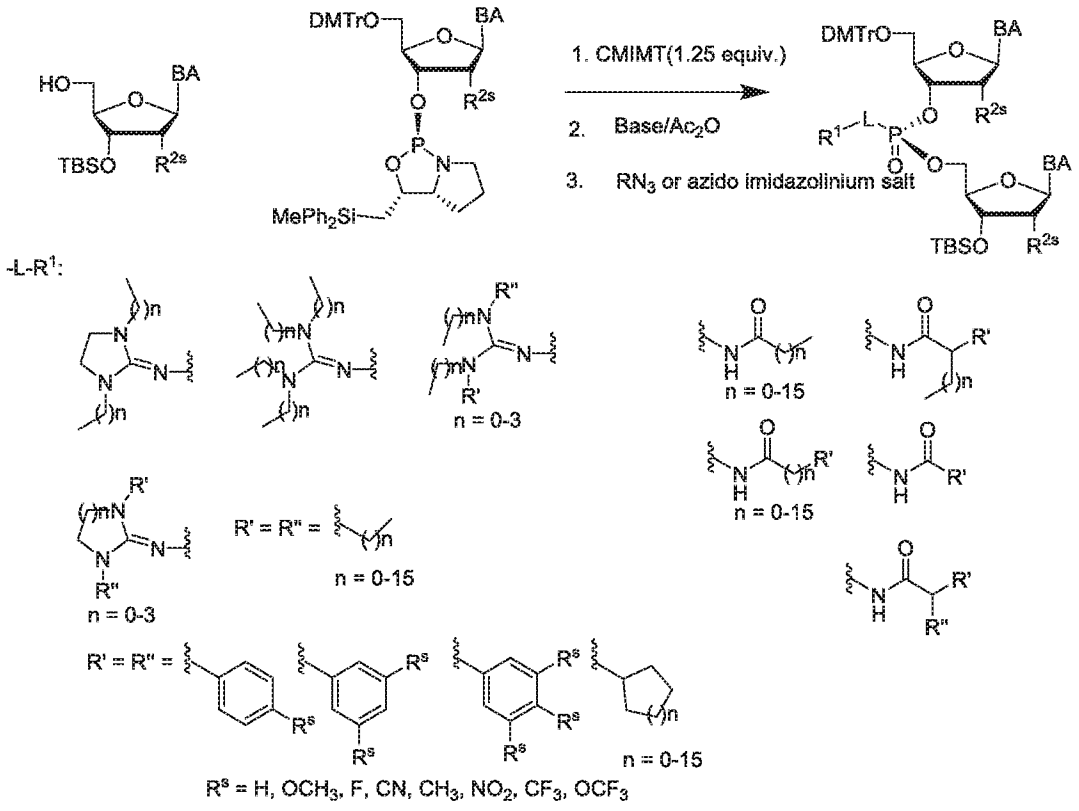


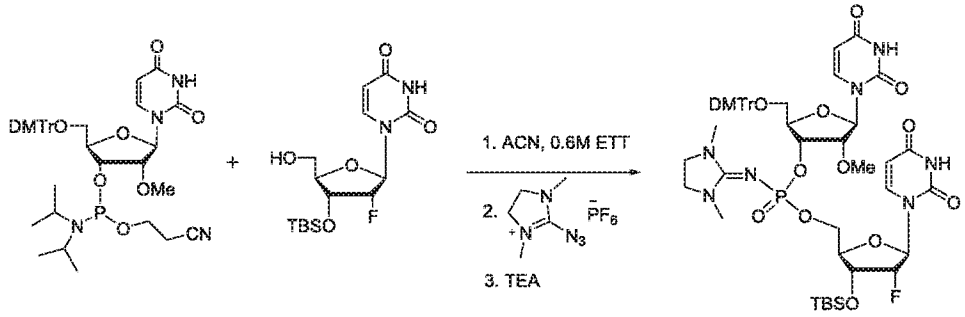


-L-R^1 = CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-,
CH_3OCH_2-, CH_3CH_2-OCH_2-$PhCH_2OCH_2$-
$CHCCH_2$-, CH_3CCCH_2-, CH_2CHCH_2-, CH_3SCH_2-
-CH_2COOCH_3, -$CH_2COOCH_2CH_3$, -CH_2COOCH_3, -$CH_2CONHCH_3$,
G^Z = Cl, Br, I, OTf, OMs, OTosyl etc.
R^{2s} = H, OCH_3, $OCH_2CH2OCH_3$, F, $OCH_2CH_2W^z$



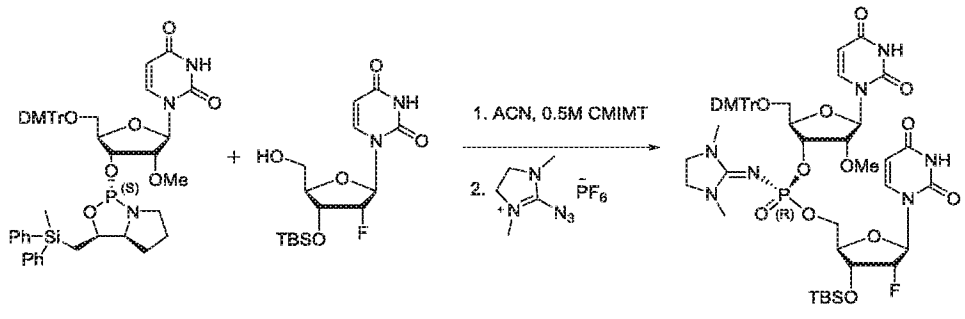

1. CMIMT(1.25 equiv.)
2. Base/Ac2O
3. RN3 or azido imidazolinium salt
-L-R1
n = 0-15
n = 0-3
R' = R" =
Rs = H, OCH3, F, CN, CH3, NO2, CF3, OCF3


1. CMIMT(1.25 equiv.)
2. Base/Ac2O
3. RN3 or azido imidazolinium salt
-L-R1:
n = 0-15
n = 0-3
R' = R" =
Rs = H, OCH3, F, CN, CH3, NO2, CF3, OCF3



1001

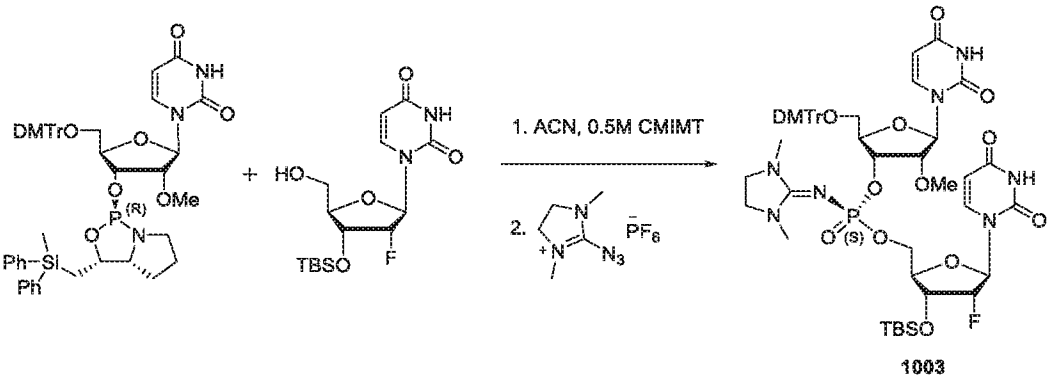
[001458] **General experimental procedure (A)**: To a stirred solution of stereorandom amidite (474 mg, 0.624 mmol, 1.5 equiv., pre-dried by co-evaporation with dry acetonitrile and kept it under vacuum for minimum 12 h) and TBS protected alcohol (150 mg, 0.41 mmol, pre-dried by co-evaporation with dry acetonitrile and kept it under vacuum for minimum 12 h) in dry acetonitrile (5.2 mL) was added 5-(Ethylthio)-*1H*-tetrazole (ETT, 2.08 ml, 0.6M, 3 equiv.) under argon atmosphere at room temperature. Resulting reaction mixture was stirred for 5 mins then monitored by LCMS and then a solution of 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (356 mg, 1.24 mmol, 3 equiv.) in acetonitrile (1 mL) was added. Once the reaction was completed (after ~ 5mins, monitored by LCMS) then triethylamine (0.17 mL, 1.24 mmol, 3 equiv.) was added and monitored LCMS. Reaction mixture was concentrated under reduced pressure and then re-dissolved in dichloromethane (50 mL) washed with water (25 mL), saturated aq. Sodium bicarbonate (25 mL) and brine (25 mL) dried with magnesium sulfate. Solvent was removed under reduced pressure. The crude product was purified by silica gel column (80 g) using DCM (2% triethylamine) and MeOH as eluent. Product containing fractions collected and evaporated. Pale yellow solid **1001** obtained. Yield: 440 mg (89%). ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.34, -1.98. MS (ES) *m/z* calculated for $C_{51}H_{65}FN_7O_{14}PSi$ $[M]^+$ 1077.40, Observed: 1078.57 $[M+H]^+$.



1002

[001459] **General experimental procedure (B) for stereopure (Rp) dimer:** To a stirred solution of L (or) D-DPSE chiral amidite (1.87 g, 2.08 mmol, 1.5 equiv., pre-dried by co-evaporation with dry acetonitrile and kept it under vacuum for minimum 12 h) and TBS protected alcohol (500 mg, 1.38 mmol,

pre-dried by co-evaporation with dry acetonitrile and kept it under vacuum for minimum 12 h) in dry acetonitrile (18 mL) was added 2-(1H-imidazol-1-yl) acetonitrile trifluoromethanesulfonate (CMIMT, 5.54 mL, 0.5M, 2 equiv.) under argon atmosphere at room temperature. Resulting reaction mixture was stirred for 5 mins then monitored by LCMS and then a solution of 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (1.18 g, 4.16 mmol, 3 equiv.) in acetonitrile (2 mL) was added. Once the reaction was completed (after ~ 5mins, monitored by LCMS) then the reaction mixture was concentrated under reduced pressure and then redissolved in dichloromethane (70 mL) washed with water (40 mL), saturated aq. sodium bicarbonate (40 mL) and brine (40 mL) dried with magnesium sulfate. Solvent was removed under reduced pressure. The crude product was purified by silica gel column (120 g) using DCM (2% triethyl amine) and MeOH as eluent. Product containing fractions are evaporated. Pale yellow foamy solid **1002** was obtained. Yield: 710 mg (47%). ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.38. MS (ES) *m/z* calculated for $C_{51}H_{65}FN_7O_{14}PSi$ $[M]^+$ 1077.40, Observed: 1078.19 $[M+H]^+$.



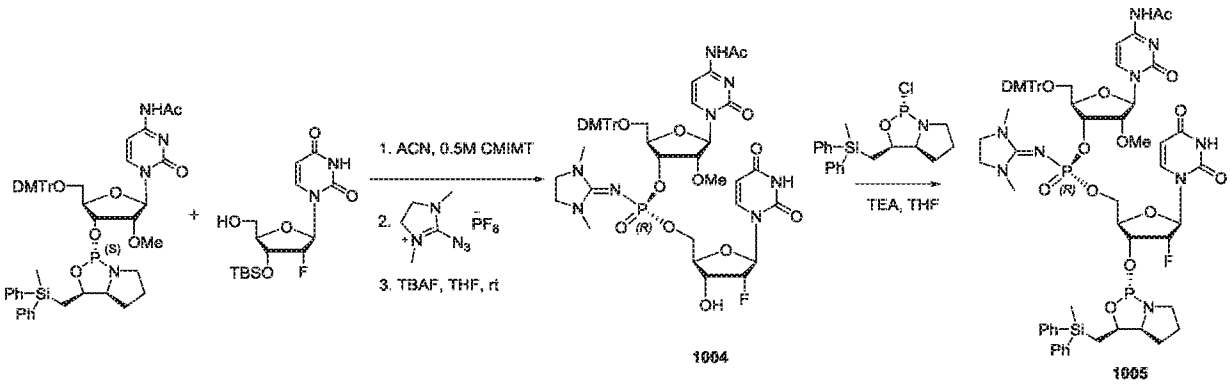
[001460] **Stereopure (Sp) dimer 1003:** The procedure B was followed as shown above. D-DPSE chiral amidite was used. Pale yellow foamy solid was obtained. Yield: 890 mg (59%). ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.93. MS (ES) *m/z* calculated for $C_{51}H_{65}FN_7O_{14}PSi$ $[M]^+$ 1077.40, Observed: 1078.00 $[M+H]^+$.

[001461] **General experimental procedure (C) for deprotection of TBS group:** To a stirred solution of TBS protected compound (9.04 mmol) in trihydrofluoride (THF) (70 mL), was added TBAF (1.0 M, 13.6 mmol) at rt. The reaction mixture was stirred at room temperature for 2-4 h. LCMS showed there was no starting material left, then concentrated followed by purification using ISCO-combiflash system (330 g gold rediSep high performance silica column pre-equilibrated 3 CV with 2% TEA in DCM) and DCM/Methanol/2% TEA as a gradient eluent. Product containing column fractions were pooled together and evaporated followed by drying under high vacuum afforded the pure product.

[001462] **General experimental procedure (D) for chiral amidites**: The TBS deprotected compound (2.5 mmol) was dried by co-evaporation with 80 mL of anhydrous toluene (30 mL x 2) at 35 °C and dried under at high vacuum for overnight. Then dried it was dissolved in dry THF (30 mL),

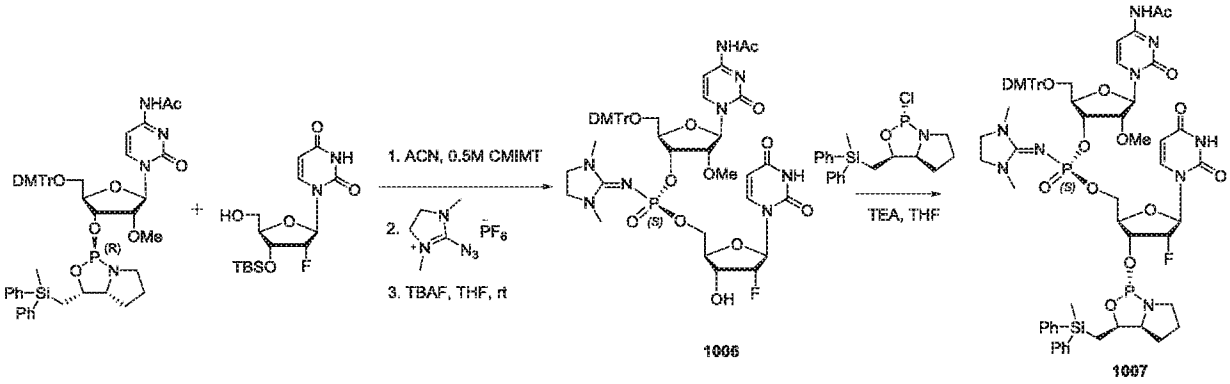
followed by the addition of triethylamine (17.3 mmol) then the reaction mixture was cooled to -65 °C [for Guanine flavors: TMS-Cl, 2.5 mmol was added at -65 °C, for non-Guanine flavors no TMS-Cl was added]. The THF solution of [(1R,3S,3aS)-1-chloro-3-((methyldiphenylsilyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (or) (1S,3R,3aR)-1-chloro-3-((methyldiphenylsilyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (1.8 equiv.) was added through syringe to the above reaction mixture over 2 min then gradually warmed to room temperature. After 20-30 min, at rt, TLC as well as LCMS indicated starting material was converted to product (reaction time: 1 h). Then the reaction mixture was filtered under argon using air free filter tube, washed with THF and dried under rotary evaporation at 26 °C afforded crude solid material, which was purified by ISCO-combiflash system (40 g gold rediSep high performance silica column (pre-equilibrated 3 CV with CH_3CN/5% TEA then 3 CV with DCM/5% TEA) using DCM/CH_3CN/5% TEA as a solvent (compound eluted at 10-40 DCM/CH_3CN/5% TEA). After evaporation of column fractions pooled together was dried under high vacuum afforded white solid to give isolated yield.

[001463] ^{31}P NMR (internal standard of Phosphoric acid at δ 0.0): 1001: -1.34 and -1.98. 1002: -1.93. 1003: -1.38. ^{1}H NMR of 1001, 1002, and 1003 demonstrated different chemical shifts for multiple hydrogens of the diastereomers. LCMS showed different retention times for the two diastereomers as well. Under one condition, the following retention times were observed: 1.90 and 2.15 for 1001, 1.92 for one diastereomer, and 2.17 for the other.



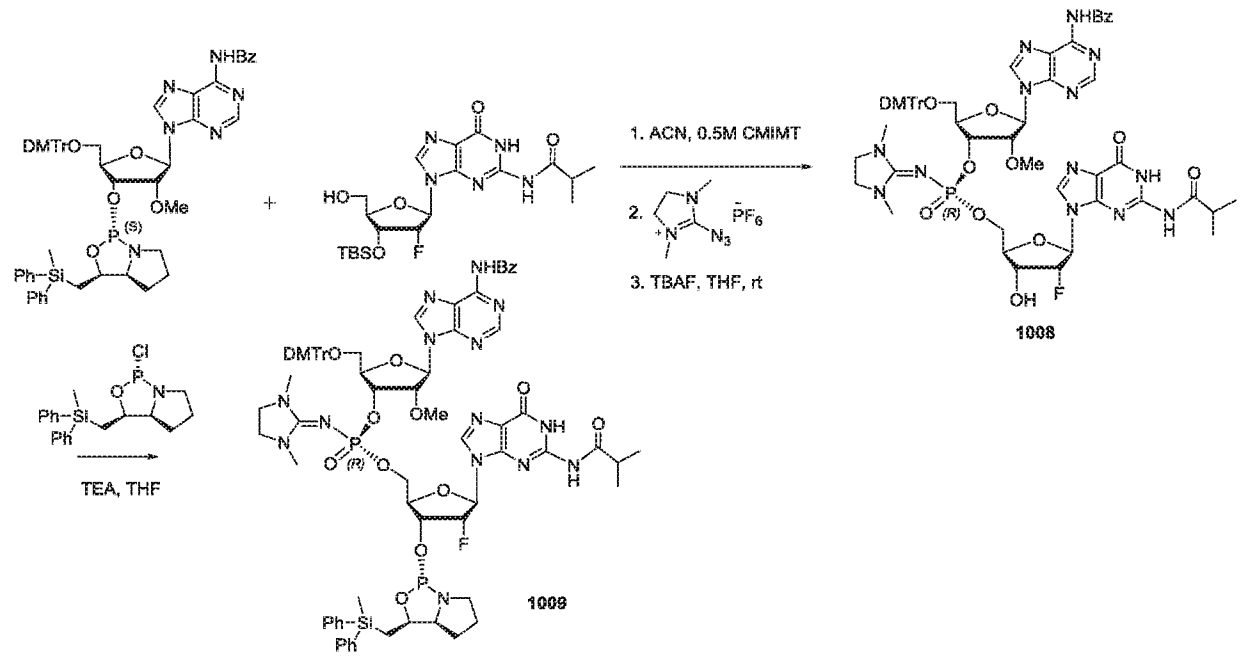
[001464] Compound **1004**: Procedures **B** and **C** followed, Off-white foamy solid, Yield: (36%). ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.23. MS (ES) *m/z* calculated for $C_{47}H_{54}FN_8O_{14}P$ $[M]^+$ 1004.34, Observed: 1043.21 $[M + K]^+$.

[001465] Compound **1005**: Procedure **D** used, Off-white foamy solid, Yield: (81%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 154.43, -2.52. MS (ES) *m/z* calculated for $C_{66}H_{76}FN_9O_{15}P_2Si$ $[M]^+$ 1343.46, Observed: 1344.85 $[M + H]^+$.



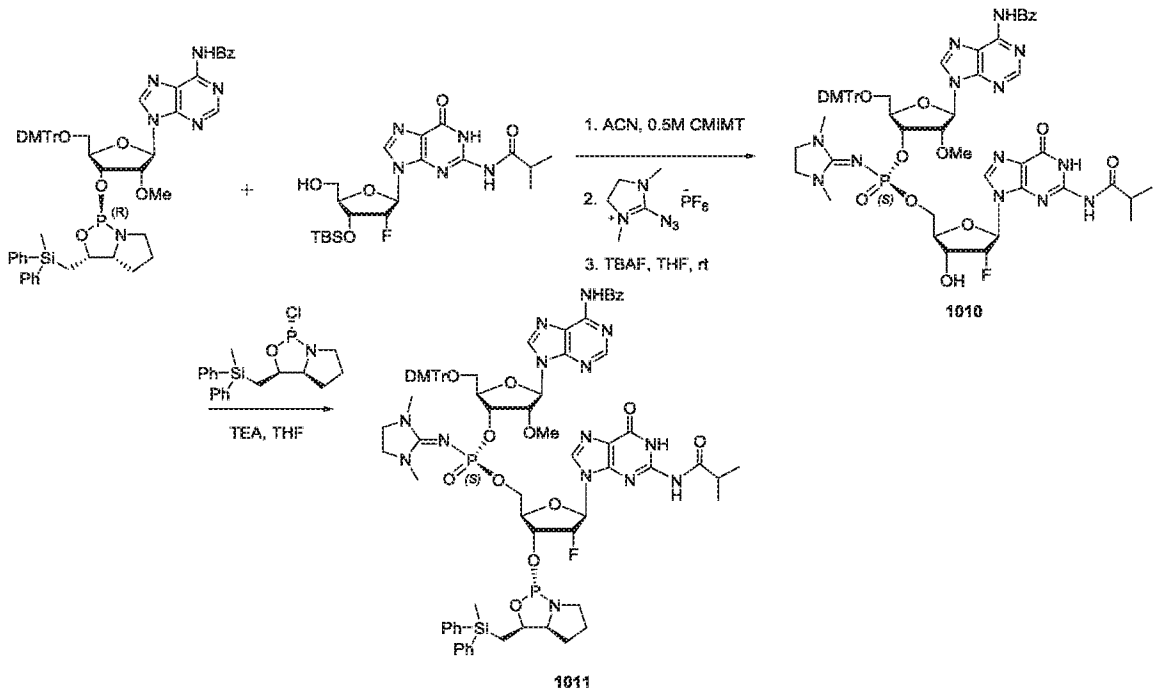
[001466] Compound **1006**: Procedures **B**, and **C** followed, Off-white foamy solid, Yield: (47%). ^{31}P NMR (162 MHz, $CDCl_3$) δ -2.54. MS (ES) *m/z* calculated for $C_{47}H_{54}FN_8O_{14}P$ $[M]^+$ 1004.34, Observed: 1043.12 $[M + K]^+$.

[001467] Compound **1007**: Procedure **D** used, Off-white foamy solid, Yield: (81%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 153.55, -2.20. MS (ES) *m/z* calculated for $C_{66}H_{76}FN_9O_{15}P_2Si$ $[M]^+$ 1343.46, Observed: 1344.75 $[M + H]^+$.



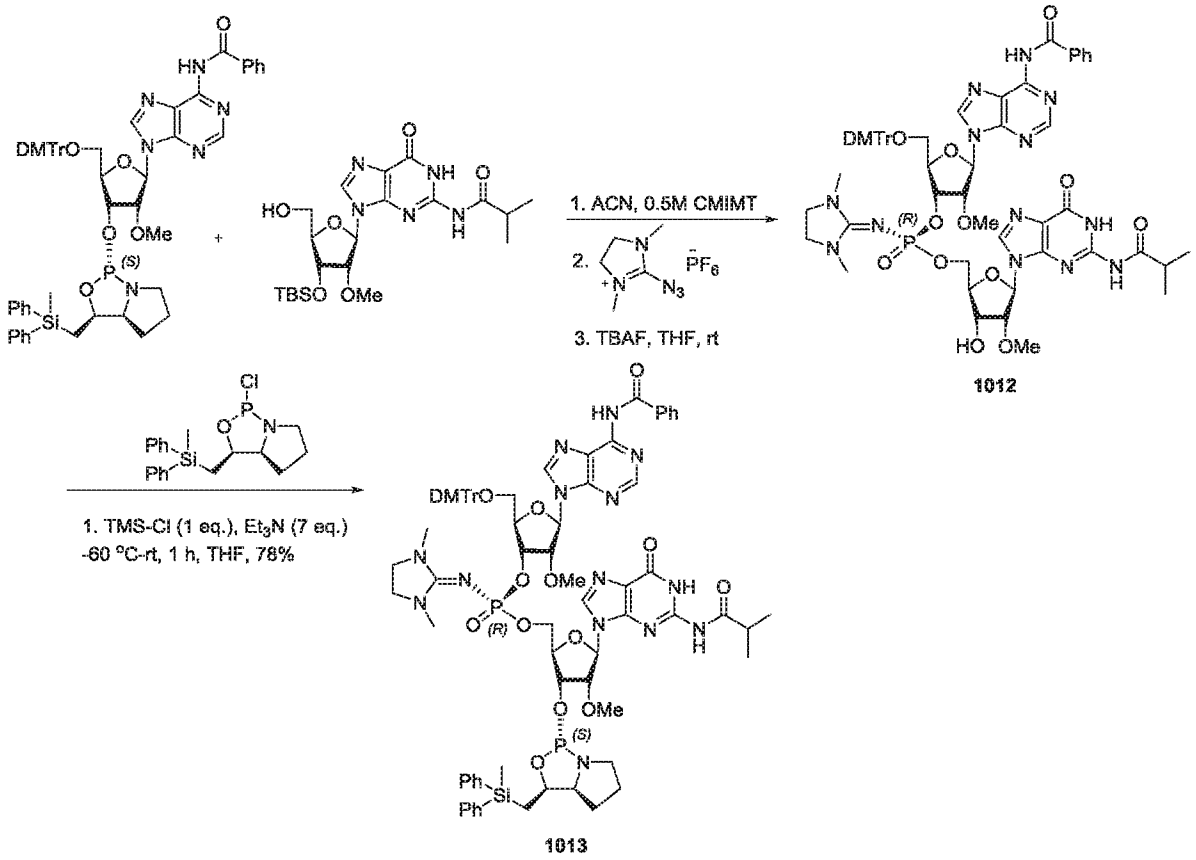
[001468] Compound **1008**: Procedures **B** and **C** followed, Off-white foamy solid, Yield: (36%). ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.38. MS (ES) *m/z* calculated for $C_{58}H_{63}FN_{13}O_{13}P$ $[M]^+$ 1199.43, Observed: 1200.76 $[M + H]^+$.

[001469] Compound **1009**: Procedure **D** used, Off-white foamy solid, Yield: (60%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 157.26, -2.86. MS (ES) *m/z* calculated for $C_{77}H_{85}FN_{14}O_{14}P_2Si$ $[M]^+$ 1538.55, Observed: 1539.93 $[M + H]^+$.



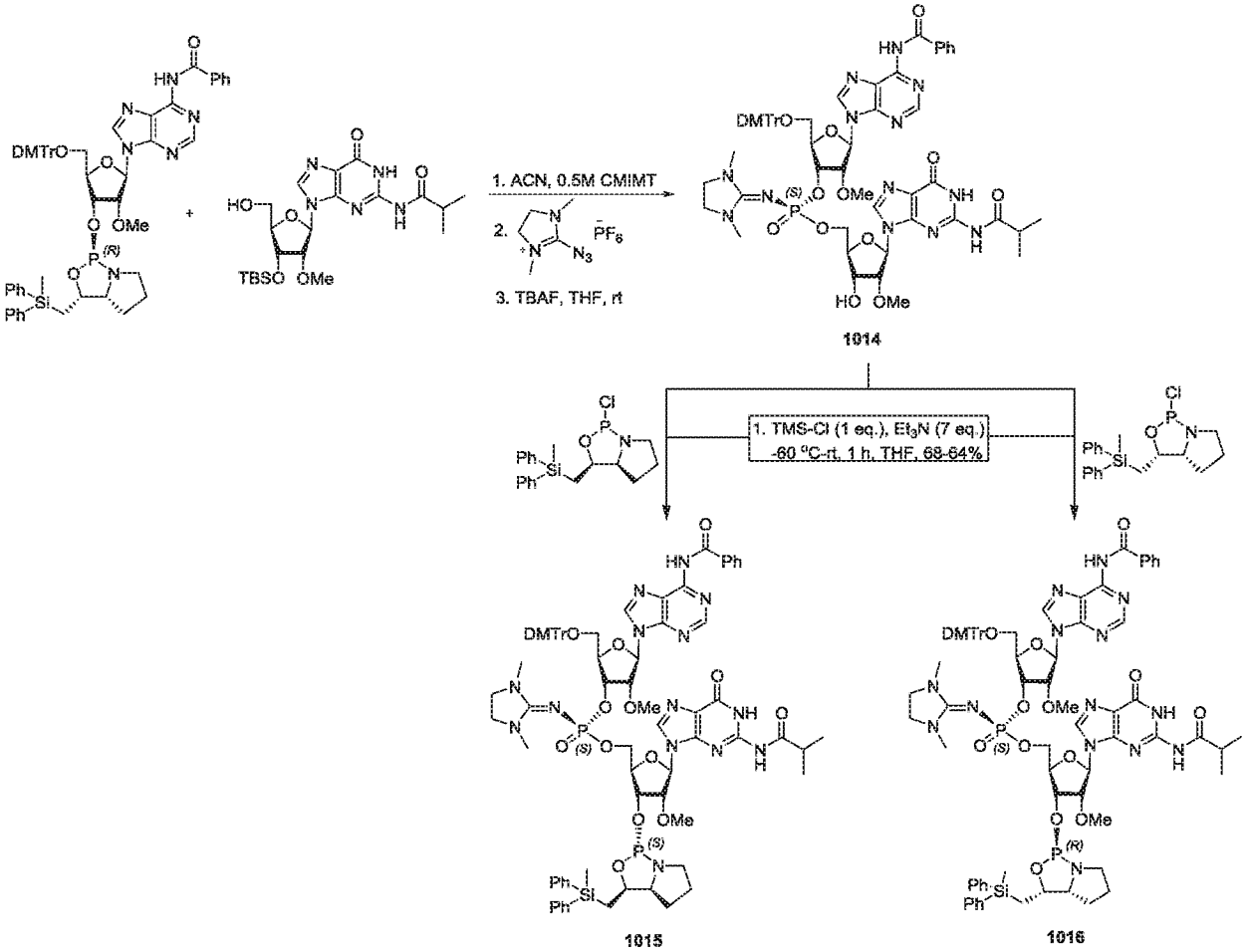
[001470] Compound **1010**: Procedures **B** and **C** followed, Off-white foamy solid, Yield: (36%). ^{31}P NMR (162 MHz, $CDCl_3$) δ -2.82. MS (ES) *m/z* calculated for $C_{58}H_{63}FN_{13}O_{13}P$ $[M]^+$ 1199.43, Observed: 1200.19 $[M + H]^+$.

[001471] Compound **1011**: Procedure **D** used, Off-white foamy solid, Yield: (63%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 159.56, -2.99. MS (ES) *m/z* calculated for $C_{77}H_{85}FN_{14}O_{14}P_2Si$ $[M]^+$ 1538.55, Observed: 1539.83 $[M + H]^+$.



[001472] Compound **1012**: Procedures B and C followed, Off-white foamy solid, Yield: (36%). $[\alpha]_D^{23}$ = - 25.74 (*c* 1.06, $CHCl_3$). ^{31}P NMR (162 MHz, Chloroform-*d*) δ -1.83. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.14 (s, 1H), 11.28 (s, 1H), 9.15 (s, 1H), 8.56 (s, 1H), 8.25 – 7.94 (m, 2H), 7.90 (s, 1H), 7.72 – 7.48 (m, 2H), 7.44 (dd, *J* = 8.2, 6.7 Hz, 2H), 7.35 – 7.26 (m, 2H), 7.24 – 7.02 (m, 8H), 6.81 – 6.56 (m, 4H), 6.04 (d, *J* = 5.2 Hz, 1H), 5.67 (d, *J* = 5.5 Hz, 1H), 4.83 (dt, *J* = 8.6, 4.4 Hz, 1H), 4.71 – 4.54 (m, 2H), 4.49 (dt, *J* = 14.2, 4.8 Hz, 2H), 4.35 (ddt, *J* = 11.0, 5.1, 3.2 Hz, 1H), 4.28 – 4.09 (m, 2H), 3.68 (s, 6H), 3.37 (d, *J* = 3.3 Hz, 7H), 3.33 – 3.17 (m, 5H), 2.82 (s, 5H), 2.74 – 2.60 (m, 1H), 1.92 (s, 2H), 1.72 – 1.50 (m, 1H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H). MS (ES) *m/z* calculated for $C_{59}H_{66}N_{13}O_{14}P$ 1211.45 $[M]^+$, Observed: 1212.42 $[M + H]^+$.

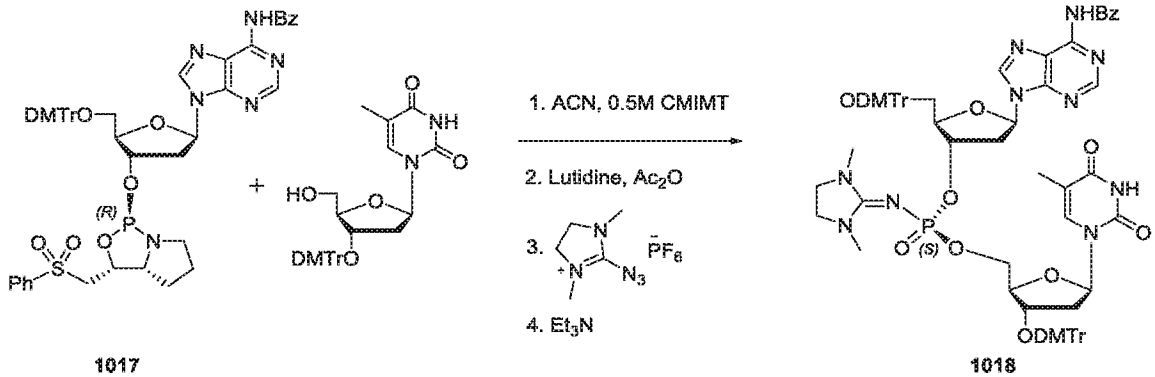
[001473] Compound **1013**: Procedure **D** used, Off-white foamy solid, Yield: (78%). $[\alpha]_D^{23}$ = -15.48 (*c* 0.96, $CHCl_3$). ^{31}P NMR (162 MHz, Chloroform-*d*) δ 159.42, -2.47. MS (ES) *m/z* calculated for $C_{78}H_{88}N_{14}O_{15}P_2Si$ 1550.57 $[M]^+$, Observed: 1551.96 $[M + H]^+$.



[001474] Compound **1014**: Procedures B and C followed, Off-white foamy solid, Yield: (30%). $[\alpha]_D^{23}$ = - 21.45 (*c* 0.55, $CHCl_3$). MS (ES) *m/z* calculated for $C_{59}H_{66}N_{13}O_{14}P$ 1211.45 $[M]^+$, Observed: 1212.80 $[M+H]^+$.

[001475] Compound **1015**: Procedure **D** used, Off-white foamy solid, Yield: (68%). $[\alpha]_D^{23}$ = - 15.63 (*c* 1.44, $CHCl_3$). MS (ES) *m/z* Calculated for $C_{78}H_{88}N_{14}O_{15}P_2Si$ 1550.57 $[M]^+$, Observed: 1551.77 $[M+H]^+$.

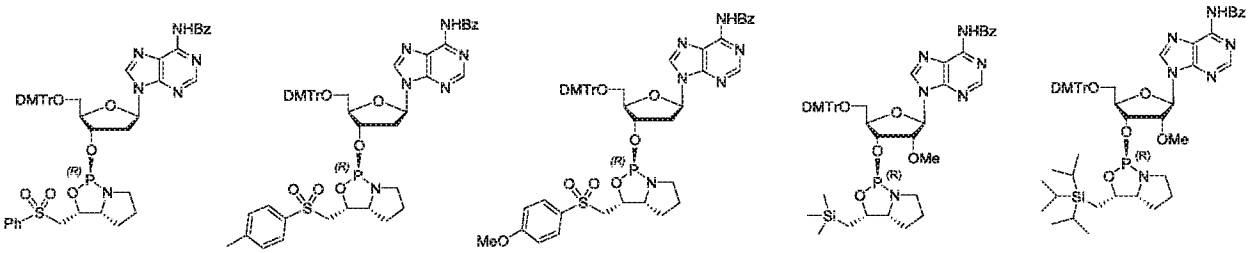
[001476] Compound **1016**: Procedure **D** used, Off-white foamy solid, Yield: (64%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 156.64, -2.67. MS (ES) *m/z* Calculated for $C_{78}H_{88}N_{14}O_{15}P_2Si$ 1550.57 $[M]^+$, Observed: 1551.77 $[M+H]^+$.



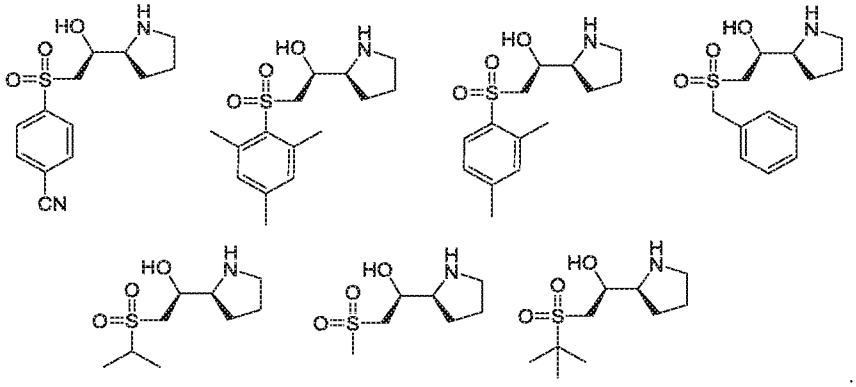
1017 1018

[001477] **General experimental procedure (E) for stereopure dimer using sulfonyl amidite**: To a stirred solution of steropure sulfonyl amidite **1017** (259 mg, 0.275 mmol, 1.5 equiv) and TBS protected alcohol (100 mg, 0.18 mmol) in dry acetonitrile (2 mL) was added 2-(1H-imidazol-1-yl) acetonitrile trifluoromethanesulfonate (CMIMT, 0.73 mL, 0.36 mmol, 0.5M, 2 equiv.) under argon atmosphere at room temperature. Resulting reaction mixture was stirred for 5 mins and monitored by LCMS then a mixture of acetic anhydride (2M in ACN, 0.18 ml, 0.36 mmol, 2 equ) and lutidine (2M in ACN, 0.18 ml, 0.36 mmol, 2 equ) was added then stirred for ~5 mins then a solution of 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (104.7 mg, 0.367 mmol, 2 equiv.) in acetonitrile (1 mL) was added. Once the reaction was completed (after ~ 5mins, monitored by LCMS) then triethylamine (0.13 mL, 0.91 mmol, 5 equiv.) was added and monitored by LCMS. Once the reaction was completed, it was concentrated under reduced pressure and then re-dissolved in dichloromethane (50 mL) washed with water (25 mL), saturated aq. Sodium bicarbonate (25 mL) and brine (25 mL) dried with magnesium sulfate. Solvent was removed under reduced pressure. The crude product was purified by silica gel column (80 g) using DCM (2% triethylamine) and MeOH as eluent. Product containing fractions collected and evaporated. Off white solid **1018** obtained. Yield: 204 mg (82%). ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.87. MS (ES) *m/z* calculated for $C_{74}H_{75}FN_{10}O_{14}P$ $[M]^+$ 1359.44, Observed: 1360.39 $[M + H]^+$.

[001478] Additional phosphoramidites that may be utilized for synthesis include:

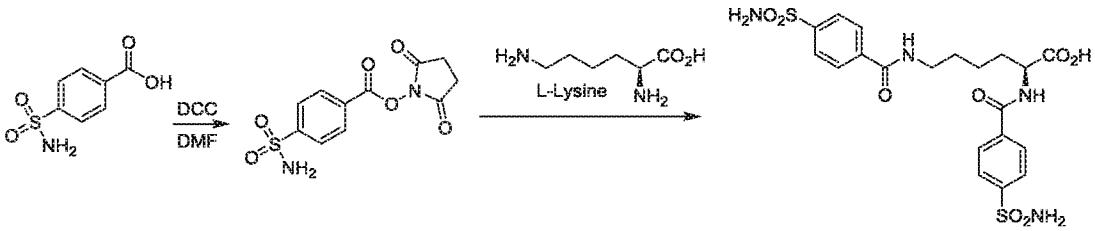


. Additional useful chiral auxiliaries include:



. Other phosphoramidites and chiral auxiliaries, such as those described in US 9695211, US 9605019, US 9598458, US 2013/0178612, US 20150211006, US 20170037399, WO 2017/015555, WO 2017/062862, WO 2017/160741, WO 2017/192664, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/223056, and/or WO 2018/237194, the chiral auxiliaries and phosphoramidites of each of which is incorporated by reference.

Example 4C. Synthesis of N^2,N^6-bis(4-sulfamoylbenzoyl)-L-lysine



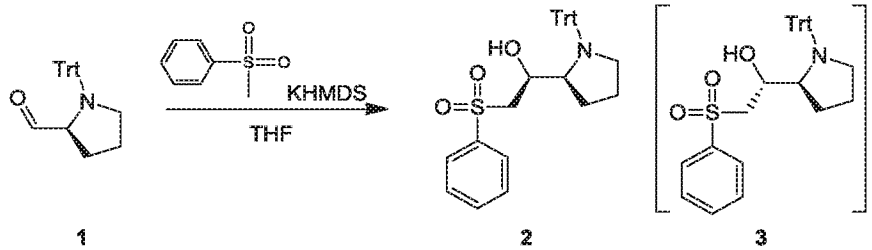
[001479] Step 1. To a solution of 4-sulfamoylbenzoic acid (10.00 g, 49.70 mmol) and HOSu (6.29 g, 54.67 mmol) in DMF (300 mL) was added DCC (10.25 g, 49.70 mmol) at 0°C. The mixture was stirred at 0°C for 16 hours. LCMS showed compound was consumed. The resulting mixture was combined and workup with another batch of crude (1 g scale). The white suspension of N,N'-dicyclohexylurea (DCU) was filtered and removed white solid. The filtrate was concentrated to give an oil. This crude product was washed with hot 2-propanol (50 mL*3) to afford an off-white solid. Compound (2,5-dioxopyrrolidin-1-yl) 4-sulfamoylbenzoate (11.80 g, 38.66 mmol, 77.78% yield, 97.713% purity) (yield from conversion rate for 10 g batch) was obtained as a white solid. Compound (2,5-dioxopyrrolidin-1-yl) 4-sulfamoylbenzoate (13 g) was totally obtained as a white solid for two batches of reactions. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.30 (d, *J*=8.4 Hz, 2H), 8.08 (d, *J*=8.3 Hz, 2H), 7.70 (s, 2H), 2.96 - 2.87 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 170.62, 161.47, 150.32, 131.40, 127.65, 127.18, 26.04; HPLC purity: 97.71%.

[001480] Step 2. To a solution of (2,5-dioxopyrrolidin-1-yl) 4-sulfamoylbenzoate (5.00 g, 16.76 mmol) and (2S)-2,6-diaminohexanoic acid (1.23 g, 8.38 mmol) in H_2O (50 mL) and DMF (50.00 mL)

was added $NaHCO_3$ (2.11 g, 25.14 mmol). The mixture was stirred at 15°C for 16 hours. LCMS showed MS with desired compound was detected. The mixture concentrated under reduced pressure to give a crude (6 g). The crude (3.5 g) was purified by prep-HPLC(column: Phenomenex luna C18 250*50mm*10 um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-30%,20min). N^2,N^6-bis(4-sulfamoylbenzoyl)-L-lysine (1.40 g, 30.40% yield, 93.268% purity) was obtained as a white solid and 2.5 g crude as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.64 (br s, 1H), 8.80 (br d, *J*=7.5 Hz, 1H), 8.65 (br t, *J*=5.3 Hz, 1H), 8.04 (d, *J*=8.2 Hz, 2H), 7.99 - 7.95 (m, 2H), 7.95 - 7.84 (m, 4H), 7.48 (br d, *J*=11.6 Hz, 4H), 4.44 - 4.32 (m, 1H), 3.28 (br d, *J*=6.1 Hz, 2H), 1.94 - 1.71 (m, 3H), 1.63 - 1.36 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 174.04, 166.08, 165.58, 146.89, 146.57, 138.05, 137.36, 128.60, 128.26, 126.05, 53.21, 30.77, 29.11, 23.84. LCMS (M-H$^+$): 511.0 (M+H)$^+$; HPLC purity: 93.268%.

Example 4D. Example technologies for chirally controlled oligonucleotide preparation - example useful chiral auxiliaries

[001481] Among other things, the present disclosure provides technologies (e.g., chiral auxiliaries, phosphoramidites, cycles, conditions, reagents, etc.) that are useful for preparing chirally controlled internucleotidic linkages. In some embodiments, provided technologies are particularly useful for preparing certain internucleotidic linkages, e.g., non-negatively charged internucleotidic linkages, neutral internucleotidic linkages, etc., comprising P–N=, wherein P is the linkage. In some embodiments, the linkage phosphorus is trivalent. In some embodiments, the linkage phosphorus is pentavalent. In some embodiments, such internucleotidic linkages have the structure of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof. Certain example technologies (chiral auxiliaries and their preparations, phosphoramidites and their preparations, cycles, conditions, reagents, etc.) are described in the Examples herein. Among other things, such chiral auxiliaries provide milder reaction conditions, higher functional group compatibility, alternative deprotection and/or cleavage conditions, higher crude and/or purified yields, higher crude purity, higher product purity, and/or higher (or substantially the same or comparable) stereoselectivity when compared to a reference chiral auxiliary (e.g., of formula O, P, Q, R or DPSE).



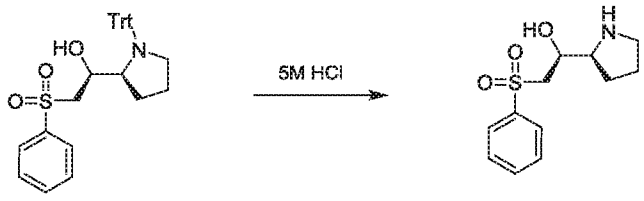
1 2 3

[001482] Two batches in parallel: To a solution of methylsulfonylbenzene (102.93 g, 658.96 mmol, 1.5 *eq.*) in THF (600 mL) was added KHMDS (1 M, 658.96 mL, 1.5 *eq.*) dropwise at -70 °C, and warmed

to -30 °C slowly over 30 min. The mixture was then cooled to -70 °C. A solution of compound **1** (150 g, 439.31 mmol, 1 *eq.*) in THF (400 mL) was added dropwise at -70 °C. The mixture was stirred at -70°C for 3 hr. TLC (Petroleum ether: Ethyl acetate = 3:1, Rf = 0.1) indicated compound **1** was consumed completely and one major new spot with larger polarity was detected. Combined 2 batches. The reaction mixture was quenched by added to the sat. NH_4Cl (aq. 1000 mL), and then extracted with EtOAc (1000 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 1000 mL solution. Then added the MeOH (600 mL), concentrated under reduced pressure to give 1000 mL solution, then filtered the residue and washed with MeOH (150 mL); the residue was dissolved with THF (1000 mL) and MeOH (600 mL), then concentrated under reduced pressure to give 1000 mL solution. Then filtered to give a residue and washed with MeOH (150 mL). And repeat one more time. Compound **2** (248 g, crude) was obtained as a white solid. And the combined mother solution was concentrated under reduced pressure to give compound **3** (200 g, crude) as yellow oil.

[001483] *Compound 2*: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.80 (d, *J* =7.5 Hz, 2H), 7.74 - 7.66 (m, 1H), 7.61 - 7.53 (m, 2H), 7.47 (d, *J* = 7.5 Hz, 6H), 7.24 - 7.12 (m, 9H), 4.50 - 4.33 (m, 1H), 3.33 (s, 1H), 3.26 (ddd, *J* = 2.9, 5.2, 8.2 Hz, 1H), 3.23 - 3.10 (m, 2H), 3.05 - 2.91 (m, 2H), 1.59 - 1.48 (m, 1H), 1.38 - 1.23 (m, 1H), 1.19 - 1.01 (m, 1H), 0.31 - 0.12 (m, 1H).

[001484] *Preparation of compound WV-CA-108.*



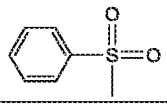
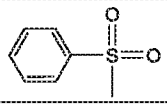
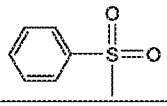
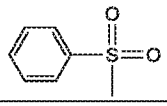
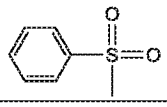
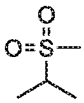
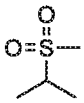
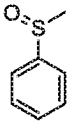
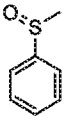
2 **WV-CA-108**

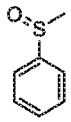
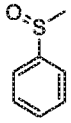
[001485] To a solution of compound **2** (248 g, 498.35 mmol, 1 *eq.*) in THF (1 L) was added HCl (5 M, 996.69 mL, 10 *eq.*). The mixture was stirred at 15 °C for 1 hr. TLC (Petroleum ether: Ethyl acetate = 3:1, Rf = 0.03) indicated compound **2** was consumed completely and one major new spot with larger polarity was detected. The resulting mixture was washed with MTBE (500 mL x 3). The combined organic layers were back-extracted with water (100 mL). The combined aqueous layer was adjusted to pH 12 with 5M NaOH aq. and extracted with DCM (500 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to afford a white solid. **WV-CA-108** (122.6 g, crude) was obtained as a white solid.

[001486] ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.95 (d, *J* = 7.5 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 2H), 4.03 (ddd, *J* = 2.6, 5.3, 8.3 Hz, 1H), 3.37 - 3.23 (m, 2H), 3.20 - 3.14 (m, 1H), 2.91 - 2.75 (m, 3H), 2.69 (br s, 1H), 1.79 - 1.54 (m, 5H); ^{13}C NMR (101 MHz, CHLOROFORM-d) δ

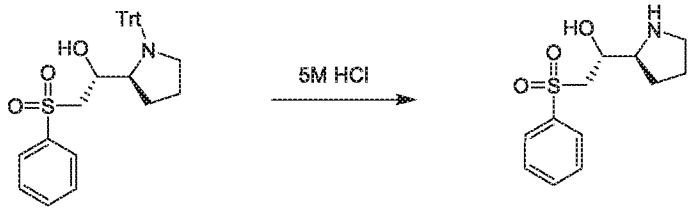
= 139.58, 133.83, 129.28, 127.98, 67.90, 61.71, 59.99, 46.88, 25.98, 25.84; LCMS $[M + H]^+$: 256.1. LCMS purity: 100%. SFC 100% purity.

[001487] Among other things, the present disclosure encompasses the recognition that bases utilized in reactions (e.g., from compound 1 to compound 2) can impact stereoselectivity of such reactions. Certain example results are described below:

S. No	Aldehyde	Nucleophile	Base	Chiral Auxiliary (Diastereoselectivity, cis/trans)
1	1		n-BuLi	WV-CA-108 (87:13)
2	1		LiHMDS	WV-CA-108 (1.85:1)
3	1		LDA	WV-CA-108 (1.85:1)
4	1		KHMDS	WV-CA-108 (10:1)
5	1		t-BuOK	WV-CA-108 (10:1)
6	4		n-BuLi	WV-CA-242 (2:1)
7	4		KHMDS	WV-CA-242 (8:1)
8	4		n-BuLi	WV-CA-243 (2:1)
9	4		KHMDS	WV-CA-243 (8:1)
10	4		n-BuLi	WV-CA-347 (5.5:1)
11	4		KHMDS	WV-CA-347 (10:1)
12	4		KHMDS	WV-CA-247 (43:57)
13	4		n-BuLi	WV-CA-247 (~1:1)

14	4		LiHMDS	WV-CA-247 (~ 39:51)
15	4		NaHMDS	WV-CA-247 (~ 40:66)

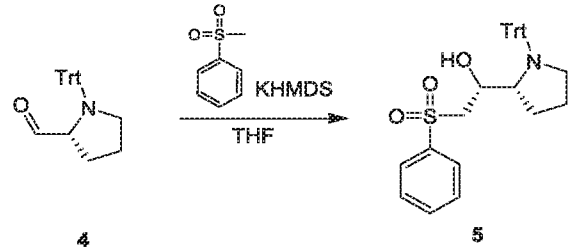
[001488] *Preparation of compound WV-CA-237.*



3 **WV-CA-237**

[001489] To a solution of compound **3** (400.00 g, 803.78 mmol) in THF (1.5 L) was added HCl (5 M, 1.61 L). The mixture was stirred at 15 °C for 2 hr. TLC indicated compound **3** was consumed completely and one major new spot with larger polarity was detected. The resulting mixture was washed with MTBE (500 mL x 3). The combined aqueous layer was adjusted to pH 12 with 5M NaOH aq. and extracted with DCM (500 mL x 1) and EtOAc (1000 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to afford as a brown solid. **WV-CA-237** (100 g, crude) was obtained as a brown solid.

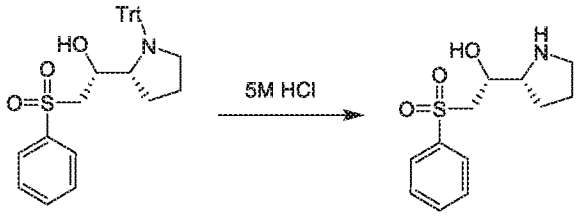
[001490] The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 3/1 to Ethyl acetate: Methanol = 1: 2) to give 24 g crude. Then the 4 g residue was purified by prep-HPLC (column: Phenomenex luna C18 250 x 50 mm x 10 um; mobile phase: [water (0.05% HCl)-ACN]; B%: 2% → 20%, 15 min) to give desired compound (2.68 g, yield 65%,) as a white solid. **WV-CA-237** (2.68 g) was obtained as a white solid. **WV-CA-237** : ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.98 - 7.88 (m, 2H), 7.68 - 7.61 (m, 1H), 7.60 - 7.51 (m, 2H), 4.04 (dt, *J* = 2.4, 5.6 Hz, 1H), 3.85 (ddd, *J* = 3.1, 5.6, 8.4 Hz, 1H), 3.37 - 3.09 (m, 3H), 2.95 - 2.77 (m, 3H), 1.89 - 1.53 (m, 4H), 1.53 - 1.39 (m, 1H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ = 139.89, 133.81, 133.70, 129.26, 129.16, 128.05, 127.96, 68.20, 61.77, 61.61, 61.01, 60.05, 46.67, 28.02, 26.24, 25.93; LCMS $[M + H]^+$:256.1. LCMS purity: 80.0%. SFC dr = 77.3 : 22.7.



4 5

[001491] To a solution of compound **4** (140 g, 410.02 mmol) in THF (1400 mL) was added methylsulfonylbenzene (96.07 g, 615.03 mmol), then added KHMDS (1 M, 615.03 mL) in 0.5 hr. The mixture was stirred at -70 ~ -40 °C for 3 hr. TLC indicated compound **4** was consumed and one new spot formed. The reaction mixture was quenched by addition sat. NH_4Cl aq. 3000 mL at 0 °C, and then diluted with EtOAc (3000 mL) and extracted with EtOAc (2000 mL x 3). Dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. To the crude was added THF (1000 mL) and MeOH (1500 mL), concentrated under reduced pressure at 45 °C until about 1000 mL residue remained, filtered the solid. Repeat 3 times. Compound **5** (590 g, 72.29% yield) was obtained as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.81 (d, *J* = 7.5 Hz, 2H), 7.75 - 7.65 (m, 1H), 7.62 - 7.53 (m, 2H), 7.48 (br d, *J* = 7.2Hz, 6H), 7.25 - 7.11 (m, 9H), 4.50 - 4.37 (m, 1H), 3.31 - 3.11 (m, 3H), 3.04 - 2.87 (m, 2H), 1.60 - 1.48 (m, 1H), 1.39 - 1.24 (m,1H), 1.11 (dtd, *J* = 4.5, 8.8, 12.8 Hz, 1H), 0.32 - 0.12 (m, 1H).

[001492] *Preparation of compound WV-CA-236.*

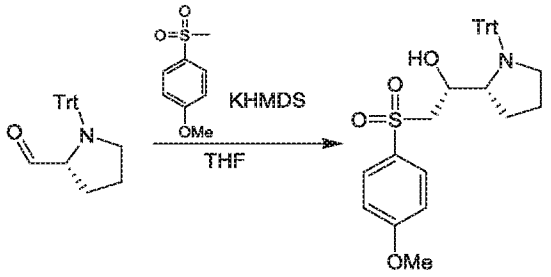


5 WV-CA-236

[001493] To a solution of compound **5** (283 g, 568.68 mmol) in THF (1100 mL) was added HCl (5 M, 1.14 L). The mixture was stirred at 25 °C for 2 hr. TLC indicated compound **5** was consumed and two new spots formed. The reaction mixture was washed with MTBE (1000 mL x 3), then the aqueous phase was basified by addition NaOH (5M) until pH = 12 at 0°C, and then extracted with DCM (1000 mL x 3) to give a residue, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. Compound **WV-CA-236** (280 g, 1.10 mol, 96.42% yield) was obtained as a yellow solid.

[001494] The crude product was added HCl/ EtOAc (1400 mL, 4M) at 0 °C, 2 hr later, filtered the white solid and washed the solid with MeOH (1000 mL x 3). LCMS showed the solid contained another peak (MS = 297). Then the white solid was added H_2O (600 mL) and washed with DCM (300 mL x 3). The aqueous phase was added NaOH (5 M) until pH = 12. Then diluted with DCM (800 mL) and

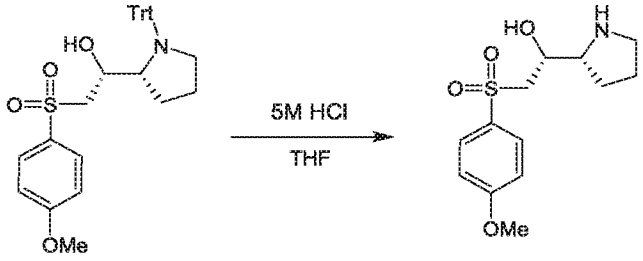
extracted with DCM (800 mL x 4). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the product. Compound **WV-CA-236** (280 g) was obtained as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 8.01 - 7.89 (m, 2H), 7.69 - 7.62 (m, 1H), 7.61 - 7.51 (m, 2H), 4.05 (ddd, *J* = 2.8, 5.2,8.4 Hz, 1H), 3.38 - 3.22 (m, 2H), 3.21 - 3.08 (m, 1H), 2.95 - 2.72 (m, 4H), 1.85 - 1.51 (m, 4H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ = 139.75, 133.76, 129.25, 127.94, 67.57, 61.90, 60.16, 46.86, 25.86. LCMS [M + H]$^+$: 256. LCMS purity: 95.94. SFC purity: 99.86%.



4 **6**

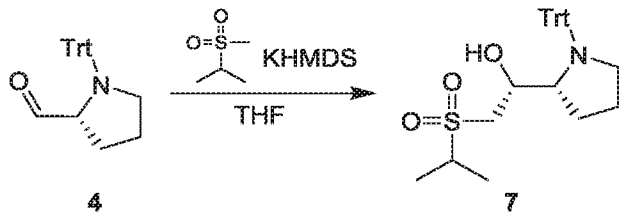
[001495] To a solution of 1-methoxy-4-methylsulfonyl-benzene (36.82 g, 197.69 mmol) in THF (500 mL) was added KHMDS (1 M, 197.69 mL) at -70 °C, 0.5 hr later added compound **4** (45 g, 131.79 mmol) in THF (400 mL) at -70 °C. The mixture was stirred at -70 → -30 °C for 4 hr, and then the mixture was added with KHMDS (1M, 131.79 mL) at -70 °C. The mixture was stirred at -70°C for 1 hr. TLC indicated compound **4** was remained, and two new spots were detected. The reaction mixture was quenched by sat. NH_4Cl (aq. 300 mL), and then extracted with EtOAc (500 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was dissolved in THF (800 mL) and MeOH (500 mL), and then concentrated under reduced pressure until 200 mL solvent left. The mixture was added with MeOH (500 mL) and concentrated under reduced pressure to 200 mL solvent left and solid appeared. The solid was filtered to give product. Repeated the trituration 2 times. Compound **6** (49.8 g, 71.61% yield) was obtained as a brown solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.73 - 7.66 (m, 2H), 7.46 (d, *J* =7.5 Hz, 6H), 7.24 - 7.11 (m, 9H), 7.04 - 6.96 (m, 2H), 4.37 (td, *J* =3.1, 8.3 Hz, 1H), 3.94 - 3.88 (m, 3H), 3.36 (s, 1H), 3.26 - 3.10 (m, 3H), 3.00 - 2.89 (m, 2H), 1.58 - 1.45 (m, 1H), 1.37 - 1.23 (m, 1H), 1.15 - 1.00 (m, 1H), 0.26 - 0.10 (m, 1H).

[001496] ***Preparation of compound WV-CA-241.***



6 WV-CA-241

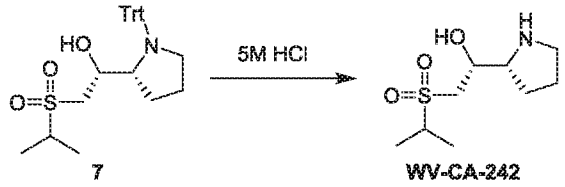
[001497] To a solution of compound **6** (50 g, 94.76 mmol) in THF (250 mL) was added HCl (5 M, 189.51 mL). The mixture was stirred at 20 °C for 3 hr. TLC indicated compound **6** was consumed and two new spots formed. The reaction mixture was extracted with MTBE (200 mL x 3) and the MTBE phases were discarded. And then the water phase was added with 5 M NaOH (aq.) to pH = 9 and extracted with DCM (200 mL x 5). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the product. **WV-CA-241** (27 g, 98.10% yield, LCMS purity: 98.24% purity) was obtained as a colorless oil. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.83 - 7.76 (m, 2H), 6.98 - 6.91 (m, 2H), 4.00 (ddd, *J* = 2.9, 5.0, 8.4 Hz, 1H), 3.81 (s, 3H), 3.33 - 3.07 (m, 5H), 2.87 - 2.75 (m, 2H), 1.74 - 1.49 (m, 4H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ = 163.79, 131.10, 130.21, 114.44, 67.66, 61.88, 60.25, 55.69, 46.85, 25.84, 25.81. LCMS $[M + H]^+$: 286.1. LCMS purity: 98.24%. SFC: dr = 0.18: 99.82. LCMS purity: 99.9%; SFC purity: 99.82%.



4 7

[001498] To a solution of 2-methylsulfonylpropane (32.21 g, 263.59 mmol) in THF (1200 mL) was added KHMDS (1 M, 263.59 mL) dropwise at -60 °C, and warm to -30 °C, slowly over 30 min. The mixture was then cooled to -70 °C. A solution of compound **4** (60 g, 175.72 mmol) in THF (300 mL) was added dropwise at -70°C → 60°C, over 30 min. The mixture was stirred at -70 °C → 60 °C for 2 hr. TLC showed compound **4** was consumed and new spot was detected. The reaction mixture was quenched with sat. aq. NH_4Cl (800 mL), and then extracted with EtOAc (1 L x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. Compound **7** (95 g, crude) was obtained as a yellow oil.

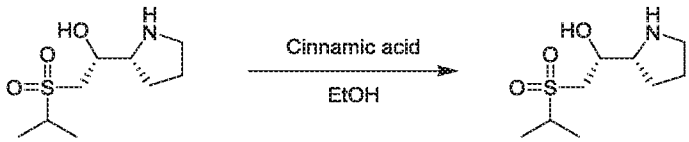
[001499] *Preparation of compound WV-CA-242.*



7 WV-CA-242

[001500] To a solution of compound 7 (95 g, 204.90 mmol) in THF (400 mL) was added HCl (5 M, 409.81 mL). The mixture was stirred at 0 → 25 °C for 2 hr. TLC indicated compound 7 was consumed and one new spot formed. The reaction mixture was washed with MTBE (300 mL x 3), then the aqueous phase was basified by addition NaOH (5 M) until pH = 12 at 0°C, and then extracted with DCM (300 mL x 3) to give a residue dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. Compound **WV-CA-242** (45 g, 99.23% yield) was obtained as a yellow oil. LCMS [M + H]$^+$: 222.0.

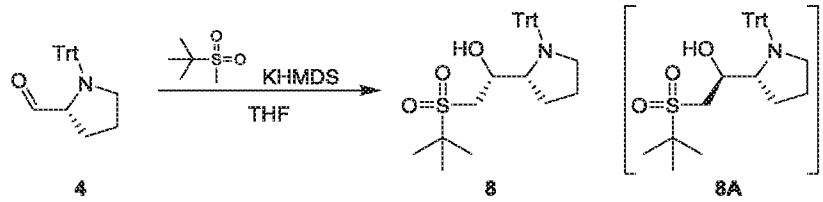
[001501] ***Purification of compound WV-CA-242.***



WV-CA-242 **WV-CA-242**

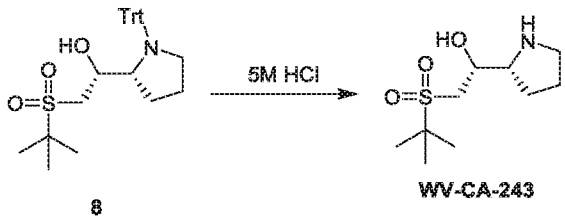
[001502] A solution of **WV-CA-242** (45 g, 203.33 mmol), (E)-3-phenylprop-2-enoic acid (30.12 g, 203.33 mmol) in EtOH (450 mL) was stirred at 80 °C for 1 hr. The reaction was concentrated in vacuo. The residue was dissolved in TBME (400 mL), and then stirred at 80°C for 15 min, and then to the mixture was added EtOH (20 mL) and MeCN (30 mL), and then the mixture was filtered, and the filtered cake was washed with TBME (30 mL x 2) and then did this for 8 times. The salt (35 g, crude) was obtained as a red solid.

[001503] To a solution of salt (34 g, 92.02 mmol) in H_2O (20 mL) was added aq. 5N NaOH (5 M, 36.81 mL). The mixture was stirred at 25°C for 10 min. The reaction was extracted with DCM (100 mL x 8), and then the organic phase was concentrated in vacuo. Compound **WV-CA-242** (18.9 g, 91.09% yield, LCMS purity: 98.16%) was obtained as an off-white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 4.13 (ddd, *J* = 2.1, 4.6, 9.5 Hz, 1H), 3.38 (spt, *J* = 6.9 Hz, 1H), 3.23 - 3.14 (m, 2H), 3.01 (dd, *J* = 2.1, 14.4 Hz, 1H), 2.95 - 2.91 (m, 2H), 1.83 - 1.60 (m, 4H), 1.40 (dd, *J* = 4.0, 6.8 Hz, 6H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ = 67.45, 61.71, 53.93, 53.42, 46.80, 25.86, 5.43, 16.03, 14.17. LCMS [M + H]$^+$: 222.1. LCMS purity: 98.17%.



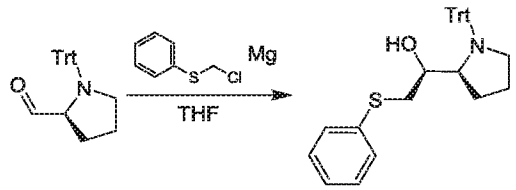
[001504] To a solution 2-methyl-2-(methylsulfonyl)propane (14.96 g, 109.83 mmol) in THF (150 mL) was added KHMDS (1 M, 109.83 mL) dropwise at -70 °C, and warm to -30 °C slowly over 30 min. The mixture was then cooled to -70 °C. A solution of compound **4** (25.00 g, 73.22 mmol) in THF (100 mL) was added dropwise at -70 °C. The mixture was stirred at -70 °C for 4 hr. TLC (Petroleum ether: Ethyl acetate = 3:1 Rf = 0.3) showed compound **4** was remained a little, and one major new spot with larger polarity was detected. The reaction mixture was quenched by added to the sat. NH_4Cl (aq., 100 mL), and then extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 30 mL solution. Then added MeOH (30 mL), concentrated under reduced pressure to give 30 mL solution, then filtered the residue and washed with MeOH (10 mL); the residue was dissolved with THF (30 mL) and MeOH (30 mL), and then concentrated under reduced pressure to give 30 mL solution. Then filtered to give a residue and washed with MeOH (10 mL). And repeat one more time to give 21 g white solid and 20 g brown oil. Compound **8** (21 g, crude) was obtained as a white solid, and Compound **8A** (20 g, crude) as a brown oil. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.56 (d, *J* = 7.5 Hz, 6H), 7.32 - 7.23 (m, 6H), 7.21 - 7.14 (m, 3H), 4.85 - 4.68 (m, 1H), 3.52 - 3.43 (m, 4H), 3.41 (td, *J* = 3.8, 8.1 Hz, 1H), 3.28 (td, *J* = 8.5, 11.9 Hz, 1H), 3.09 - 2.91 (m, 2H), 2.78 (dd, *J* = 2.6, 13.6 Hz, 1H), 1.65 - 1.50 (m, 1H), 1.37 (s, 10H), 1.16 - 0.98 (m, 2H), 0.39 - 0.21 (m, 1H). LCMS $[M+H]^+$: 235.9.

[001505] ***Preparation of compound WV-CA-243.***



[001506] To a solution of compound **8** (20 g, 41.87 mmol) in THF (200 mL) was added HCl (5 M, 83.74 mL). The mixture was stirred at 15 °C for 3 hr. TLC indicated compound **8** was consumed completely and one major new spot with larger polarity was detected. The resulting mixture was washed with MTBE (100 mL x 3). The combined aqueous layer was adjusted to pH 12 with 5M NaOH aq. and extracted with DCM (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to afford a white solid. **WV-CA-243** (9 g, 90.42% yield, 99% purity) was obtained as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 4.18 (ddd, *J* = 2.8, 5.8, 8.2 Hz, 1H),

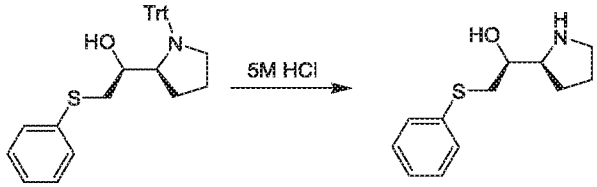
3.29 - 3.21 (m, 1H), 3.19 (d, *J* = 2.6 Hz, 1H), 3.16 - 3.08 (m, 1H), 2.92 (t, *J* = 6.6 Hz, 2H), 2.74 (br s, 1H), 1.92 - 1.81 (m, 1H), 1.81 - 1.61 (m, 3H), 1.42 (s, 10H); ^{13}CNMR (101 MHz, CHLOROFORM-*d*) δ = 68.01, 62.00, 59.73, 49.79, 46.96, 26.77, 25.80, 23.22. LCMS [M + H]$^+$: 236.1. LCMS purity: 99.46%.



1 9

[001507] To a solution (chloromethyl)(phenyl)sulfane of Mg (17.08 g, 702.90 mmol, 4 *eq.*) and I_2 (0.50 g, 1.97 mmol, 396.83 uL, 1.12 – 2 *eq.*) in THF (100 mL) was added with 1,2-dibromoethane (1.25 g, 6.63 mmol, 0.5 mL, 3.77 – 2 *eq.*). Once the mixture turned to be colorless, chloromethylsulfanylbenzene (111.51 g, 702.90 mmol, 4 *eq.*) in THF (100 mL) was dropwise added at 10 – 20°C for 1 hr. After addition, the mixture was stirred at 10 – 20 °C for 1 hr, most of Mg was consumed. And then the mixture was added in the mixture of compound **1** (60 g, 175.72 mmol, 1 *eq.*) in THF (600 mL) at -78 °C, the mixture was stirred at -78 °C – 20 °C for 4 hr. TLC (Petroleum ether: Ethyl acetate = 9: 1, R_f = 0.26) indicated compound **1** was remained and two new spots formed. The reaction mixture was quenched by addition water (100 mL) at 0 °C, and then extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 200/1 to 10:1) 2 times. Compound **9** (80 g, 171.80 mmol, 97.77% yield) was obtained as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.52 (d, *J* = 7.5 Hz, 6H), 7.31 - 7.09 (m, 14H), 4.24 - 4.14 (m, 1H), 3.54 - 3.44 (m, 1H), 3.30 - 3.18 (m, 1H), 3.08 - 2.96 (m, 1H), 2.91 (s, 1H), 2.80 (d, *J* = 7.0 Hz, 2H), 1.69 - 1.53 (m, 1H), 1.39 - 1.30 (m, 1H), 1.15 - 1.01 (m, 1H), 0.30 - 0.12 (m, 1H).

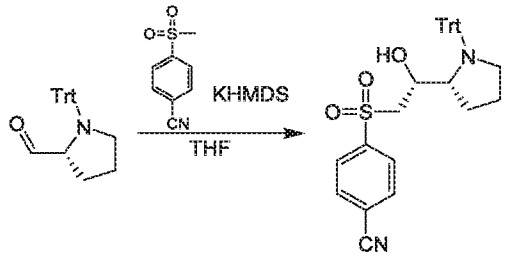
[001508] ***Preparation of compound WV-CA-244.***



9 **WV-CA-244**

[001509] To a solution of compound **9** (80 g, 171.80 mmol, 1 *eq.*) in EtOAc (350 mL) was added HCl (5 M, 266.30 mL, 7.75 *eq.*). The mixture was stirred at 15 °C for 18 hr. TLC (Petroleum ether: Ethyl acetate = 9:1, R_f = 0.01) indicated compound **9** was consumed and new spots formed. The reaction mixture was extracted with MTBE (200 mL x 3) and the MTBE phases were discarded. And then the water phase was added with 2 M NaOH (aq.) to pH = 9 and extracted with EtOAc (200 mL x 5). The

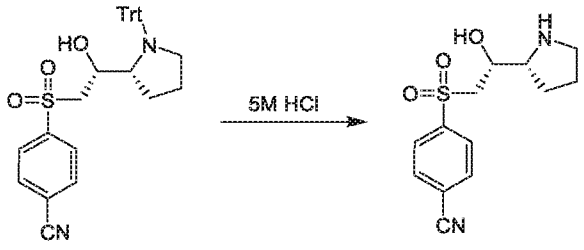
combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. To the crude product was added EtOAc (100 mL) at 70°C. The mixture was stirred at 70 °C → 20 °C for 1 hr. The reaction mixture was filtered, and the filter cake was dried to give the product. **WV-CA-244** (31.9 g, 142.84 mmol, 94.66% yield) was obtained as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.37 (d, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.7 Hz, 2H), 7.20 - 7.12 (m, 1H), 3.74 - 3.65 (m, 1H), 3.24 - 3.15 (m, 1H), 3.13 - 3.00 (m, 2H), 3.00 - 2.21 (m, 4H), 1.77 - 1.59 (m, 4H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ = 136.04, 129.35, 128.95, 126.15, 70.75, 61.64, 46.86, 38.54, 25.86, 25.17. LCMS [M + H]$^+$: 224.1. LCMS purity: 99.57%.



4 **10**

[001510] To a solution of 4-methylsulfonylbenzonitrile (47.76 g, 263.59 mmol, 1.5 *eq.*) in THF (800 mL) was added KHMDS (1 M,263.59 mL, 1.5 *eq.*) at -70 °C → -40 °C, 0.5 hr later, added compound **4** (60.00 g, 175.72 mmol, 1 *eq.*) in THF (400 mL) at -70 °C. The mixture was stirred at -70 °C for 2.5 hr. TLC (Petroleum ether: Ethyl acetate = 1:1, R_f = 0.4) indicated compound **4** was consumed and one new spot formed. The reaction mixture was quenched by addition sat. NH_4Cl (20 mL) at 0 °C and extracted with DCM (600 mL x 3). Dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was washed with MeOH (500 mL x 5) to get compound **10** (28 g, 53.57 mmol, 30.49% yield) as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.84 - 7.74 (m, 2H), 7.73 - 7.65 (m, 2H), 7.32 (d, *J* = 7.2 Hz, 6H), 7.15 - 6.99 (m, 9H), 4.20 (td, *J* = 2.9, 5.6 Hz, 1H), 3.22 (ddd, *J* = 3.1, 5.7, 8.3 Hz, 1H), 3.12 - 3.03 (m, 2H), 3.02 - 2.92 (m, 1H), 2.90 - 2.77 (m, 2H), 1.39 - 1.26 (m, 1H), 1.20 - 0.93 (m, 2H), 0.13 - 0.11 (m, 1H).

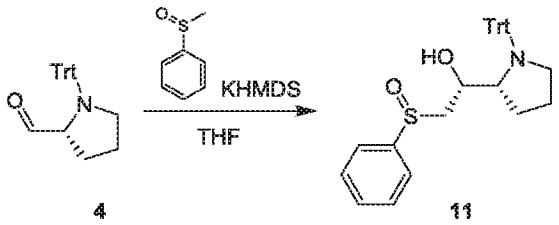
[001511] *Preparation of compound WV-CA-238.*



10 **WV-CA-238**

[001512] To a solution of compound **10** (28 g, 53.57 mmol, 1 *eq.*) in DCM (196 mL) was added TFA (12.22 g, 107.15 mmol, 7.93 mL, 2 *eq.*). The mixture was stirred at 0 °C for 3 hr. TLC and LCMS

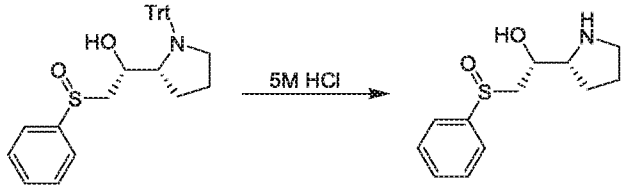
indicated compound **10** was consumed and two new spots formed. The reaction mixture was washed with MTBE (100 mL x 3), then the aqueous phase was basified by addition NaOH (5 M) until pH = 12 at 0 °C, and then extracted with DCM (50 mL x 3) to give a residue dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. Compound **WV-CA-238** (9.5 g, 33.42 mmol, 62.38% yield, 98.62% purity) was obtained as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 8.09 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 4.06 (ddd, *J* = 2.9, 4.9, 8.3 Hz, 1H), 3.38 - 3.16 (m, 3H), 2.96 - 2.79 (m, 2H), 1.81 - 1.64 (m, 3H), 1.61 - 1.45 (m, 1H). ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ = 144.05, 132.88, 128.93, 117.48, 117.15, 67.63, 61.50, 60.09, 46.83, 25.88, 25.55. LCMS [M + H]$^+$: 281.1. LCMS purity: 98.62%. SFC: dr = 99.75: 0.25.



4 11

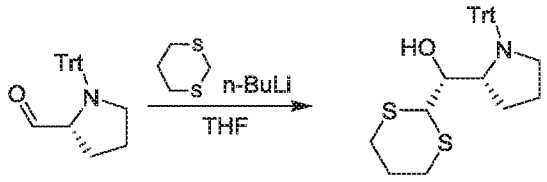
[001513] To a solution of methylsulfinylbenzene (25 g, 178.31 mmol, 1.5 *eq.*) in THF (400 mL) was added KHMDS (1 M, 178.31 mL, 1.5 *eq.*) dropwise at -60 °C, and warm to -30°C slowly over 30 min. The mixture was then cooled to -70 °C. A solution of compound **4** (40.59 g, 118.88 mmol, 1 eq.) in THF (100 mL) was added dropwise at -70 °C. The mixture was stirred at -70 °C → -50 °C for 2 hr. TLC (Petroleum ether: Ethyl acetate = 3:1) showed compound **4** was remained. The reaction mixture was cooled to -70 °C, additionally added KHMDS (1M, 40 mL), and stirred at -70 °C →~ -40 °C for 2 hr. TLC (Petroleum ether: Ethyl acetate = 3:1) showed compound **4** was little remained. The reaction mixture was quenched with sat. NH_4Cl (aq. 300 mL), and the separated aqueous layer was extracted with EtOAc (200 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to afford a residue as a yellow gum, which was crystallized in MeOH (100 mL), filtered and rinsed with MeOH (50 mL) to give an off-white solid (17 g), and the filtrate was concentrated to afford a yellow gum (50 g). The white solid product (17 g) was re-dissolved in THF (150 mL), and added MeOH (80 mL), and the mixture was concentrated to remove THF, filtered and dried to give an off-white solid, which was re-dissolved in THF (150 mL), and added MeOH (80 mL), and the mixture was concentrated to remove THF, filtered and dried to give the product as an off-white solid (13 g). The filtrate was concentrated to give 4 g crude. No further purification. The product compound **11** (13 g, 26.99 mmol, 22.70% yield) was obtained as an off-white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.62 - 7.56 (m, 2H), 7.55 - 7.52 (m, 3H), 7.51 - 7.45 (m, 6H), 7.25 - 7.12 (m, 9H), 4.60 (td, *J* = 2.4, 10.1 Hz, 1H), 3.72 (s, 1H), 3.27 - 3.13 (m, 2H), 3.04 - 2.84 (m, 2H), 2.46 (dd, *J* = 2.2, 13.5 Hz, 1H), 1.71 - 1.53 (m, 1H), 1.42 - 1.28 (m, 1H), 1.07 - 0.90 (m, 1H), 0.37 - 0.21 (m, 1H).

[001514] *Preparation of compound WV-CA-247.*



11 WV-CA-247

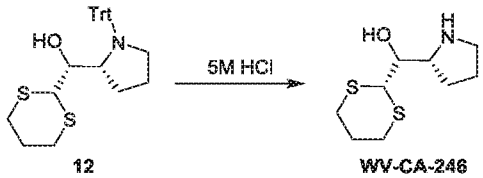
[001515] To a solution of compound **11** (13 g, 26.99 mmol, 1 *eq.*) in THF (45 mL) was added HCl (5 M, 52.00 mL, 9.63 *eq.*) aqueous. The mixture was stirred at 20 °C for 2 hr. TLC (Petroleum ether: Ethyl acetate = 3: 1) showed the reaction was completed. The resulting mixture was washed with MTBE (60 mL x 3). The combined aqueous layer was adjusted to pH 12 with 5 M NaOH aq. and extracted with DCM (80 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a white solid (5.8 g). Without further purification. The compound **WV-CA-247** (5.8 g, 24.17 mmol, 89.55% yield, 99.74% purity) was obtained as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.67 - 7.60 (m, 2H), 7.55 - 7.42 (m, 3H), 4.17 (ddd, *J* = 2.6, 4.2, 9.9 Hz, 1H), 3.74 - 3.23 (brs, 2H), 3.13 (dt, *J* = 4.3, 7.3 Hz, 1H), 2.96 - 2.74 (m, 4H), 1.81 - 1.52 (m, 4H). ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ = 143.99, 130.93, 129.32, 123.92, 66.97, 62.23, 61.58, 46.86, 25.88, 25.3. LCMS $[M + H]^+$: 240. LCMS purity: 99.74%. SFC: dr = 99.48: 0.52.



4 12

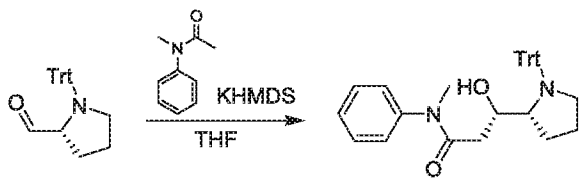
[001516] To a solution of 1,3-dithiane (13.21 g, 109.83 mmol) in THF (250 mL) was added n-BuLi (2.5 M, 29.29 mL) at -20 °C, 0.5 hr later added compound **1** (25 g, 73.22 mmol) in THF (250 mL) at -70 °C. The mixture was stirred at -70 → 20 °C for 16 hr. TLC indicated compound **4** was remained, and one new spot was detected. The reaction mixture was quenched by sat. NH_4Cl (200 mL), and then extracted with EtOAc (200 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by MPLC (SiO_2, Petroleum ether/Ethyl acetate = 50/1 to 10/1, 5% TEA) 2 times. Compound **12** (16 g, 47.33% yield) was obtained as a yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.59 (d, *J* = 7.0 Hz, 5H), 7.29 - 7.25 (m, 6H), 7.20 - 7.14 (m, 3H), 4.39 (dd, *J* = 2.4, 10.3 Hz, 1H), 4.03 (ddd, *J* = 2.4, 5.6, 8.2 Hz, 1H), 3.38 (d, *J* = 10.1 Hz, 1H), 3.28 (ddd, *J* = 7.0, 10.1, 12.3 Hz, 1H), 3.07 - 2.99 (m, 1H), 2.93 - 2.85 (m, 1H), 2.63 - 2.54 (m, 1H), 2.34 - 2.18 (m, 2H), 1.97 - 1.82 (m, 2H), 1.59 - 1.45 (m, 1H), 1.22 - 1.11 (m, 1H), 0.22 - 0.06 (m, 1H).

[001517] *Preparation of compound WV-CA-246.*



12 WV-CA-246

[001518] To a solution of compound **12** (16 g, 34.66 mmol) in EtOAc (80 mL) was added HCl (5 M, 69.31 mL). The mixture was stirred at 15 °C for 16 hr. TLC indicated compound **12** was consumed completely and new spots formed. The reaction mixture was extracted with TBME (100 mL x 3) and the TBME phases were discarded. And then the water phase was added with 5 M NaOH (aq.) to pH = 9 and extracted with DCM (100 mL x 5). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The residue was purified by prep-HPLC (column: Phenomenex luna C18 250 x 50mm x 10 um; mobile phase: [water (0.1% TFA) - ACN]; B%: 0% - 15%,20 min and column: Phenomenex luna (2) C18 250 x 50 x 10um; mobile phase: [water (0.1% TFA) - ACN]; B%: 0%-12%,20 min). **WV-CA-246** (4.2 g, 55.25% yield) was obtained as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.13 (d, *J* = 7.2 Hz, 1H), 3.83 (dd, *J* = 5.1, 7.2 Hz, 1H), 3.49 (dt, *J* = 5.1, 7.3 Hz, 1H), 3.13 - 2.76 (m, 6H), 2.60 (br s, 2H), 2.20 - 2.05 (m, 1H), 2.04 - 1.90 (m, 1H), 1.89 - 1.62 (m, 4H). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 73.76, 59.94, 50.42, 46.83, 28.95, 28.45, 25.87, 25.32. HPLC purity: 97.75%. LCMS $[M + H]^+$: 220.1. SFC: dr = 0.22: 99.78.

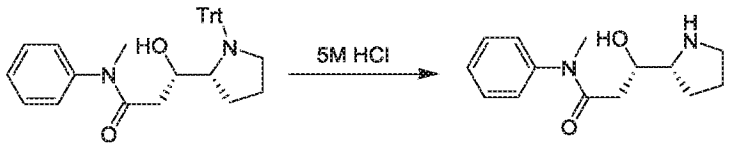


4 13

[001519] To a solution of N-methyl-N-phenyl-acetamide (18.5 g, 124.00 mmol) in THF (250 mL) was added KHMDS (1 M, 124.00 mL) dropwise at -70 °C, and to warm to -30 °C slowly over 30 min. The mixture was then cooled to -70 °C. A solution of compound **4** (28.23 g, 82.67 mmol) in THF (150 mL) was added dropwise at -70 °C. The mixture was stirred at -70 °C ~ -50 °C for 3 hr. TLC showed the reaction was almost completed. The reaction mixture was quenched with sat. NH_4Cl (aq., 30 mL), and extracted with EtOAc (25 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to afford a residue as yellow gum. The crude was purified by column chromatography on silica gel (Petroleum ether: Ethyl acetate = 10: 1, 3: 1, 1: 1, 1: 2, 5% TEA). Compound **13** (38 g, 93.7% yield) was obtained as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.53 (br d, *J* = 7.5 Hz, 6H), 7.44 - 7.31 (m, 4H), 7.26 - 7.09 (m, 12H), 4.46 - 4.40 (m, 1H), 3.90 (br

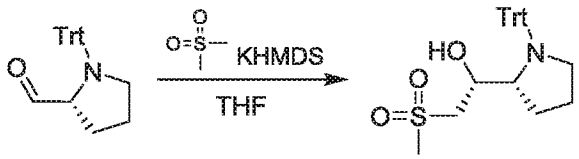
s, 1H), 3.31 - 3.19 (m, 4H), 3.15 - 3.07 (m, 1H), 3.00 - 2.91 (m, 1H), 1.48 - 1.26 (m, 2H), 0.86 - 0.74 (m, 1H), 0.33 - 0.19 (m, 1H).

[001520] *Preparation of compound WV-CA-248.*



13 WV-CA-248

[001521] To a solution of compound **13** (38 g, 77.45 mmol) in THF (125 mL) was added HCl (5 M, 152.00 mL) aqueous. The mixture was stirred at 20 °C for 2 hr. TLC showed the reaction was completed. The resulting mixture was washed with MTBE (80 mL x 3), EtOAc (100 mL x 3), and DCM (100 mL x 2) in turn. The combined aqueous layer was adjusted to pH = 12 with 5M NaOH aq. and extracted with DCM (120 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to afford a yellow gum. The crude of **WV-CA-248** (15.2 g, 73.26% yield, 92.7% purity) appears a yellow gum. To a solution of **WV-CA-248** (14.5 g, 58.39 mmol) in EtOH (150 mL) was added (E)-3-phenylprop-2-enoic acid (8.65 g, 58.39 mmol). The mixture was stirred at 80°C for 1 hr. The mixture was concentrated in vacuo. The residue was dissolved in TBME (50 mL), and then the mixture was added MeCN (3 mL), the mixture was turned clear, then the solution was standed, and then solid was appeared, and the mixture was filtered, and the filtered cake was washed with TMBE (10 mL x 2), and the filtered cake was desired compound. The residue (6.5 g, crude) was obtained as a yellow solid. The residue was dissolved in H_2O (10 mL) was added aq. NaOH (5 M, 6.56 mL, 2 eq.). The mixture was stirred at 25 °C for 10 min. The pH of the mixture was 13. The solution was extracted with DCM (40 mL x 6), and the organic phase was concentrated in vacuo. Compound **WV-CA-248** (4 g, 91.74% yield, 93.4% purity) was obtained as a brown oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.49 - 7.31 (m, 3H), 7.21 (br d, *J* = 7.3 Hz, 2H), 4.00 (td, *J* = 4.3, 8.6 Hz, 1H), 3.48 (br s, 2H), 3.28 (s, 3H), 3.10 - 2.98 (m, 1H), 2.97 - 2.80 (m, 2H), 2.36 - 2.17 (m, 2H), 1.79 - 1.47 (m, 3H), 1.79 - 1.47 (m, 1H). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 172.38, 143.42, 129.89, 128.04, 127.27, 69.90, 62.29, 46.77, 37.98, 37.23, 25.99, 25.65. LCMS $[M + H]^+$: 249.1. LCMS purity: 93.35%. SFC: SFC purity de = 94.26%.



4 14

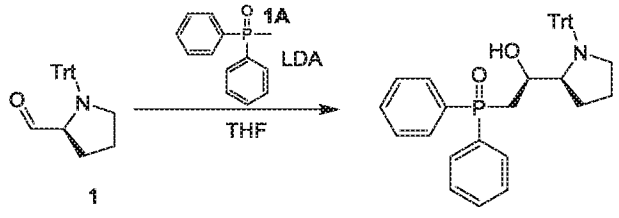
[001522] To a solution of methylsulfonylmethane (8.27 g, 87.86 mmol) in THF (150 mL) was

added KHMDS (1 M, 87.86 mL) at -70 °C ~ -40 °C, 0.5 hr later added compound **1** (20 g, 58.57 mmol) in THF (100 mL). The mixture was stirred at -70 °C for 1.5 hr. TLC indicated compound **4** was remained a little and one new spot formed. The reaction mixture was quenched by addition sat. NH_4Cl (aq. 200 mL) at 0 °C, and then diluted with EtOAc (200 mL) and extracted with EtOAc (200 mL x 3). Dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/ Ethyl acetate = 1/ 0 → 0: 1). Compound **14** (12 g, crude, HNMR showed cis/trans isomer ratio ~ 10:1) was obtained as a yellow oil. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.58 - 7.47 (m, 7H), 7.26 - 7.22 (m, 5H), 7.20 - 7.13 (m, 3H), 4.51 - 4.46 (m, 1H), 3.99 - 3.88 (m, 1H), 3.48 - 3.39 (m, 1H), 3.21 - 2.97 (m, 4H), 2.96 - 2.91 (m, 3H), 2.68 (br d, *J* = 14.6 Hz, 1H), 1.57 - 1.43 (m, 1H), 1.36 - 1.26 (m, 1H), 1.20 - 1.10 (m, 1H), 0.57 - 0.44 (m, 1H), 0.25 - 0.04 (m, 1H).

[001523] *Preparation of WV-CA-252.*

14 **WV-CA-252**

[001524] To a solution of compound **14** (18 g, 41.32 mmol) in THF (82 mL) was added HCl (5 M, 82.65 mL). The mixture was stirred at 25 °C for 3 hr. TLC indicated compound **14** was consumed and two new spots formed. The reaction mixture was washed with MTBE (50 mL x 3), then the aqueous phase was basified by addition NaOH (5M) until pH = 12 at 0 °C, and then extracted with DCM (50 mL x 6) to give a residue dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude compound **WV-CA-252** (6.5 g, 81.4% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 4.13 (ddd, *J* = 1.8, 4.0, 9.7 Hz, 1H), 3.23 (dt, *J* = 4.2, 7.4 Hz, 1H), 3.18 - 3.09 (m, 1H), 3.05 (s, 4H), 3.00 - 2.90 (m, 3H), 1.95 - 1.68 (m, 4H), 1.67 - 1.48 (m, 1H). LCMS [M + H]$^+$: 194.0.



1 **15**

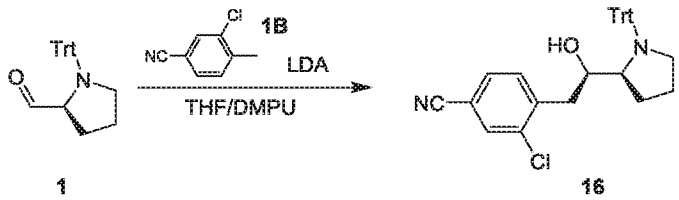
[001525] A mixture of compound **1A** (52.24 g, 241.62 mmol) in THF (500 mL) was degassed and purged with N_2 for 3 times, and then the mixture was cooled to -70 °C, and then to the mixture was added LDA (2 M, 112.76 mL). The mixture was stirred at -40 °C for 30 min, and then to the mixture was added

compound **1** (55 g, 161.08 mmol) in THF (250 mL) at -70 °C. The mixture was stirred at -70 °C for 2 hr under N_2 atmosphere. TLC indicated compound **1** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction was quenched by sat. aq. NH_4Cl (300 mL) and then extracted with EtOAc (100 mL x 3). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was dissolved in MeOH (300 mL) and filtered; the filtered cake was the desired product. Compound **2** (53 g, crude) was obtained as a white solid.

[001526] *Preparation of compound WV-CA-245.*

15 **WV-CA-245**

[001527] To a solution of compound **15** (72 g, 129.11 mmol) in THF (400 mL) was added HCl (5 M, 258.22 mL). The mixture was stirred at 25 °C for 1 hr. LC-MS showed compound **15** was consumed completely and one main peak with desired mass was detected. The reaction was extracted with TBME (100 mL x 3), added aq. 5 N NaOH to pH = 13, and then extracted with DCM (50 mL x 3), and the combined organic phase was concentrated in vacuo. **WV-CA-245** (38 g, 92.82% yield, 99.5% purity) was obtained as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.81 - 7.71 (m, 4H), 7.58 - 7.44 (m, 6H), 4.01 - 3.92 (m, 1H), 3.16 - 3.09 (m, 1H), 2.92 - 2.79 (m, 2H), 2.63 - 2.44 (m, 2H), 1.82 - 1.60 (m, 4H). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 133.88, 132.89, 132.86, 131.95, 131.88, 130.73, 128.74, 68.98, 68.94, 63.79, 63.67, 47.03, 34.21, 33.49, 26.37, 25.88. LCMS $[M + H]^+$: 316.1. LCMS purity: 99.45%. SFC: SFC purity de = 99.5%.

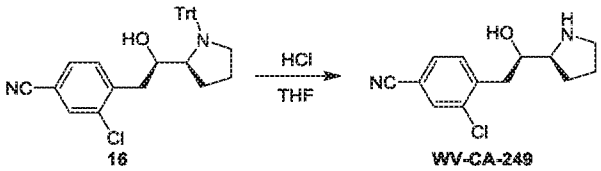


1 **16**

[001528] To a solution of compound **1B** (13.32 g, 87.86 mmol) in THF (200 mL) was added KHMDS (1 M, 82.00 mL) at -70 °C under N_2, and then the mixture was stirred at -70 °C for 10 min, and then to the mixture was added compound **1** (20 g, 58.57 mmol) in THF (100 mL), the reaction was stirred at – 70 °C for 30 min. TLC indicated compound **1** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was quenched with sat. aq. NH_4Cl (100 mL), and then extracted with EtOAc (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography

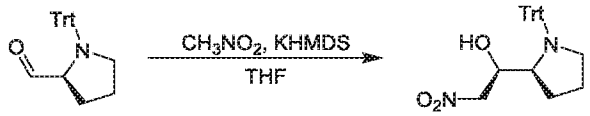
(SiO_2, Petroleum ether/Ethyl acetate = 50: 1, 20: 1, 10: 1, 1: 1, 0: 1). Compound **16** (12 g, crude) was obtained as a yellow solid.

[001529] *Preparation of compound WV-CA-249.*



16 **WV-CA-249**

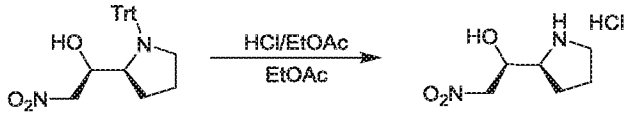
[001530] To a solution of compound **16** (12 g, 24.34 mmol) in THF (50 mL) was added aq. HCl (5 M, 48.68 mL). The mixture was stirred at 25 °C for 30 min. TLC indicated compound **16** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction was extracted with TBME (100 mL x 3), and then to the mixture was added 5N aq. NaOH to pH = 13, extracted with DCM (100 mL x 3), and then the organic phase was concentrated in vacuo. **WV-CA-249** (5.36 g, 87.84% yield, 100.00% purity) was obtained as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.64 (s, 1H), 7.49 (d, *J* = 0.9 Hz, 2H), 3.88 (td, *J* = 3.6, 9.4 Hz, 1H), 3.24 - 3.16 (m, 1H), 3.02 - 2.89 (m, 3H), 2.78 (dd, *J* = 9.4, 14.0 Hz, 1H), 1.84 - 1.70 (m, 4H). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 143.11, 134.94, 132.60, 132.33, 130.12, 117.63, 111.52, 70.86, 62.02, 46.76, 37.90, 25.88, 24.21. LCMS $[M + H]^+$: 251.0. LCMS purity: 100.000%. SFC: SFC purity de = 98.28%.



1 **17**

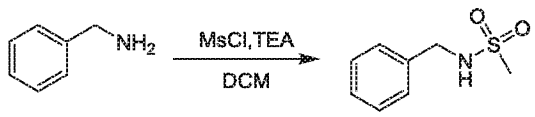
[001531] To a solution of nitromethane (30.59 g, 501.15 mmol) in THF (300 mL) was added KHMDS (1 M, 263.59 mL) at 20-25 °C and stirred for 1 hr. Compound **1** (30 g, 87.86 mmol) in THF (90 mL) was added to the mixture at 20-25 °C and stirred for 0.5 hr. TLC showed that the starting material was consumed mostly, and desired product was formed. The mixture was quenched by saturated aq. NH_4Cl (300 mL) and extracted with ethyl acetate (100 mL × 3). The organic phase was washed by saturated aq. NaCl (100 mL × 3) and dried with anhydrous Na_2SO_4, then concentrated under reduced pressure to remove the solvent. The crude product was purified by MPLC (SiO_2, Ethyl acetate/Petroleum ether = 0% → 20%) to obtain compound **17** (26.55 g, 75.08% yield) as yellow solid. The product was detected by ^{1}H NMR. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.54 - 7.44 (m, 6H), 7.28 - 7.21 (m, 6H), 7.20 - 7.14 (m, 3H), 4.64 (td, *J* = 3.0, 9.4 Hz, 1H), 4.53 - 4.06 (m, 3H), 3.60 - 3.40 (m, 1H), 3.24 - 2.96 (m, 3H), 1.52 - 1.41 (m, 1H), 1.40 - 1.28 (m, 1H), 1.17 - 0.94 (m, 1H), 0.67 - 0.50 (m, 1H), 0.23 (quin d, *J* = 8.8, 11.6 Hz, 1H).

[001532] *Preparation of compound WV-CA-250.*



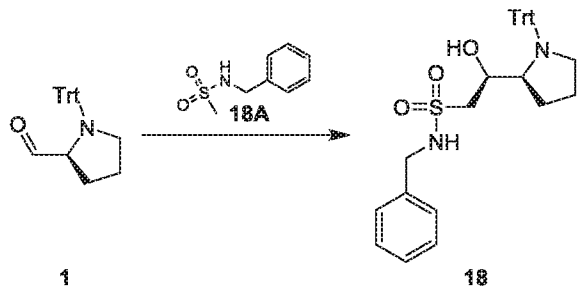
2 WV-CA-250

[001533] To a solution of compound **17** (7.5 g, 18.63 mmol) in EtOAc (35 mL) was added HCl/EtOAc (4 M, 50 mL) at 20-25 °C and stirred for 1 hr. TLC showed that the starting material was consumed completely. Poured the supernatant liquid of the mixture, the yellow gum on the bottle wall was concentrated under reduced pressure to remove the solvent. **WV-CA-250** (2.10 g, 56.70% yield, 98.927% purity, HCl salt) was obtained as yellow gum. The product was detected by ^{1}H NMR, ^{13}C NMR and LCMS. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.89 - 9.54 (m, 1H), 9.03 - 8.75 (m, 1H), 8.94 (br s, 1H), 4.97 - 4.78 (m, 1H), 4.65 - 4.35 (m, 2H), 3.70 - 3.41 (m, 4H), 3.22 - 3.03 (m, 2H), 2.06 - 1.65 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 79.42, 79.00, 67.89, 66.82, 61.53, 60.77, 45.44, 45.25, 26.93, 24.57, 23.95, 23.81. LCMS $[M+H]^+$: 161.1, purity: 98.92%.



18A

[001534] To a solution of compound benzylamine (30 g, 279.97 mmol) and TEA (56.66 g, 559.95 mmol) in DCM (60 mL) was added MsCl (38.49 g, 335.97 mmol) in DCM (30 mL) at 0 °C. The mixture was stirred at 0 °C for 2 hr. LC-MS showed compound **18A** was consumed and many new peaks were detected. The reaction mixture was washed with HCl (1 M, 50 mL x 3) and sat. $NaHCO_3$ (aq. 50 mL x 3). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. TLC showed one main spot. The residue was purified by MPLC (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 1:1). Compound **18A** (35 g, 67.49% yield) was obtained as a light-yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.44 - 7.24 (m, 5H), 4.82 (br s, 1H), 4.31 (d, J = 6.2 Hz, 2H), 2.85 (s, 3H).

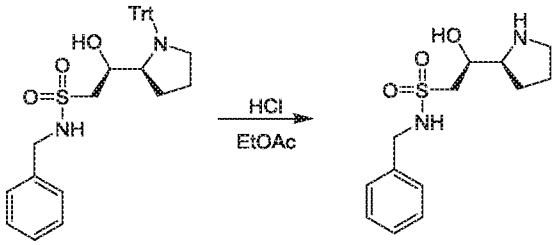


1 18

[001535] To a solution of compound **18A** (16.28 g, 87.86 mmol) in THF (60 mL) was added with LDA (2 M, 87.86 mL) at 0 °C. The mixture was stirred at 0-25 °C for 0.5 hr. And then compound **1** (15 g, 43.93 mmol) in THF (60 mL) was added to above solution at -70 °C. The mixture was stirred at -70-25

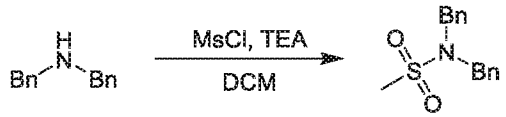
°C for 4 hr. TLC indicated compound **1** was consumed completely and many new spots formed. The reaction mixture was added with sat. NH_4Cl (aq. 50 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate=5/1, 2% TEA). Compound **18** (22 g, 95.08% yield) was obtained as a yellow oil.

[001536] *Preparation of compound WV-CA-255.*



18 **WV-CA-255**

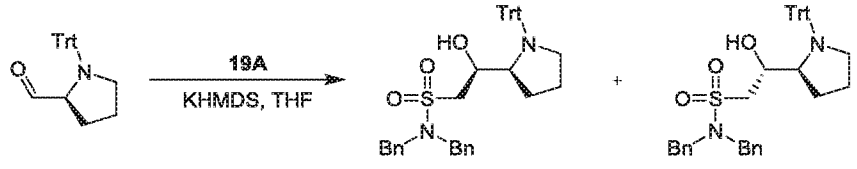
[001537] To a solution of compound **18** (22 g, 41.77 mmol) in EtOAc (15 mL) was added HCl (4 M in ethyl acetate, 31.33 mL) at 0 °C. The mixture was stirred at 0-25 °C for 2 hr. And solid appeared in the reaction mixture. TLC indicated compound **18** was consumed completely and many new spots formed. The reaction mixture was filtered. The filter cake was dissolved in water (10 mL), washed with MTBE (40 mL x 3). The water phase was added with Na_2CO_3 (powder) to pH = 8~9 and extracted with DCM (50 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. **WV-CA-255** (11 g, 92.60% yield) was obtained as a brown solid. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.46 - 7.25 (m, 5H), 4.65 - 3.72 (m, 5H), 3.14 - 3.01 (m, 3H), 2.95 - 2.77 (m, 2H), 1.89 - 1.34 (m, 4H). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 136.99, 128.71, 128.62, 128.19, 128.09, 127.85, 69.12, 67.58, 61.98, 61.70, 55.55, 55.36, 47.36, 47.30, 46.60, 46.28, 28.05, 26.16, 25.71, 24.92. LCMS $[M + H]^+$: 285.0, LCMS purity: 99.8%. SFC : dr (trans/cis) = 32.36: 67.64.



19A

[001538] To a solution of compound dibenzylamine (30 g, 152.07 mmol) in DCM (250 mL) was added TEA (15.39 g, 152.07 mmol). The mixture was cooled to 0 °C, and to the mixture was added MsCl (17.42 g, 152.07 mmol) in DCM (50 mL), and then the mixture was stirred at 25 °C for 12 hours. LC-MS showed desired mass was detected. The reaction was quenched by H_2O (100 mL) and the organic phase was extracted with H_2O (100 mL×3), the organic phase was dried by Na_2SO_4, and then concentrated in vacuum. No need further purification. Compound **19A** (39 g, crude) was obtained as a white solid. ^1H

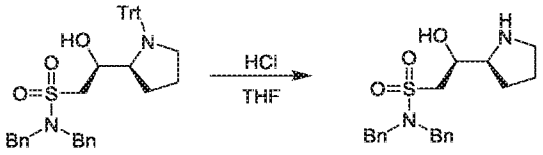
NMR (400 MHz, CHLOROFORM-d) δ = 7.41 - 7.29 (m, 9H), 4.36 (s, 4H), 2.82 - 2.75 (m, 3H). LCMS $[M + H]^+$: 298.0, purity: 86.6%.



1 19 20

[001539] To a solution of compound **19A** (19.36 g, 70.29 mmol) in THF (200 mL) was added KHMDS (1 M, 76.15 mL) dropwise at -78 °C to -70 °C under N_2. The mixture was warmed to -40 °C and stirred for 0.5 hr, then cooled to -78 °C. To the mixture was added compound **1** (20 g, 58.57 mmol) in THF (100 mL) at -78 °C to -70 °C and stirred for 1 hr under N_2. TLC showed that the starting material was consumed completely. The mixture was quenched by saturated aq. NH_4Cl (200 mL) and extracted with ethyl acetate (70 mL × 3). The organic phase was washed by saturated aq. NaCl (70 mL × 3) and dried with anhydrous Na_2SO_4, then concentrated under reduced pressure to remove the solvent to obtain the crude product as yellow gum. The crude product was re-dissolved with methanol (200 mL) and standing at 20-25 °C for 12 hours. Compound **19** (20.4 g, 99.99% yield) was crystallized from the solvent as white solid, then filtered and dried in vacuum. The filtrate was concentrated under reduced pressure to remove the solvent to give compound **20** (28.4 g, crude) as brown gum. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.47 - 7.42 (m, 6H), 7.23 - 7.05 (m, 19H), 4.36 (td, *J* = 3.0, 8.6 Hz, 1H), 4.23 - 4.12 (m, 4H), 3.29 - 3.19 (m, 1H), 3.29 - 3.19 (m, 1H), 3.11 (ddd, *J* = 7.1, 9.5, 12.1 Hz, 1H), 2.97 - 2.82 (m, 2H), 2.59 (dd, *J* = 3.1, 14.2 Hz, 1H), 1.37 - 1.27 (m, 1H), 1.24 - 1.14 (m, 1H), 1.00 - 0.92 (m, 1H), 0.16 - 0.02 (m, 1H).

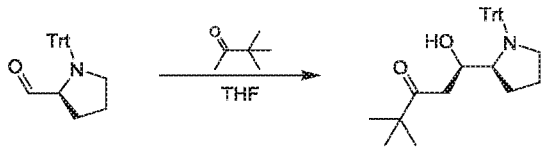
[001540] *Preparation of compound WV-CA-263.*



19 WV-CA-263

[001541] To a solution of compound **19** (20 g, 32.42 mmol) in THF (100 mL) was added HCl (5 M, 64.85 mL) at 20-25 °C and stirred for 0.5 hr. TLC showed that the starting material was consumed completely. The mixture was extracted with TBME (80 mL × 3), then adjusted the pH of the mixture with aq. NaOH (65 mL, 5M) to 11-13 and extracted with DCM (100 mL × 3). The organic phase was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to remove the solvent. The crude product was used for the next step without any purification. **WV-CA-263** (10.04 g, 82.68% yield, 100% purity) was obtained as white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.38 - 7.28 (m, 10H),

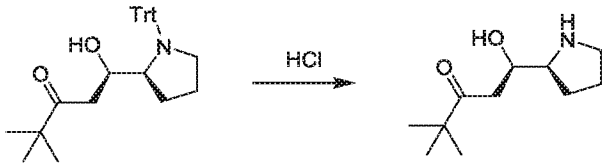
4.38 (s, 4H), 4.01 (ddd, *J*=2.6, 5.6, 8.5 Hz, 1H), 3.20 - 3.13 (m, 2H), 3.10 - 3.02 (m, 1H), 2.91 (t, *J*=6.5 Hz, 2H), 1.89 (br d, *J*=8.6 Hz, 1H), 1.82 - 1.66 (m, 4H), 1.62 - 1.52 (m, 1H). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 135.62, 128.77, 128.70, 127.98, 77.35, 76.87 (d, *J*=31.5 Hz, 1C), 68.84, 61.51, 57.03, 50.35, 46.96, 26.27, 25.88. LCMS $[M + H]^+$: 375.1, purity: 100.00%. SFC: dr = 99.55: 0.45.



1 21

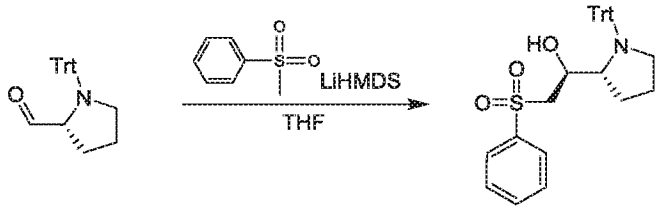
[001542] To a solution of 3,3-dimethylbutan-2-one (11.00 g, 109.83 mmol) in THF (125 mL) was added LDA (2 M, 54.91 mL) dropwise at -70 °C, and it was stirred at -70 °C ~ -60 °C for 1 hr. A solution of compound **1** (25 g, 73.22 mmol) in THF (125 mL) was added dropwise at -70 °C ~ -60 °C. The mixture was stirred at -70°C for 1.5 hr. TLC showed compound **1** was almost consumed. The reaction mixture was quenched with sat. NH_4Cl (aq., 200 mL), and the separated aqueous layer was extracted with EtOAc (150 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to afford a residue as a light-yellow solid. The crude was purified by column chromatography on silica gel (Petroleum ether + 5% TEA; Petroleum ether: Ethyl acetate (20: 1) + 5% TEA). Compound **21** (17 g, 52.6% yield) was obtained as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ= 7.37 - 7.25 (m, 6H), 7.03 - 6.95 (m, 6H), 6.94 - 6.84 (m, 3H), 4.22 (td, *J* = 2.7, 9.2 Hz, 1H), 3.09 (td, *J* = 4.1, 7.6 Hz, 1H), 3.04 - 2.92 (m, 2H), 2.75 (ddd, *J* = 2.9, 8.5, 12.0 Hz, 1H), 2.26 (dd, *J* = 9.3, 17.0 Hz, 1H), 2.04 (dd, *J* = 3.4, 16.9 Hz, 1H), 1.43 - 1.24 (m, 2H), 1.14 - 1.01 (m, 1H), 0.84 (s, 9H), 0.81 - 0.71 (m, 1H), 0.09 - -0.07 (m, 1H).

[001543] ***Preparation of compound WV-CA-289.***



21 **WV-CA-289**

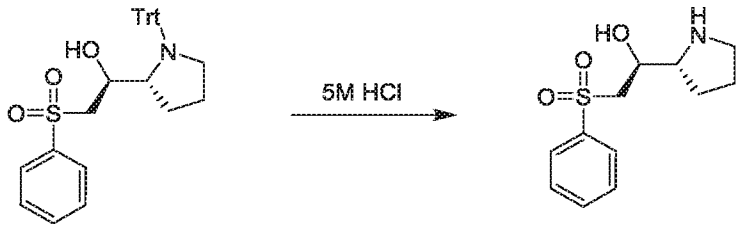
[001544] To a solution of compound **21** (16 g, 36.23 mmol) in EtOAc (25 mL) was added 4 M HCl/EtOAc (100 mL). The mixture was stirred at 25 °C for 0.5 hr. TLC showed the reaction was completed. The resulting mixture was filtered, and the solid was stirred in EtOAc (150 mL), filtered and re-triturated with EtOAc/MeOH (150 mL/5 mL), filtered and dried to afford compound **WV-CA-289** (7.5 g, 87.8% yield, HCl salt) as a white solid. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 4.43 (ddd, *J* = 3.5, 4.6, 7.8 Hz, 1H), 3.71 (dt, *J* =3 .5, 8.0 Hz, 1H), 3.42 - 3.22 (m, 2H), 2.92 (dd, *J* = 7.6, 17.7 Hz, 1H), 2.73 (dd, *J* = 4.9, 17.7 Hz, 1H), 2.23 - 1.90 (m, 4H), 1.28 - 1.05 (m, 9H). $[M + H]^+$: 200.1, purity: 100.00%.



4 22

[001545] To a solution of methylsulfonylbenzene (13.72 g, 87.86 mmol) in THF (100 mL) was added LiHMDS (1 M, 87.86 mL) in 0.5 hr at -70 °C - 0 °C, then added compound **4** in THF (100 mL). The mixture was stirred at -70 °C in 2.5 hr. TLC indicated compound **4** was remained a little and two new spots formed. The reaction mixture was quenched by addition sat. NH_4Cl aq. (300 mL) at 0 °C, extracted with DCM (200 mL x 3). Dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude was added THF (100 mL) and MeOH (150 mL), concentrated under reduced pressure at 45 °C until about 100 mL residue remained, filtered the solid. Repeated 3 times. Got solid 20 g, the mother liquid was concentrated under reduced pressure to get compound **22** (20 g, crude) was obtained as a yellow oil. Compound (1R)-2-(benzenesulfonyl)-1-[(2R)-1-tritylpyrrolidin-2-yl]ethanol (20 g, 68.61% yield) was obtained as a white solid.

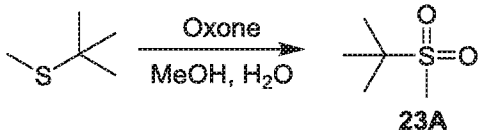
[001546] *Preparation of compound WV-CA-290.*



22 WV-CA-290

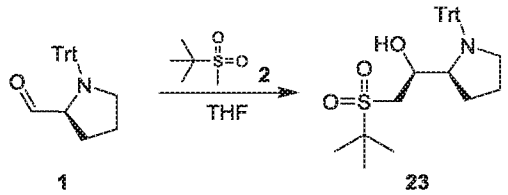
[001547] To a solution of compound **22** (20 g, 40.19 mmol) in THF (80 mL) was added HCl (5 M, 80.38 mL) at 0 °C. The mixture was stirred at 25 °C for 2 hr. TLC showed the compound **22** was consumed and two new spots formed. The reaction mixture was washed with MTBE (50 mL x 3), then the aqueous phase was basified by addition NaOH (5M) until pH = 12 at 0 °C, and then extracted with DCM (50 mL x 3) to give a residue dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 250 x 50mm x 10 um; mobile phase: [water (0.1% TFA) - ACN]; B%: 0% - 15%, 20 min). Compound **WV-CA-290** (0.7 g, 6.78% yield, 99.39% purity) was obtained as a yellow solid. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.95 - 7.85 (m, 2H), 7.64 - 7.56 (m, 1H), 7.55 - 7.46 (m, 2H), 3.79 (ddd, *J* = 3.2, 5.4, 8.4 Hz, 1H), 3.28 - 3.05 (m, 3H), 2.92 - 2.72 (m, 2H), 1.84 - 1.54 (m, 3H), 1.51 - 1.37 (m, 1H). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 139.81, 133.74, 129.19, 128.07, 68.15, 61.55, 60.97,46.67, 28.03, 26.27. SFC: (AD_MeOH_IPAm _10_40_25_35_6min), 100% purity. LCMS $[M + H]^+$: 256.1.

LCMS purity: 99.39%.



23A

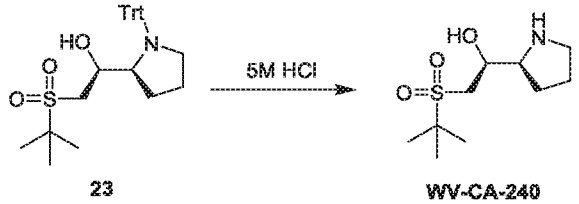
[001548] Two batches in parallel: To a solution of compound tert-butyl(methyl)sulfane (25 g, 239.89 mmol) in MeOH (625 mL) was added Oxone (457.18 g, 743.67 mmol) in H_2O (625 mL) at 0 °C. The mixture was stirred at 15 °C for 12 hr. HNMR showed compound tert-butyl(methyl)sulfane was consumed completely and desired compound was detected. Combined two batches of the reaction mixture, filtered and concentrated under reduced pressure to evaporate the MeOH, and then extracted with EtOAc (400 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound **23A** (55 g, crude) was obtained as a colorless oil, confirmed by HNMR. ^{1}HNMR (400 MHz, CHLOROFORM-d) δ = 7.26 (s, 1H), 5.30 (s, 8H), 2.81 (s, 3H), 1.43 (s, 9H).



1 23

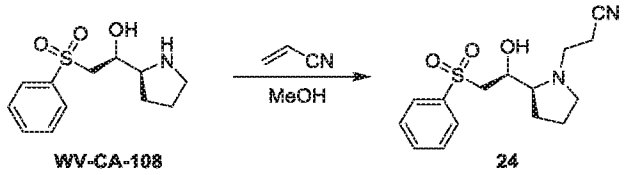
[001549] To a solution of compound **23A** (50 g, 367.07 mmol) in THF (510 mL) was added KHMDS (1 M, 367.07 mL) dropwise at -70 °C, and warm to -30 °C slowly over 30 min. The mixture was then cooled to -70 °C. A solution of compound **1** (83.56 g, 244.72 mmol) in THF (340 mL) was added dropwise at -70 °C. The mixture was stirred at -70 °C for 4 hr. TLC showed compound **1** was remained a little, and one major new spot with larger polarity was detected. The reaction mixture was quenched by added to the sat. NH_4Cl (aq. 800 mL), and then extracted with EtOAc (500 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give brown oil. The crude was dissolved with THF (300 mL) then concentrated under reduced pressure (40 °C) to give 150 mL clarified solution. Then added to 300 mL MeOH and concentrated under reduced pressure to give 200 mL solution, then filtered to give a residue and washed with MeOH (10 mL). The mother solution was concentrated under reduced pressure to give 100 mL solution then filtered to give a residue and washed with MeOH (10 mL). Combined all the residue, repeated two times to give 60 g residue. Compound **23** (60 g, crude) was obtained as a white solid. ^{1}HNMR (400 MHz, CHLOROFORM-d) δ = 7.56 (d, *J* = 7.5 Hz, 6H), 7.32 - 7.23 (m, 6H), 7.21 - 7.14 (m, 3H), 4.85 - 4.68 (m, 1H), 3.41 (td, *J* = 3.8, 8.1 Hz, 1H), 3.28 (td, *J* = 8.5, 11.9 Hz, 1H), 3.09 - 2.91 (m, 2H), 2.78 (dd, *J* = 2.6, 13.6 Hz, 1H), 1.65 - 1.50 (m, 1H), 1.37 (s, 9H), 1.16 - 0.98 (m, 2H), 0.39 - 0.21 (m, 1H).

[001550] *Preparation of compound WV-CA-240.*



23 WV-CA-240

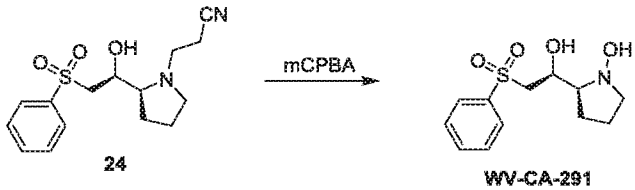
[001551] To a solution of compound **23** (59 g, 123.52 mmol) in THF (500 mL) was added HCl (5 M, 247.04 mL). The mixture was stirred at 20 °C for 3 hr. TLC indicated compound **23** was consumed completely and one major new spot with larger polarity was detected. The resulting mixture was washed with MTBE (500 mL x 3). The combined aqueous layer was adjusted to pH 12 with 5 M NaOH aq. and extracted with DCM (200 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to afford a white solid. **WV-CA-240** (23.6 g, 81.14% yield, 99.95% purity) was obtained as a white solid. ^{1}HNMR (400 MHz, CHLOROFORM-d) δ = 4.18 (ddd, *J* = 2.8, 5.8, 8.2 Hz, 1H), 3.29 - 3.21 (m, 1H), 3.19 (d, *J* = 2.6 Hz, 1H), 3.16 - 3.08 (m, 1H), 2.92 (t, *J* = 6.6 Hz, 2H), 2.74 (br s, 2H), 1.92 - 1.81 (m, 1H), 1.81 - 1.61 (m, 3H), 1.42 (s, 9H). ^{13}CNMR (101 MHz, CHLOROFORM-d) δ = 68.01, 62.00, 59.73, 49.79, 46.96, 26.77, 25.80, 23.22. LCMS $[M + H]^+$: 236.1. LCMS purity 99.95%.



WV-CA-108 24

[001552] To a solution of **WV-CA-108** (37 g, 144.91 mmol, 1 *eq.*) in MeOH (370 mL) was added prop-2-enenitrile (7.69 g, 144.91 mmol, 9.61 mL, 1 *eq.*). The mixture was stirred at 20 °C for 3 hr., (TLC, Petroleum ether: Ethyl acetate = 1:3, Rf = 0.31) showed **WV-CA-108** was consumed completely and in LCMS one main peak with desired MS was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Compound **24** (44 g, crude) was obtained as a white solid. LCMS $[M + H]^+$: 308.9.

[001553] *Preparation of compound WV-CA-291.*



24 WV-CA-291

[001554] A solution of compound **24** (44 g, 142.67 mmol, 1 *eq.*) in DCM (220 mL) and MeOH (220 mL) was cooled to -78 °C. Then mCPBA (36.93 g, 214.01 mmol, 1.5 *eq.*) and K_2CO_3 (29.58 g, 214.01 mmol, 1.5 *eq.*) was added. After addition, the mixture was stirred at -78 °C for 3 hr. And the

resulting mixture was stirred at 20 °C for 12 hr. LC-MS showed compound **24** was consumed completely and one main peak with desired MS was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient at 100 mL/min). **WV-CA-291** (12 g, 42.05 mmol, 29.47% yield, 95.08% purity) was obtained as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ= 7.98 - 7.92 (m, 2H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.61 - 7.53 (m, 2H), 4.50 - 4.39 (m, 1H), 3.33 - 3.15 (m, 3H), 2.97 - 2.78 (m, 2H), 1.89 - 1.64 (m, 4H). ^{13}CNMR (101 MHz, CHLOROFORM-d) δ = 139.61, 133.90, 129.31, 128.02, 71.21, 64.96, 60.05, 58.12, 21.23, 20.29. LCMS $[M + H]^{+}$: 272.0. LCMS purity 95.08%.

Example 4E. Example technologies for chirally controlled oligonucleotide preparation - example useful phosphoramidites

[001555] Among other things, the present disclosure provides phosphoramidites useful for oligonucleotide synthesis. In some embodiments, provided phosphoramidites are particularly useful for preparation of chirally controlled internucleotidic linkages. In some embodiments, provided phosphoramidites are particularly useful for preparing chirally controlled internucleotidic linkages, e.g., non-negatively charged internucleotidic linkages or neutral internucleotidic linkages, etc., that comprise P–N=. In some embodiments, the linkage phosphorus is trivalent. In some embodiments, the linkage phosphorus is pentavalent. In some embodiments, such internucleotidic linkages have the structure of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof.

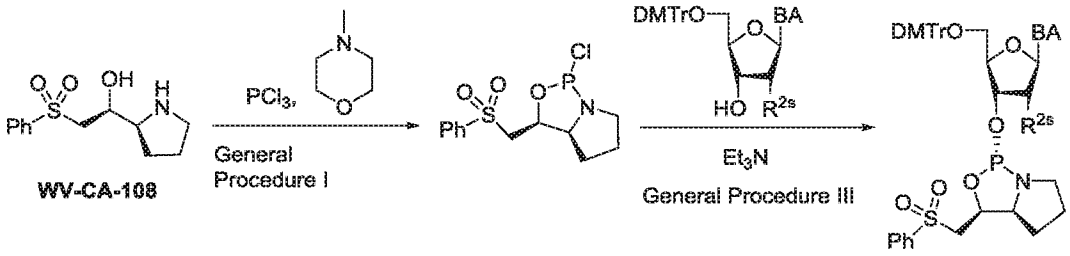
[001556] **General Procedure I for Chloroderivative:** In some embodiments, in an example procedure, a chiral auxiliary (174.54 mmol) was dried by azeotropic evaporation with anhydrous toluene (80 mL x 3) at 35 °C in a rota-evaporator and dried under high vacuum for overnight. A solution of this dried chiral auxiliary (174.54 mmol) and 4-methylmorpholine (366.54 mmol) dissolved in anhydrous THF (200 mL) was added to an ice-cooled (isopropyl alcohol-dry ice bath) solution of trichlorophosphine (37.07 g, 16.0 mL, 183.27 mmol) in anhydrous THF (150 mL) placed in three neck round bottomed flask through cannula under Argon (start Temp: -10.0 °C, Max: temp 0 °C, 28 min addition) and the reaction mixture was warmed at 15 °C for 1 hr. After that the precipitated white solid was filtered by vacuum under argon using airfree filter tube (Chemglass: Filter Tube, 24/40 Inner Joints, 80 mm OD Medium Frit, Airfree, Schlenk). The solvent was removed with rota-evaporator under argon at low temperature (25 °C) and the crude semi-solid obtained was dried under vacuum overnight (~15 h) and was used for the next step directly.

[001557] **General Procedure I for Chloroderivative:** In some embodiments, in an example

procedure, a chiral auxiliary (174.54 mmol) was dried by azeotropic evaporation with anhydrous toluene (80 mL x 3) at 35 °C in a rota-evaporator and dried under high vacuum for overnight. A solution of this dried chiral auxiliary (174.54 mmol) and 4-methylmorpholine (366.54 mmol) dissolved in anhydrous THF (200 mL) was added to an ice-cooled (isopropyl alcohol-dry ice bath) solution of trichlorophosphine (37.07 g, 16.0 mL, 183.27 mmol) in anhydrous THF (150 mL) placed in three neck round bottomed flask through cannula under Argon (start Temp: -10.0 °C, Max: temp 0 °C, 28 min addition) and the reaction mixture was warmed at 15 °C for 1 hr. After that the precipitated white solid was filtered by vacuum under argon using airfree filter tube (Chemglass: Filter Tube, 24/40 Inner Joints, 80 mm OD Medium Frit, Airfree, Schlenk). The solvent was removed with rota-evaporator under argon at low temperature (25 °C) and the crude semi-solid obtained was dried under vacuum overnight (~15 h) and was used for the next step directly.

[001558] **General Procedure III for Coupling:** In some embodiments, in an example procedure, a nucleoside (9.11 mmol) was dried by co-evaporation with 60 mL of anhydrous toluene (60 mL x 2) at 35 °C and dried under high vacuum for overnight. The dried nucleoside was dissolved in dry THF (78 mL), followed by the addition of triethylamine (63.80 mmol) and then cooled to -5 °C under Argon (for 2'F-dG/2'OMe-dG case 0.95 eq of TMS-Cl used). The THF solution of the crude (made from general procedure I (or) II, 14.57 mmol), was added through cannula over 3 min then gradually warmed to room temperature. After 1 hr at room temperature, TLC indicated conversion of SM to product (total reaction time 1 h), the reaction mixture was then quenched with H_2O (4.55 mmol) at 0 °C, and anhydrous $MgSO_4$ (9.11 mmol) was added and stirred for 10 min. Then the reaction mixture was filtered under argon using airfree filter tube, washed with THF, and dried under rotary evaporation at 26 °C to afford white crude solid product, which was dried under high vacuum overnight. The crude product was purified by ISCO-Combiflash system (rediSep high performance silica column pre-equilibrated with Acetonitrile) using Ethyl acetate/Hexane with 1% TEA as a solvent (compound eluted at 100% EtOAc/Hexanes/1% Et_3N) (for 2'F-dG case Acetonitrile/Ethyl acetate with 1% TEA used). After evaporation of column fractions pooled together, the residue was dried under high vacuum to afford the product as a white solid.

[001559] *Preparation of amidites (1030-1039).*



1030: R^{2s} = F, BA = G^{iBu}
1031: R^{2s} = F, BA = U
1032: R^{2s} = F, BA = C^{Ac}
1033: R^{2s} = F, BA = A^{Bz}
1034: R^{2s} = OMe, BA = A^{Bz}
1035: R^{2s} = MOE, BA = A^{Bz}
1036: R^{2s} = MOE, BA = G^{iBu}
1037: R^{2s} = MOE, BA = T
1038: R^{2s} = OMOE, BA = 5-Methyl-C^{Bz}
1039: R^{2s} = H, B = C^{Ac}

[001560] **Preparation of 1030**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (73%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 153.32. (ES) *m/z* Calculated for $C_{47}H_{50}FN_6O_{10}PS$: 940.98 $[M]^+$, Observed: 941.78 $[M + H]^+$.

[001561] **Preparation of 1031**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (78%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 153.62. (ES) *m/z* Calculated for $C_{42}H_{43}FN_3O_{10}PS$: 831.85 $[M]^+$, Observed: 870.58 $[M + K]^+$.

[001562] **Preparation of 1032**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (68%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 153.95. (ES) *m/z* Calculated for $C_{44}H_{46}FN_4O_{10}PS$: 872.26 $[M]^+$, Observed: 873.62 $[M + H]^+$.

[001563] **Preparation of 1033**: General Procedure I followed by General Procedure III used. white foamy solid. Yield: (87%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 151.70. (ES) *m/z* Calculated for $C_{50}H_{48}FN_6O_9PS$: 958.29 $[M]^+$, Observed: 959.79, 960.83 $[M + H]^+$.

[001564] **Preparation of 1034**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (65%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 154.80. (ES) *m/z* Calculated for $C_{51}H_{51}N_6O_{10}PS$: 971.31 $[M]^+$, Observed: 971.81 $[M + H]^+$.

[001565] **Preparation of 1035**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (76%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 156.50. (ES) *m/z* Calculated for $C_{53}H_{55}N_6O_{11}PS$: 1014.33 $[M]^+$, Observed: 1015.81 $[M + H]^+$.

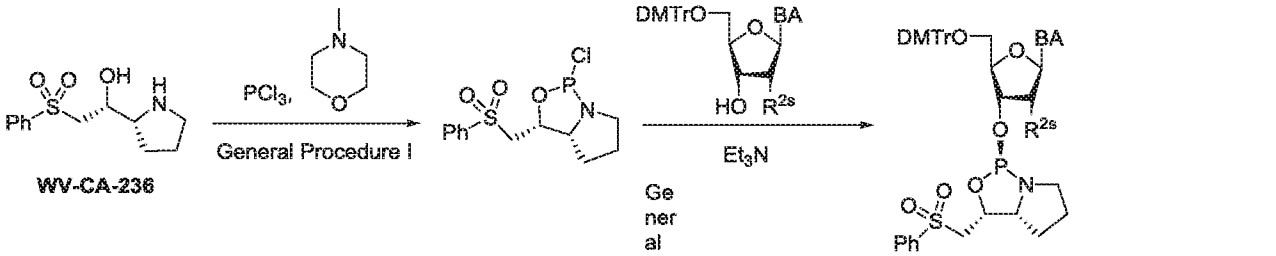
[001566] **Preparation of 1036**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (78%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 156.40. (ES) *m/z* Calculated for $C_{50}H_{57}N_6O_{12}PS$: 996.34 $[M]^+$, Observed: 997.90 $[M + H]^+$.

[001567] **Preparation of 1037**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (73%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 154.87. (ES) *m/z* Calculated for $C_{46}H_{52}N_3O_{12}PS$: 901.30 $[M]^+$, Observed: 940.83 $[M + K]^+$.

[001568] **Preparation of 1038**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (75%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 154.94. (ES) *m/z* Calculated for $C_{53}H_{57}N_4O_{12}PS$: 1004.34 $[M]^+$, Observed: 1005.86 $[M + H]^+$.

[001569] **Preparation of 1039**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (80%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 153.52. (ES) *m/z* Calculated for $C_{44}H_{47}N_4O_{10}PS$: 854.28 $[M]^+$, Observed: 855.41 $[M + H]^+$.

[001570] ***Preparation of amidites (1040-1049).***



1040: R^{2s} = F, BA = G^{iBu}
1041: R^{2s} = F, BA = U
1042: R^{2s} = F, BA = C^{Ac}
1043: R^{2s} = F, BA = A^{Bz}
1044: R^{2s} = OMe, BA = A^{Bz}
1045: R^{2s} = OMOE, BA = A^{Bz}
1046: R^{2s} = OMOE, BA = G^{iBu}
1047: R^{2s} = OMOE, BA = T
1048: R^{2s} = OMOE, BA = 5-Methyl-C^{Bz}
1049: R^{2s} = H, B = C^{Ac}

[001571] **Preparation of 1040**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (78%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 157.80. (ES) *m/z* Calculated for $C_{47}H_{50}FN_6O_{10}PS$: 940.98 $[M]^+$, Observed: 941.68 $[M + H]^+$.

[001572] **Preparation of 1041**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (78%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 157.79. (ES) *m/z* Calculated for $C_{42}H_{43}FN_3O_{10}PS$: 831.85 $[M]^+$, Observed: 870.68 $[M + K]^+$.

[001573] **Preparation of 1042**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (78%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 158.07. (ES) *m/z* Calculated for $C_{44}H_{46}FN_4O_{10}PS$: 872.26 $[M]^+$, Observed: 873.62 $[M + H]^+$.

[001574] **Preparation of 1043**: General Procedure I followed by General Procedure III used. white foamy solid. Yield: (86%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 156.48. (ES) *m/z* Calculated for $C_{50}H_{48}FN_6O_9PS$: 958.29 $[M]^+$, Observed: 959.79, 960.83 $[M + H]^+$.

[001575] **Preparation of 1044**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (65%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 154.80. (ES) *m/z* Calculated for $C_{51}H_{51}N_6O_{10}PS$: 971.31 $[M]^+$, Observed: 971.81 $[M + H]^+$.

[001576] **Preparation of 1045**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (77%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 154.74. (ES) *m/z* Calculated for $C_{53}H_{55}N_6O_{11}PS$: 1014.33 $[M]^+$, Observed: 1015.81 $[M + H]^+$.

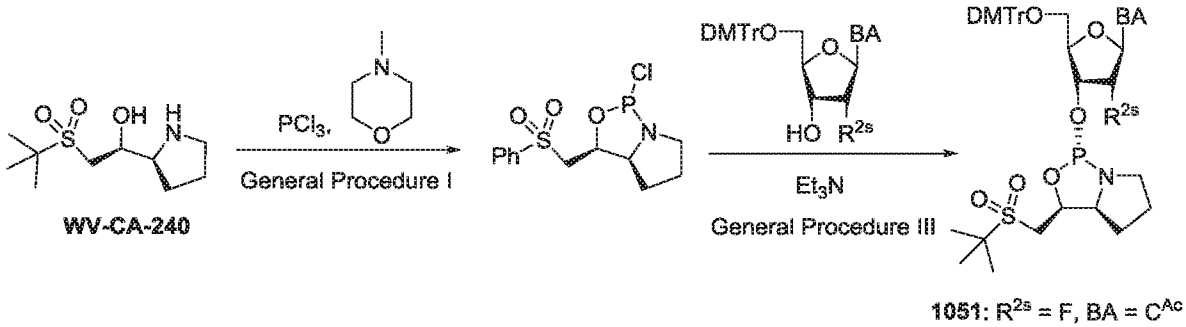
[001577] **Preparation of 1046**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (76%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 155.05. (ES) *m/z* Calculated for $C_{50}H_{57}N_6O_{12}PS$: 996.34 $[M]^+$, Observed: 997.90 $[M + H]^+$.

[001578] **Preparation of 1047**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (75%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 155.44. (ES) *m/z* Calculated for $C_{46}H_{52}N_3O_{12}PS$: 901.30 $[M]^+$, Observed: 940.83 $[M + K]^+$.

[001579] **Preparation of 1048**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (73%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 155.96. (ES) *m/z* Calculated for $C_{53}H_{57}N_4O_{12}PS$: 1004.34 $[M]^+$, Observed: 1005.86 $[M + H]^+$.

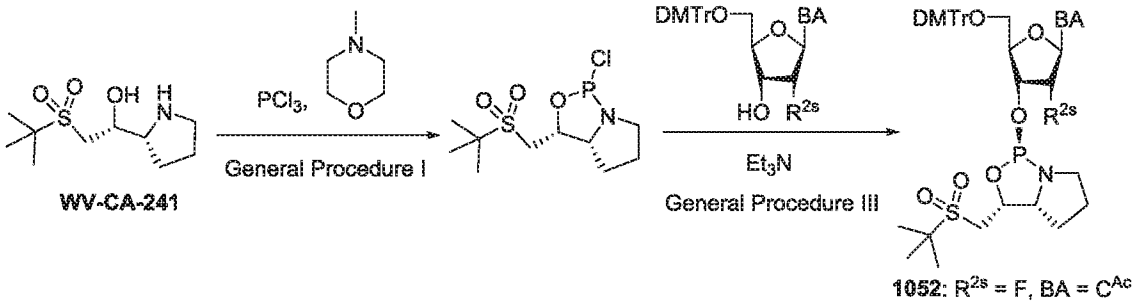
[001580] **Preparation of 1049**: General Procedure I followed by General Procedure III used. Off-white foamy solid. Yield: (80%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 156.37. (ES) *m/z* Calculated for $C_{44}H_{47}N_4O_{10}PS$: 854.28 $[M]^+$, Observed: 855.31 $[M + H]^+$.

[001581] ***Preparation of Amidites (1051).***



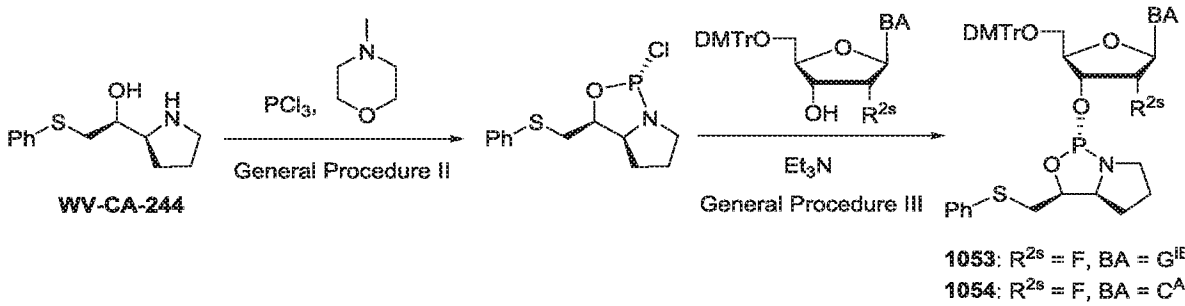
[001582] **Preparation of 1051**: General Procedure II followed by General Procedure III used. Off-white foamy solid. Yield: (72%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 154.26. (ES) *m/z* Calculated for $C_{42}H_{50}FN_4O_{10}PS$: 852.29 $[M]^+$, Observed: 853.52 $[M + H]^+$.

[001583] ***Preparation of Amidites (1052).***



[001584] **Preparation of 1052**: General Procedure II followed by General Procedure III used. Off-white foamy solid. Yield: (76%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 156.37. (ES) *m/z* Calculated for $C_{42}H_{50}FN_4O_{10}PS$: 852.29 $[M]^+$, Observed: 853.52 $[M + H]^+$.

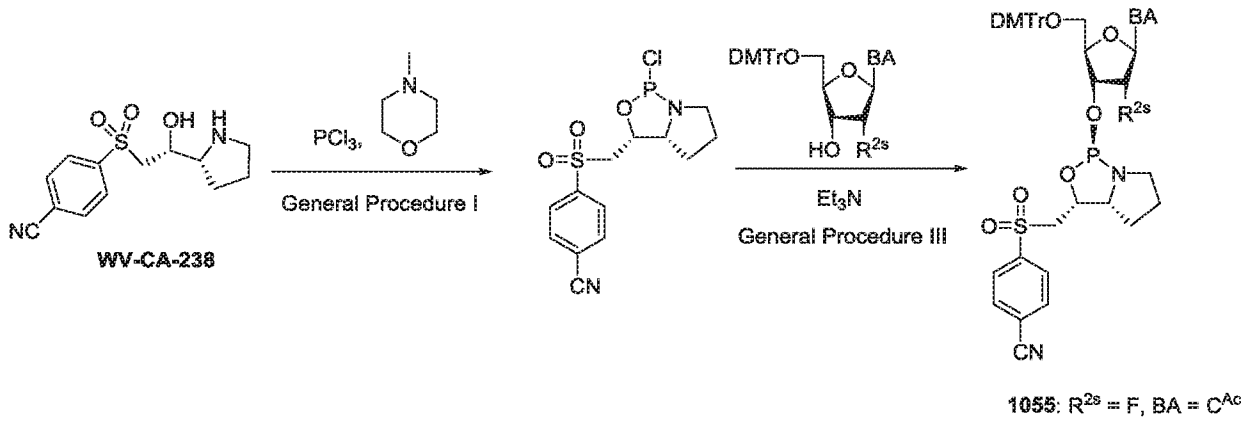
[001585] ***Preparation of Amidites (1053, 1054).***



[001586] **Preparation of 1053**: General Procedure II followed by General Procedure III used. Off-white foamy solid. Yield: (80%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 156.62. (ES) *m/z* Calculated for $C_{47}H_{50}FN_6O_8PS$: 908.98 $[M]^+$, Observed: 909.36 $[M + H]^+$.

[001587] **Preparation of 1054**: General Procedure II followed by General Procedure III used. Off-white foamy solid. Yield: (79%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 157.62. (ES) *m/z* Calculated for $C_{44}H_{46}FN_4O_8PS$: 840.90 $[M]^+$, Observed: 841.67 $[M + H]^+$.

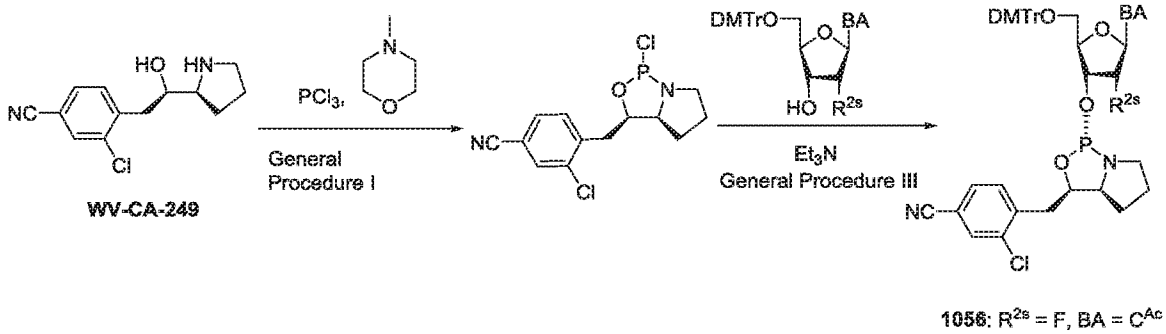
[001588] ***Preparation of Amidites (1055).***



[001589] **Preparation of 1055**: General Procedure II followed by General Procedure III used.

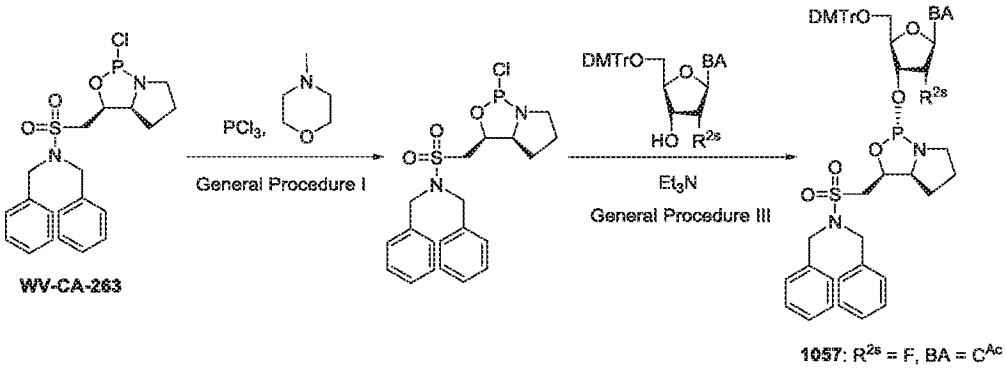
White foamy solid. Yield: (77 %). ^{31}P NMR (162 MHz, $CDCl_3$) δ 160.00. (ES) *m/z* Calculated for $C_{45}H_{45}FN_5O_{10}PS$: 897.26 $[M]^+$, Observed: 898.74 $[M + H]^+$.

[001590] *Preparation of Amidites (1056).*



[001591] **Preparation of 1056**: General Procedure II followed by General Procedure III used. Off-white foamy solid. Yield: (84%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 154.80. (ES) *m/z* Calculated for $C_{45}H_{44}ClFN_5O_8P$: 867.26 $[M]^+$, Observed: 868.69 $[M + H]^+$.

[001592] *Preparation of Amidites (1057).*



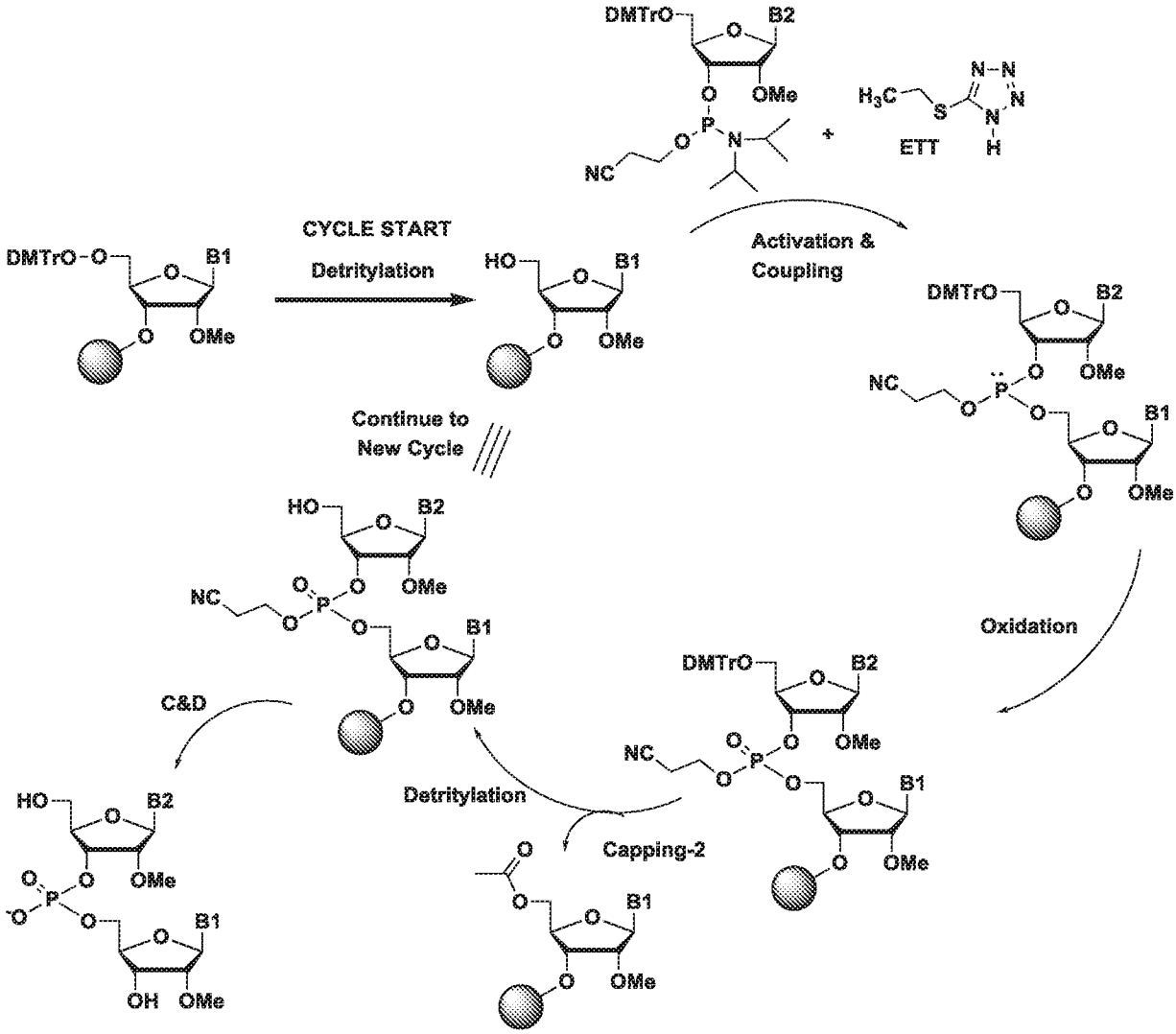
[001593] **Preparation of 1057**: General Procedure II followed by General Procedure III used. white foamy solid. Yield: (91%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 154.48. (ES) *m/z* Calculated for $C_{52}H_{55}FN_5O_{10}PS$: 991.34 $[M]^+$, Observed: 992.87 $[M + H]^+$.

Example 4F. Example technologies for chirally controlled oligonucleotide preparation - example cycles, conditions and reagents for oligonucleotide synthesis

[001594] In some embodiments, the present disclosure provides technologies (e.g., reagents, solvents, conditions, cycle parameters, cleavage methods, deprotection methods, purification methods, etc.) that are particularly useful for preparing chirally controlled internucleotidic linkages. In some embodiments, such internucleotidic linkages, e.g., non-negatively charged internucleotidic linkages or neutral internucleotidic linkages, etc., comprise P–N=, wherein P is the linkage phosphorus. In some embodiments, the linkage phosphorus is trivalent. In some embodiments, the linkage phosphorus is pentavalent. In some embodiments, such internucleotidic linkages have the structure of formula **I-n-1**, **I-**

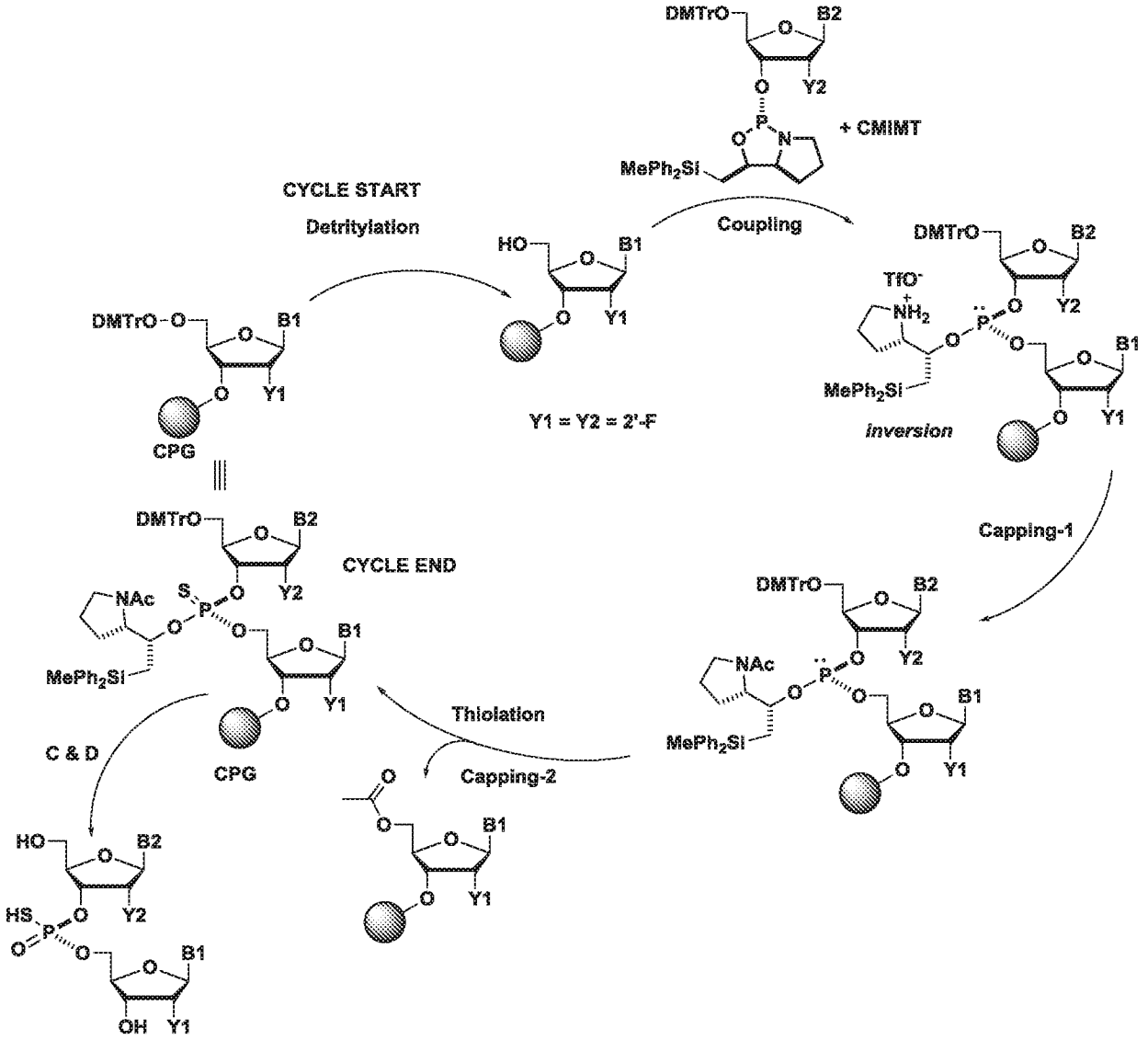
n-2, I-n-3, I-n-4, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1, II-d-2, or a salt form thereof. As demonstrated herein, technologies of the present disclosure can provide mild reaction conditions, high functional group compatibility, alternative deprotection and/or cleavage conditions, high crude and/or purified yields, high crude purity, high product purity, and/or high stereoselectivity.

[001595] In some embodiments, a cycle for preparing natural phosphate linkages comprises or consists of deprotection (e.g., detritylation), coupling, oxidation (e.g., using I_2/Pyr/Water or other suitable methods available in the art) and capping (e.g., cap 2 described herein or other suitable methods available in the art). An example cycle is depicted below, wherein B1 and B2 are independently nucleobases. As appreciated by those skilled in the art, various modifications, e.g., sugar modifications, base modifications, etc. are compatible and may be included.

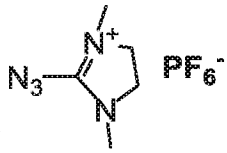


[001596] In some embodiments, a cycle for preparing non-natural phosphate linkages (e.g., phosphorothioate internucleotidic linkages) comprises or consists of deprotection (e.g., detritylation),

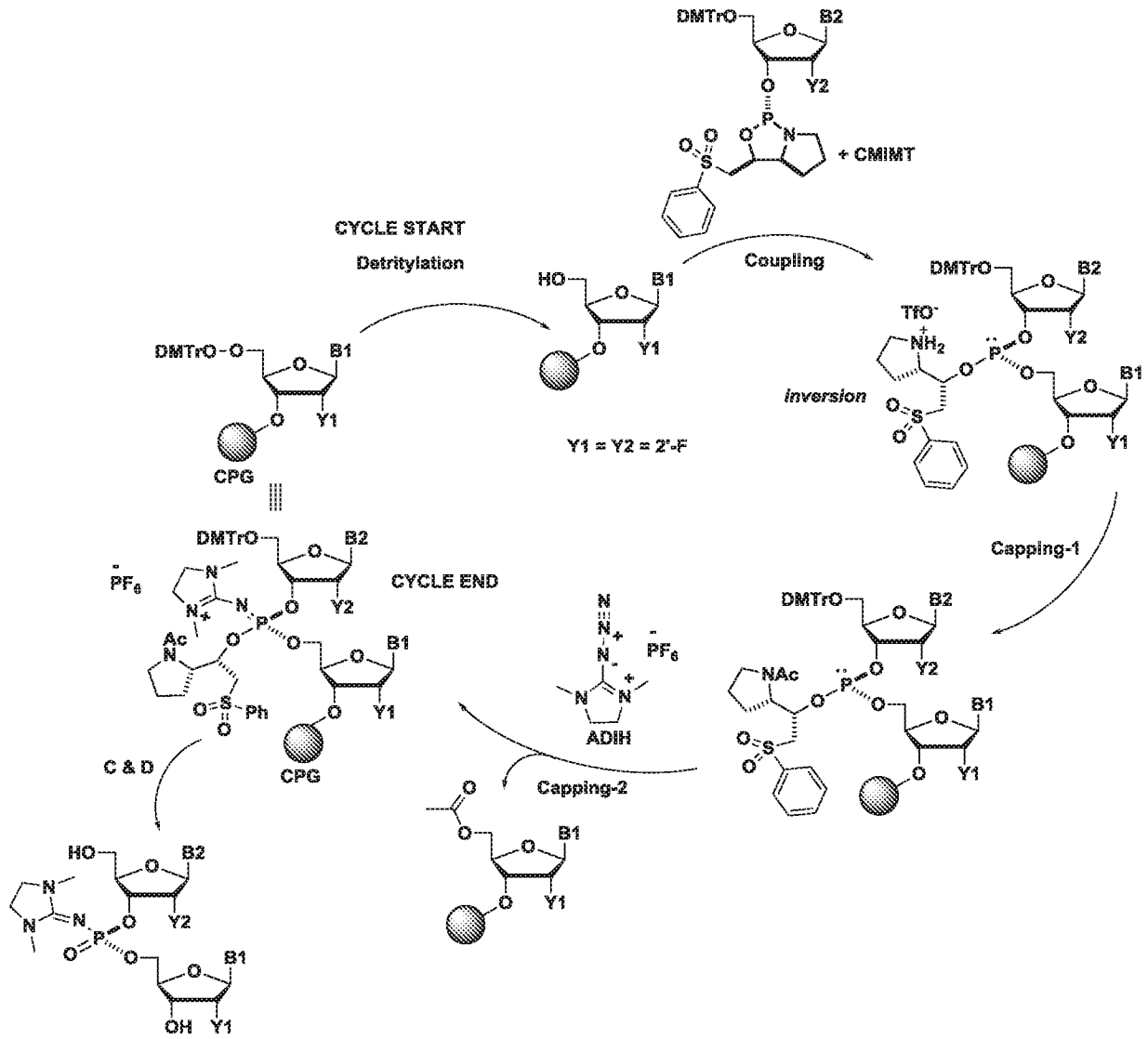
coupling, a first capping (e.g., capping-1 as described herein), modification (e.g., thiolation using XH or other suitable methods available in the art), and a second capping (e.g., capping-2 as described herein or other suitable methods available in the art). An example cycle is depicted below, wherein B1 and B2 are independently nucleobases. As appreciated by those skilled in the art, various modifications, e.g., sugar modifications, base modifications, etc. are compatible and may be included. In some embodiments, a cycle using a DPSE chiral auxiliary is referred to as a DPSE cycle or DPSE amidite cycle.



[001597] In some embodiments, a cycle for preparing non-natural phosphate linkages (e.g., certain non-negatively charged internucleotidic linkages, neutral internucleotidic linkages, etc.), particularly those comprising P–N=, wherein P is the linkage phosphorus and/or those have the structure of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, **III**, or a salt form thereof, comprises or consists of deprotection (e.g., detritylation), coupling, a first capping (e.g., capping-



1 as described herein), modification (e.g., using ADIH (, 2-azido-1,3-dimethyl-4,5-dihydro-1H-imidazol-3-ium hexafluorophosphate(V)) or other suitable methods available in the art), and a second capping (e.g., capping-2 as described herein or other suitable methods available in the art). An example cycle is depicted below, wherein B1 and B2 are independently nucleobases. In some embodiments, a chiral auxiliary utilized in such a cycle for preparing a chirally controlled internucleotidic linkage comprises an electron-withdrawing group as described herein, e.g., various chiral auxiliaries having a G^2 comprising an electron-withdrawing group. In some embodiments, G^2 comprises a $-SO_2R$ group as described herein (e.g., in some embodiments, R is optionally substituted phenyl; in some embodiments, R is optionally substituted alkyl (e.g., t-butyl); in some embodiments, it was observed that R being alkyl (e.g., R being t-butyl (e.g., WV-CA-240)) can provide comparable results to R being optionally substituted phenyl (e.g., R being phenyl (PSM))). As appreciated by those skilled in the art, various modifications, e.g., sugar modifications, base modifications, etc. are compatible and may be included. In some embodiments, a cycle using a PSM chiral auxiliary is referred to as a PSM cycle or PSM amidite cycle.



[001598] Various cleavage and deprotection methods may be utilized in accordance with the present disclosure. In some embodiments, as appreciated by those skilled in the art, parameters of cleavage and deprotection (e.g., bases, solvents, temperatures, equivalents, time, etc.) can be adjusted in view of, e.g., structures of oligonucleotides to be prepared (e.g., nucleobases, sugars, internucleotidic linkages, and modifications/protections thereof), solid supports, reaction scales, etc. In some embodiments, cleavage and deprotection comprise one, or two or more, individual steps. For example, in some embodiments, a two-step cleavage and deprotection is utilized. In some embodiments, a cleavage and deprotection step comprises a fluoride-containing reagent (e.g., TEA-HF, optionally buffered with additional bases such as TEA) in a suitable solvent (e.g., DMSO/H_2O) at a suitable amount (e.g., about 100 or more (e.g., 100 ± 5) mL/mmol) and is performed at a suitable temperature (e.g., about 0-100, 0-80, 0-50, 0-40, 0-30, 0, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 °C (e.g., in one example, 27 ± 2 °C)) for a suitable period of time (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22,

23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50 or more hours (e.g., in one example, 6 ± 0.5 h)). In some embodiments, a cleavage and deprotection step comprises a suitable base (e.g., NR_3) in a suitable solvent (e.g., water) (e.g., conc. NH_4OH) at a suitable amount (e.g., about 200 or more (e.g., 200 ± 5) mL/mmol) and is performed at a suitable temperature (e.g., about 0-100, 0-80, 0-50, 0-40, 0-30, 0, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 °C (e.g., in one example, 37 ± 2 °C)) for a suitable period of time (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50 or more hours (e.g., in one example, 24 ± 1 h)). In some embodiments, cleavage and deprotection comprises or consists of two steps, wherein one step (e.g., step 1) is 1 x TEA-HF in $DMSO/H_2O$, 100 ± 5 mL/mmol, 27 ± 2 °C and 6 ± 0.5 h, and the other step (e.g., step 2) is conc. NH_4OH, 200 ± 5 mL/mmol, 37 ± 2 °C and 24 ± 1 h. Certain examples of cleavage and deprotection processes are described here.

[001599] As appreciated by those skilled in the art, oligonucleotide synthesis is often performed on solid support. Many types of solid support are commercially available and/or can be otherwise prepared/obtained and can be utilized in accordance with the present disclosure. In some embodiments, a solid support is CPG. In some embodiments, a solid support is NittoPhase HL. Types and sizes of solid support can be selected based on desired applications, and in some cases, for a specific use one type of solid support may perform better than the other. In some embodiments, it was observed that for certain preparations CPG can deliver higher crude yields and/or purities compared to certain polymer solid supports such as NittoPhase HL.

[001600] Amidites are typically dissolved in solvents at suitable concentrations. In some embodiments, amidites are dissolved in ACN. In some embodiments, amidites are dissolved in a mixture of two or more solvents. In some embodiments, amidites are dissolved in a mixture of ACN and IBN (e.g., 20% ACN/ 80% IBN). Various concentrations of amidites may be utilized, and may be adjusted in view of specific conditions (e.g., solid support, oligonucleotides to be prepared, reaction times, scales, etc.). In some embodiments, a concentration of about 0.01-0.5, 0.05-0.5, 0.1-0.5, 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45 or 0.5 M is utilized. In some embodiments, a concentration of about 0.2 M is utilized. In many embodiments, amidite solutions are dried. In some embodiments, 3 Å molecular sieves are utilized to dry amidite solutions (or keep amidite solutions dry). In some embodiments, molecular sieves are utilized at about 15-20% v/v.

[001601] Various equivalents of amidites may be useful for oligonucleotide synthesis. As those skilled in the art will appreciate, equivalents of amidites can be adjusted in view of specific conditions (e.g., solid support, oligonucleotides to be prepared, reaction times, scales, etc.), and the same or different equivalents may be utilized during synthesis. In some embodiments, equivalents of amidites are about 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5 or more. In some embodiments, a suitable equivalent is about 2. In some embodiments, a suitable equivalent is about 2.5. In some embodiments, a suitable equivalent is about 3.

In some embodiments, a suitable equivalent is about 3.5. In some embodiments, a suitable equivalent is about 4.

[001602] A number of activators are available in the art and may be utilized in accordance with the present disclosure. In some embodiments, an activator is ETT. In some embodiments, an activator is CMIMT. In some embodiments, CMIMT is utilized for chirally controlled synthesis. As appreciated by those skilled in the art, the same or different activators may be utilized for different amidites, and may be utilized at different amounts. In some embodiments, activators are utilized at about 40-100%, e.g., 40%, 50%, 60%, 70%, 80% or 90% delivery. In some embodiments, a delivery is about 60% (e.g., for ETT). In some embodiments, a delivery is about 70% (e.g., for CMIMT). In some embodiments, molar ratio of activator/amidite is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more. In some embodiments, a molar ratio is about 3-6. In some embodiments, a molar ratio is about 1. In some embodiments, a molar ratio is about 2. In some embodiments, a molar ratio is about 3. In some embodiments, a molar ratio is about 4. In some embodiments, a molar ratio is about 5. In some embodiments, a molar ratio is about 6. In some embodiments, a molar ratio is about 7. In some embodiments, a molar ratio is about 8. In some embodiments, a molar ratio is about 9. In some embodiments, a molar ratio is about 10. In some embodiments, a molar ratio is about 2-5, 2-4 or 3-4 (e.g., for ETT). In some embodiments, a molar ratio is about 3.7 (e.g., for ETT). In some embodiments, a molar ratio is about 3-8, 4-8, 4-7, 4-6, 5-7, 5-8 or 5-6 (e.g., for CMIMT). In some embodiments, a molar ratio is about 5.8 (e.g., for CMIMT).

[001603] As appreciated by those skilled in the art, various suitable flowrates and reaction times may be utilized for oligonucleotide synthesis, and may be adjusted according to oligonucleotides to be prepared, scales, synthetic setups, etc. In some embodiments, a recycle flow rate utilized for synthesis is about 200 cm/h. In some embodiments, a recycle time is about 1-10 minutes. In some embodiments, a recycle time is about 8 minutes. In some embodiments, a recycle time is about 10 minutes.

[001604] Many technologies are available to modify P(III) linkages, e.g., after coupling. For example, various methods are available to convert a P(III) linkage to a P(V) P(=O)-type linkage, e.g., via oxidation. In some embodiments, I_2/Pyr/H_2O is utilized. Similarly, many methods are available to convert a P(III) linkage to a P(V) P(=S)-type linkage, e.g., via sulfurization. In some embodiments, as illustrated herein, XH is utilized as a thiolation reagent. Technologies for converting P(III) linkages to P(V) P(=N−)-type linkages are also widely available and can be utilized in accordance with the present disclosure. In some embodiments, as illustrated herein ADIH is employed. Suitable reaction parameters are described herein. In some embodiments, ADIH is used at a concentration of about 0.01-0.5, 0.05-0.5, 0.1-0.5, 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45 or 0.5 M. In some embodiments, concentration of ADIH is about 0.25 M. In some embodiments, concentration of ADIH is about 0.3 M. In some embodiments, ADIH is utilized at about 1-50, 1-40, 1-30, 1-25, 1-20, 1-10, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,

11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45 or 50 or more equivalent. In some embodiments, equivalent of ADIH is about 7.5. In some embodiments, equivalent of ADIH is about 10. In some embodiments, equivalent of ADIH is about 15. In some embodiments, equivalent of ADIH is about 20. In some embodiments, equivalent of ADIH is about 23. In some embodiments, equivalent of ADIH is about 25. In some embodiments, equivalent of ADIH is about 30. In some embodiments, equivalent of ADIH is about 35. In some embodiments, one experiment, ADIH was utilized at 15.2 equivalent, and 15 min contact time. In some embodiments, depending on amidites, concentrations, equivalents, contact times, etc. of reagents, e.g., ADIH, may be adjusted.

[001605] Technologies of the present disclosure are suitable for preparation at various scales. In some embodiments, synthesis is performed at hundreds of umol or more. In some embodiments, a scale is about 200 umol. In some embodiments, a scale is about 300 umol. In some embodiments, a scale is about 400 umol. In some embodiments, a scale is about 500 umol. In some embodiments, a scale is about 550 umol. In some embodiments, a scale is about 600 umol. In some embodiments, a scale is about 650 umol. In some embodiments, a scale is about 700 umol. In some embodiments, a scale is about 750 umol. In some embodiments, a scale is about 800 umol. In some embodiments, a scale is about 850 umol. In some embodiments, a scale is about 900 umol. In some embodiments, a scale is about 950 umol. In some embodiments, a scale is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25, or more mmol. In some embodiments, a scale is about 1 mmol or more. In some embodiments, a scale is about 2 mmol or more. In some embodiments, a scale is about 5 mmol or more. In some embodiments, a scale is about 10 mmol or more. In some embodiments, a scale is about 15 mmol or more. In some embodiments, a scale is about 20 mmol or more. In some embodiments, a scale is about 25 mmol or more.

[001606] In some embodiments, observed yields were 85-90 OD/umol (e.g., 85,000 OD/mmol for a 10.2 mmol synthesis, with 58.4% crude purity (%FLP)).

[001607] Technologies of the present disclosure, among other things, can provide various advantages when utilized for preparing oligonucleotides comprising chirally controlled internucleotidic linkages, e.g., those comprising P–N= wherein P is a linkage phosphorus (e.g., internucleotidic linkages of **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof, etc.). For example, as demonstrated herein, technologies of the present disclosure can provide high crude purities and yields (e.g., in many embodiments, about 55-60% full-length product for a 20-mer oligonucleotide) with minimal amount of shorter oligonucleotides (e.g., from incomplete coupling, decomposition, etc.). Such high crude yields and/or purities, among other things, can significantly reduce downstream purification and can significantly reduce production cost and cost of goods, and in some

embodiments, greatly facilitate or make possible large scale commercial production, clinical trials and/or commercial sales.

[001608] ***Example procedure for preparing chirally controlled oligonucleotide compositions - WV-13864.***

[001609] Described below are example procedures for preparing WV-13864 using controlled pore glass (CPG) low bulk density solid support(e.g., 2'-fC (acetyl) via CNA linker CPG (600Å LBD)). Useful phosphoramidites include 5′-ODMTr-2′-F-dA(N6-Bz)-(L)-DPSE phosphoramidite, 5′-ODMTr-2′-F-dC(N4-Ac)-(L)-DPSE phosphoramidite, 5′-ODMTr-2′-F-dG(N2-iBu)-(L)-DPSE phosphoramidite, 5′-ODMTr-2′-F-dU-(L)-DPSE phosphoramidite, 5′-ODMTr-2′-OMe-G(N^2-iBu)-(L)-DPSE phosphoramidite, 5′-ODMTr-2′-F-dC(N4-Ac)-(L)-PSM phosphoramidite, 5′-ODMTr-2′-F-dG(N2-iBu)-(L)-PSM phosphoramidite, 5'-DMT-2'-OMe-A (Bz)-*β*-Cyanoethyl phosphoramidite, and 5'-DMT-2'-OMe-C (Ac)-*β*-Cyanoethyl phosphoramidite.

[001610] 0.1 M Xanthane hydride solution (XH) was used for thiolation. Neutral PN linkages were formed utilizing 0.3 M of 2-azido-1,3-dimethyl-imidazolinium hexafluorophosphate (ADIH) in acetonitrile. Oxidation solution was 0.04-0.06 M iodine in pyridine/water, 90/10, v/v. Cap A was *N*-Methylimidazole in acetonitrile, 20/80, v/v. Cap B was acetic anhydride/2,6-Lutidine/Acetonitrile, 20/30/50, v/v/v. Deblocking was performed using 3% dichloroacetic acid in toluene. NH_4OH used was 28-30% concentrated ammonium hydroxide.

[001611] Detritylation.

[001612] To initiate the synthesis, the 5'-*O*DMTr-2'-F-dC(*N*4-Ac)-CPG solid support was subjected to acid catalyzed removal of the DMTr protecting group from the 5'-hydroxyl by treatment with 3% (DCA) in toluene. The DMTr removal step was usually visualized with strong red or orange color and can be monitored by UV watch command at the wavelength of 436 nm.

[001613] DMTr removal can be repeated at the beginning of a synthesis cycle. In every case, following detritylation, the support-bound material was washed with acetonitrile in preparation for the next step of the synthesis.

[001614] Coupling.

[001615] Amidites were dissolved either in acetonitrile (ACN) or in 20% isobutyronitrile (IBN)/80% ACN at a concentration of 0.2M without density correction. The solutions were dried over molecular sieves (3Å) not less than 4 h before use (15-20%, v/v).

Amidite	Solvent	Concentration	MS3Å
5'-*O*DMTr-2'-*O*Me-A(*N*6-Bz)-CE	ACN	0.2M	15-20%, v/v
5'-*O*DMTr-2'-*O*Me-C(*N*4-Ac)-CE	ACN	0.2M	15-20%, v/v

5'-*O*DMTr-2'-F-dA(*N*6-Bz)-(*L*)-DPSE	ACN	0.2M	15-20%, v/v
5'-*O*DMTr-2'-F-dC(*N*4-Ac)-(*L*)-DPSE	ACN	0.2M	15-20%, v/v
5'-*O*DMTr-2'-F-dU-(*L*)-DPSE	20% IBN/ 80% ACN	0.2M	15-20%, v/v
5'-*O*DMTr-2'-F-dG(*N*2-iBu)-(*L*)-DPSE	ACN	0.2M	15-20%, v/v
5'-*O*DMTr-2'-*O*Me-G(*N*2-iBu)-(*L*)-DPSE	20% IBN/ 80% ACN	0.2M	15-20%, v/v
5'-*O*DMTr-2'-F-dC(*N*4-Ac)-(*L*)-PSM	ACN	0.2M	15-20%, v/v
5'-*O*DMTr-2'-F-dG(*N*2-iBu)-(*L*)-PSM	ACN	0.2M	15-20%, v/v

[001616] Dual activators (CMIMT and ETT) coupling approach were utilized. Both activators were dissolved in ACN at a concentration of 0.5M. CMIMT has been used for chirally controlled coupling with CMIMT to amidite molar ratio of 5.833/1. ETT was used for the coupling of standard amidites (for natural phosphate linkages) with ETT to amidite molar ratio of 3.752/1. Recycle time for all DPSE and PSM amidites was 10 min except mG-L-DPSE which was 8 min. All standard amidites were coupled for 8 min.

[001617] Cap-1 (Capping-1, first capping).

[001618] Cap B (Ac_2O / 2,6-lutidine / MeCN (2:3:5, v/v/v)) was used. In some embodiments, Cap-1 capped secondary amine groups, e.g., on the chrial auxiliaries. In some embodiments, incomplete protection of secondary amines may lead side reaction resulting in a failed coupling or formation of one or more by-products. In some embodiments, Cap-1 may not be an efficient condition for esterification (e.g., a condition less efficient than Cap-2 (the second capping) for capping unreacted 5'-OH).

[001619] Thiolation for DPSE Cycles.

[001620] Following Cap-1, phosphite intermediates, P(III), were modified with sulfurizing reagent. In an example preparation, 1.2 CV (6-7 equivalent) of sulfurizing reagent (0.1 M XH / pyridine-ACN, 1:1, v/v) was delivered through the synthetic column via flow through mode over 6 min contact time to form P(V).

[001621] Azide Reaction for PSM Cycles.

[001622] After Cap-1, a suitable reagent (e.g., comprising $-N_3$ such as ADIH), in ACN was used to form neutral internucleotidic linkages (PN linkages). In an example preparation, 10.3 eq. of 0.25 M ADIH over 10 min contact time for fG-L-PSM and 25.8 eq. of 0.3 M ADIH over 15 min contact time for fC-L-PSM were utilized in the respective cycles.

[001623] Oxidation for Standard Nucleotide Cycles.

[001624] Cap-1 step was not necessary for standard amidite cycle. After coupling of a standard amidite onto the solid support, the phosphite intermediate, P(III), was oxidized with 0.05 M of iodine/water/pyridine solution to form P(V). In an example preparation, 3.5 eq. of oxidation solution delivered to the column by a flow through mode over 2 min contact time for efficient oxidation.

[001625] Cap-2 (capping-2, a second capping).

[001626] Coupling efficiency on the solid phase oligonucleotide synthesis for each cycle was approx. 97-100% and monitored by, e.g., release of DMTr cation. Residual uncoupled 5'-hydroxyl groups, typically 1-3% by detrit monitoring, on the solid support were blocked with Cap A (20% *N*-Methylimidazole in acetonitrile (NMI/ACN = 20/80, v/v)) and Cap B (20%:30%:50% = Ac_2O:2,6-Lutidine: ACN (v/v/v)) reagents (e.g., 1:1). Both reagents (e.g., 0.4 CV) were delivered to the column by flow through mode over 0.8 min contact time to prevent formation of failure sequences. Uncapped amine groups may also be protected in this step.

[001627] As illustrated herein, in some embodiments, a DPSE amidite or DPSE cycle is Detritylation -> Coupling -> Cap-1 (Capping-1, first capping) -> Thiolation -> Cap-2 (Capping-1, Post-capping, second capping); in some embodiments, a PSM amidite or PSM cycle is Detritylation -> Coupling -> Cap-1 (Capping-1, first capping) -> Azide reaction -> Cap-2 (Capping-1, Post-capping, second capping); in some embodiments, a standard amidite or standard cycle (traditional, non-chirally controlled) is Detritylation -> Coupling -> Oxidation -> Cap-2 (Capping-1, Post-capping, second capping).

[001628] Synthetic cycles were selected and repeated until the desired length was achieved.

[001629] Amine wash.

[001630] In some embodiments, provided technologies are particularly effective for preparing oligonucleotides comprising internucleotidic linkages that comprise P–N=, wherein P is the linkage phosphorus. In some embodiments, provided technologies comprise contacting an oligonucleotide intermediate with a base. In some embodiments, a contact is performed after desired oligonucleotide lengths have been achieved. In some embodiments, such a contact provides an oligonucleotide comprising internucleotidic linkages that comprise P–N=, wherein P is the linkage phosphorus (e.g., those of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof). In some embodiments, a contact removes a chiral auxiliary (e.g., those with a G^2 that is connected to the rest of the molecule through a carbon atom, and the carbon atom is connected to at least one electron-withdrawing group (e.g., WV-CA-231, WV-CA-236, WV-CA-240, etc.)). In some embodiments, a contact is performed utilizing a base or a solution of a base which is substantially free of OH^- or water (anhydrous). In some embodiments, a base is an amine (e.g., $N(R)_3$). In some embodiments, an amine has the structure of $NH(R)_2$, wherein each R is independently optionally substituted C1-6 aliphatic; in some embodiments, each R is independently optionally

substituted C1-6 alkyl. In some embodiments, a base is *N*, *N*-diethylamine (DEA). In some embodiments, a base solution is 20% DEA/ACN. In some embodiments, such a contact with a base lowers levels of by-products which, at one or more locations of internucleotidic linkages that comprise P–N=, have instead natural phosphate linkages.

[001631] In an example preparation, an on-column amine wash was performed after completion of oligonucleotide nucleotide synthesis cycles, by five column volume of 20% DEA in acetonitrile over 15 min contact time.

[001632] In some embodiments, contact with a base may also remove 2-cyanoethyl group used for construction of standard natural phosphate linkage. In some embodiments, contact with a base provide a natural phosphate linkage (e.g., in a salt form in which the cation is the corresponding ammonium salt of the amine base).

[001633] Cleavage and deprotection.

[001634] After contact with a base, oligonucleotides are exposed to further cleavage and deprotection. In an example preparation, auxiliary removal (e.g., DPSE), cleavage & deprotection was a two steps process. In step 1, CPG solid support with oligonucleotides was treated with 1 x TEA-HF solution (DMSO: Water: TEA.3HF: TEA = 43: 8.6: 2.8: 1 = v/v/v/v, 100 ± 5 uL/ umol) for 6 ± 0.5h at 27 ± 2 °C. The bulk slurry was then treated with concentrated ammonium hydroxide (28-30%, 200 ± 10 mL/mmol) for 24 ± 1h at 37 ± 2 °C (step 2) to release oligonucleotide from the solid support. Crude product was collected by filtration. Filtrates were combined with washes (e.g., water) of the solid support. In some embodiments, observed yields were about 80-90 OD/umole.

[001635] ***Example procedure for preparing chirally controlled oligonucleotide compositions - WV-13835.***

[001636] In an example preparation, WV-13835 was prepared at a 1.2 mmol scale starting from CPG 2'-F-U. DPSE was utilized as chiral auxiliary for chirally controlled internucleotidic linkages. The preparation comprised multiple cycles comprising a de-blocking step (detritylation under an acidic condition), a coupling step (with a DPSE phosphoramidite), a pre-modification capping step (e.g., Cap B), a modification step (e.g., thiolation using 0.1M XH in Pyr/CAN), a post-modification capping step (e.g., under a cap 2 condition (1:1 Cap A + Cap B). In some embodiments, a cycle comprises a modification step which is or comprises oxidation with I_2/Pyr/H_2O. Cleavage and deprotection included two steps, wherein step one utilized TEA-HF at 100 mL/mmol and 27 ± 2.5 °C, and step 2 utilized conc. NH_4OH at 200 mL/mmol and 37 ± 2.5 °C. Total crude yield was 91800 OD (76500 OD/mmol). Neat % FLP was 53.6% and NAP (after de-salting) % FLP was 58.3%. % FLP in crude was 1.71 g.

[001637] *Example procedure for preparing chirally controlled oligonucleotide compositions - WV-14791.*

[001638] In an example preparation, WV-14791 was prepared at a 402 umol scale starting from CPG 2'-F-U. DPSE was utilized as chiral auxiliary for chirally controlled phosphorothioate internucleotidic linkages, and PSM for chirally controlled n001. The preparation comprised multiple cycles comprising a de-blocking step (detritylation under an acidic condition), a coupling step (with a DPSE (for a chirally controlled phosphorothioate internucleotidic linkage) or PSM phosphoramidites (for a chirally controlled n001 internucleotidic linkage)), a pre-modification capping step (e.g., Cap B), a modification step (e.g., thiolation using 0.1M XH in Pyr/CAN for phosphorothioate internucleotidic linkages, 2-azido-1,3-dimethyl-imidazolinium hexafluorophosphate in CAN for n001), a post-modification capping step (e.g., under a cap 2 condition (1:1 Cap A + Cap B). In some embodiments, a cycle comprises a modification step which is or comprises oxidation with I_2/Pyr/H_2O. Total crude yield was 27000 OD (67.1 OD/umol). Neat % FLP was 45.7% and NAP (after de-salting) % FLP was 51.8%. % FLP in crude was 445 mg.

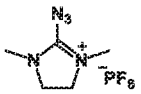
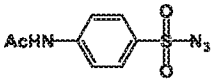
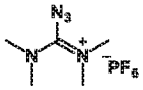
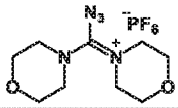
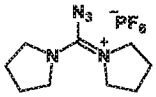
[001639] *Example procedure for preparing chirally controlled oligonucleotide compositions - WV-14344.*

[001640] In an example preparation, WV-14344 was prepared at a 400 umol scale starting from CPG 2'-F-C. DPSE was utilized as chiral auxiliary for chirally controlled phosphorothioate internucleotidic linkages, and PSM for chirally controlled n001. The preparation comprised multiple cycles comprising a de-blocking step (detritylation under an acidic condition), a coupling step (with a DPSE (for a chirally controlled phosphorothioate internucleotidic linkage) or PSM phosphoramidites (for a chirally controlled n001 internucleotidic linkage)), a pre-modification capping step (e.g., Cap B), a modification step (e.g., thiolation using 0.1M XH in Pyr/CAN for phosphorothioate internucleotidic linkages, 2-azido-1,3-dimethyl-imidazolinium hexafluorophosphate in CAN for n001), a post-modification capping step (e.g., under a cap 2 condition (1:1 Cap A + Cap B). In some embodiments, a cycle comprises a modification step which is or comprises oxidation with I_2/Pyr/H_2O. Total crude yield was 32000 OD (80 OD/umol). Neat % FLP was 48.8% and NAP (after de-salting) % FLP was 59.2%. % FLP in crude was 571 mg.

[001641] *Example preparation of additional chirally controlled oligonucleotide compositions.*

[001642] Various oligonucleotide compositions including chirally controlled oligonucleotide composition were prepared utilizing technologies described herein. In some embodiments, oligonucleotide compositions were prepared using automated solid-phase synthesis. Certain preparations were performed at 25 umol using TWIST™ columns 10um/15um column (GlenResearch, catalog #20-0040) filled with 325 mg of CNA linked nucleosides-CPG. Example cycles and azide modification reagents for chirally controlled internucleotidic linkages at 25 umol were shown below.

Step	Operation	Reagents	Volume	Waiting time
1	Deblocking (detritylation)	3% DCA/DCM	10 mL	1 min
2	Coupling	0.2M monomer/MeCN 0.6M CMIMT/MeCN	0.5 mL 1 mL	8 min
3	Pre-modification capping (cap-1)	Cap-B	2 mL	2 min
4	Modification (sulfurization or azide reaction)	0.2M XH/pyridine or 0.5M azide reagent/MeCN	2 mL 2 mL	6 min 10 min
5	Post-modification capping (cap-2)	Cap-A + Cap-B	2 mL	45 s

Final linkage	Azide Reagent	Final linkage	Azide reagent
n001		n006	
n003		n008	
n004			

[001643] After cycles were completed, the CPG support was treated with 20% DEA in MeCN for 12 min, washed with dry MeCN and dried under argon and vacuum. The dried CPG support was transferred into a 15 mL plastic tube, treated with 1X solution (1M HF-TEA in H_2O-DMSO (1:5, v/v), 100 uL/umol) for 6 h at 28 °C, then added conc. NH_3 (200 uL/umol) and reacted for 24 h at 37 °C. The mixture was cooled to room temperature and the CPG was removed by membrane filtration, and the product was analyzed by LTQ and RP-UPLC with a linear gradient of MeCN (1–15%/15 min) in (10 mM TEA, 100 mM HFIP in water) at 55 °C at a rate of 0.8 mL/min. Crude oligonucleotides were purified by AEX-HPLC eluting with 20 mM NaOH to 2.5M NaCl, and desalted to obtain the target oligonucleotide compositions.

[001644] Example preparations were listed below, with crude UPLC purity ranging from about 9% to about 58% percent. Higher crude HPLC purities were observed for preparation of the same and/or other oligonucleotides.

Oligonucleotide	Scale (umol)	Observed Mass
WV-16006	70	6912.3
WV-16007	70	7068.9
WV-24092	24	7282
WV-24098	24	7237.1
WV-24104	24	7399.1
WV-24109	24	7355.1
WV-25536	24	6729.1
WV-25537	24	6705.2
WV-25538	24	6739.1
WV-25539	24	6702
WV-25540	24	6726.9
WV-25541	25	7012.6
WV-25542	25	7014.1
WV-25543	25	6989.9
WV-25544	25	7024.2

[001645] Among other things, provided technologies provided high crude purities and/or yields. In many preparations (various scales, reagents concentrations, reaction times, etc.), about 55-60% crude purities (% FLP) were obtained, with minimal amount of shorter oligonucleotides (e.g., from incomplete coupling, decomposition, side-reactions, etc.). In many embodiments, amounts of the most significant shorter oligonucleotide are no more than about 2-10%, often no more than 2-4% (e.g., in some embodiments, as low as about 2% (the most significant shorter oligonucleotide being N-3)).

[001646] Various technologies are available for oligonucleotide purification and can be utilized in accordance with the present disclosure. In some embodiments, crude products were further purified (e.g., over 90% purity) using, e.g., AEX purification, and/or UF/DF.

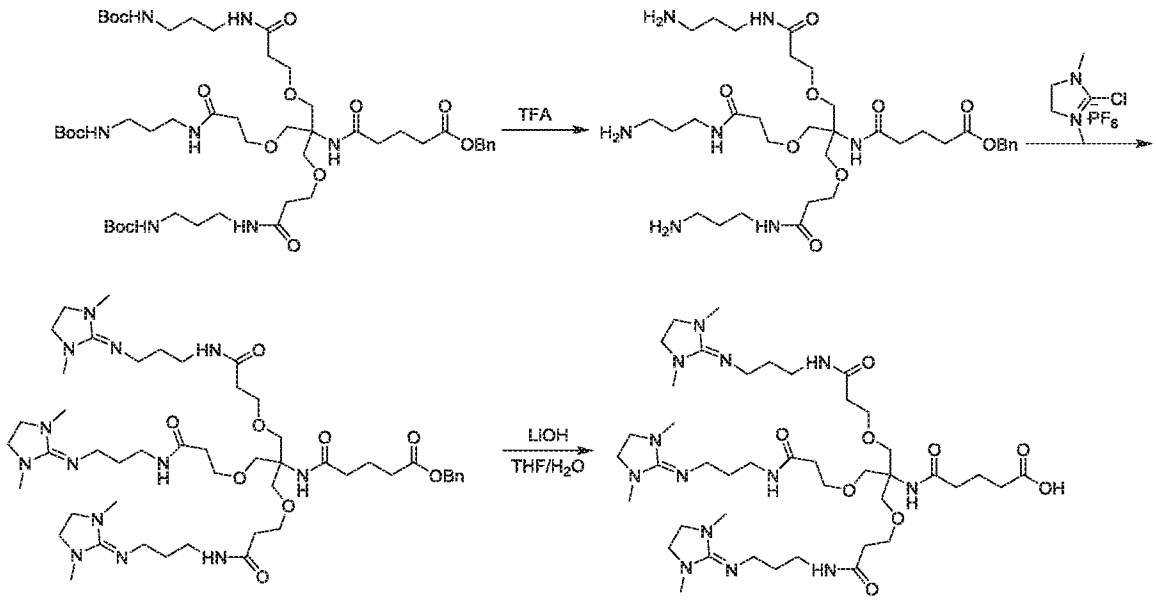
[001647] Using technologies described herein, various oligonucleotides comprising diverse base sequences, modifications (e.g., nucleobase, sugar, and internucleotidic linkage modifications) and/or patterns thereof, linkage phosphorus stereochemistry and/or patterns thereof, etc. were prepared at various scales from umol to mmol. Such oligonucleotides have various targets and may function through various mechanisms. Certain such oligonucleotides were presented in the Tables of the present disclosure.

[001648] As appreciated by those skilled in the art, examples described herein are for illustration only. Those skilled in the art will appreciate that various conditions, parameters, etc. may be adjusted according to, e.g., instrumentation, scales, reagents, reactants, desired outcomes, etc. Certain results may be further improved using various technologies in accordance with the present disclosure. Among other things, provided oligonucleotides and compositions thereof can provide significantly improved properties and/or activities, e.g., in various assays and in vivo models, and may be particularly useful for preventing and/or treating various conditions, disorders or diseases. Certain data are provided in Examples herein.

Example 4G. Synthesis of certain reagents for incorporation of Mod

[001649] As described in the present disclosure, oligonucleotide of the present disclosure may comprise various additional chemical moieties (e.g., various Mods) in addition to the oligonucleotide chain moiety. In some embodiments, the present disclosure provides oligonucleotide comprising a Mod described herein. In some embodiments, such additional moieties provide improved properties, activities, deliveries, etc. In some embodiments, the present disclosure provides useful additional chemical moieties, and technologies for preparing and incorporating such additional chemical moieties. Certain examples are described below. Those skilled in the art appreciates and various technologies related to additional chemical moieties (e.g., structures, preparations, incorporation, uses, etc.), e.g., those described in US 9394333, US 9744183, US 9605019, US 9598458, US 2015/0211006, US 2017/0037399, WO 2017/015555, WO 2017/192664, WO 2017/015575, WO 2017/062862, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/223056, WO 2018/237194, WO 2019/055951, etc., such technologies of each of which are independently incorporated by reference, may be utilized in accordance with the present disclosure.

[001650] Synthesis of 5-((1,19-bis((1,3-dimethylimidazolidin-2-ylidene)amino)-10-((3-((3-((1,3-dimethylimidazolidin-2-ylidene)amino)propyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoic acid.



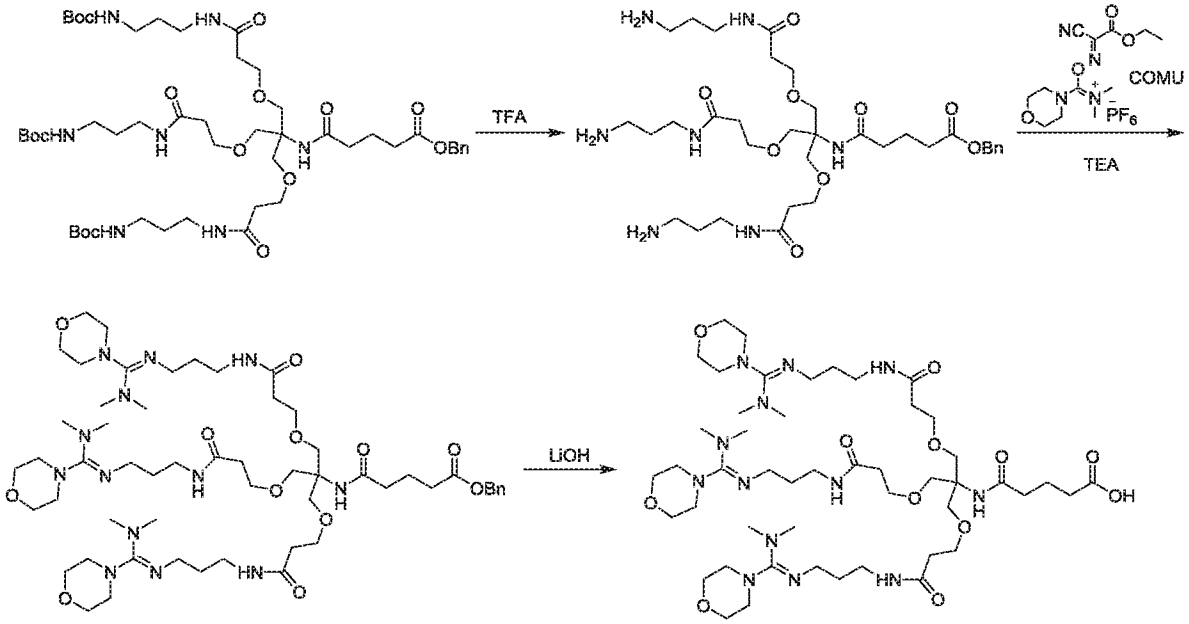
[001651] Step 1. To a solution of benzyl 15,15-bis(13,13-dimethyl-5,11-dioxo-2,12-dioxa-6,10-diazatetradecyl)-2,2-dimethyl-4,10,17-trioxo-3,13-dioxa-5,9,16-triazahenicosan-21-oate (5 g, 4.95 mmol, 1 *eq.*) in DCM (50 mL) was added TFA (16.93 g, 148.48 mmol, 10.99 mL, 30 *eq.*) at 0 °C. The mixture was stirred at 0 - 25 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to

remove solvent. Then added ACN (5 mL), and MTBE (40 mL), filtered the viscous liquid. The crude benzyl 5-((1,19-diamino-10-((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate (5.21 g, crude, 3TFA) was obtained as a yellowish oil. LCMS: ($M+H^+$): 710.6; ($M+Na^+$): 732.7.

[001652] Step 2. To a solution of benzyl 5-((1,19-diamino-10-((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate (5.21 g, crude, 3TFA) in DCM (35 mL) was added DIEA (6.39 g, 49.45 mmol, 8.61 mL, 10 *eq.*) and 2-chloro-1,3-dimethyl-4,5-dihydroimidazol-1-ium;hexafluorophosphate (4.55 g, 16.32 mmol, 3.3 *eq.*). The mixture was stirred at 25 °C for 15 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude was purified by RP-MPLC (Spec: C18, 330g, 20~35 micron, 100 Å). The product benzyl 5-((1,19-bis((1,3-dimethylimidazolidin-2-ylidene)amino)-10-((3-((3-((1,3-dimethylimidazolidin-2-ylidene)amino)propyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate (4.94 g, crude) was obtained as a yellow oil. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.39 - 7.29 (m, 5H), 3.70 - 3.62 (m, 28H), 3.45 (q, *J*=6.6 Hz, 7H), 3.30 - 3.26 (m, 6H), 3.08 - 2.99 (m, 21H), 2.47 - 2.39 (m, 9H), 2.23 (t, *J*=7.4 Hz, 2H), 1.92 - 1.78 (m, 10H).

[001653] Step 3. To a solution of benzyl 5-((1,19-bis((1,3-dimethylimidazolidin-2-ylidene)amino)-10-((3-((3-((1,3-dimethylimidazolidin-2-ylidene)amino)propyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate (2 g, 2.00 mmol, 1 *eq.*) in THF (10 mL) and H_2O (2 mL) was added $LiOH.H_2O$ (588.51 mg, 14.02 mmol, 7 *eq.*). The mixture was stirred at 25 °C for 3 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Phenomenex luna C18 250*50 mm*10 um; mobile phase: [water (0.1%TFA)- ACN]; B%: 0%-25%,20min). 5-((1,19-bis((1,3-dimethylimidazolidin-2-ylidene)amino)-10-((3-((3-((1,3-dimethylimidazolidin-2-ylidene)amino)propyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoic acid (0.6 g, 651.84 umol, 32.54% yield, 98.66% purity) was obtained as a yellow gum. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.03 (br t, J = 5.6 Hz, 3H), 7.75 (br t, J = 5.6 Hz, 3H), 7.08 (s, 1H), 3.62 - 3.54 (m, 24H), 3.34 (q, J = 6.6 Hz, 7H), 3.12 (q, J = 6.2 Hz, 5H), 2.96 (s, 18H), 2.30 (br t, J = 6.4 Hz, 6H), 2.23 - 2.03 (m, 4H), 1.79 - 1.59 (m, 8H); LCMS: ($M/2+H^+$): 454.9; LCMS purity: 98.66%.

[001654] Synthesis of (E)-2-methyl-14,14-bis((E)-2-methyl-3-morpholino-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-3-morpholino-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-oic acid.

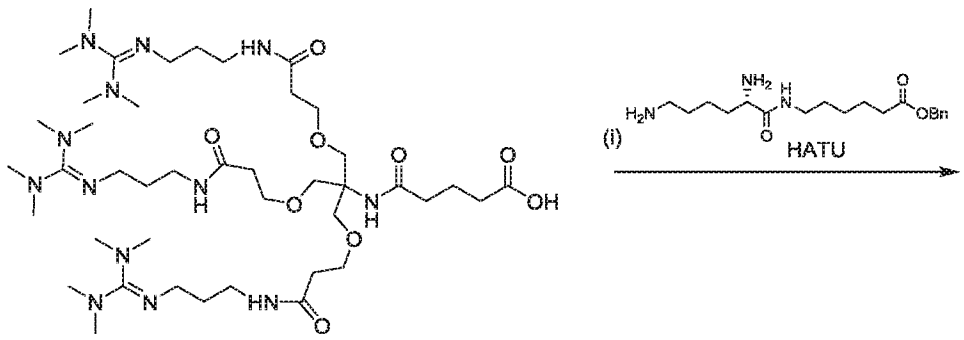


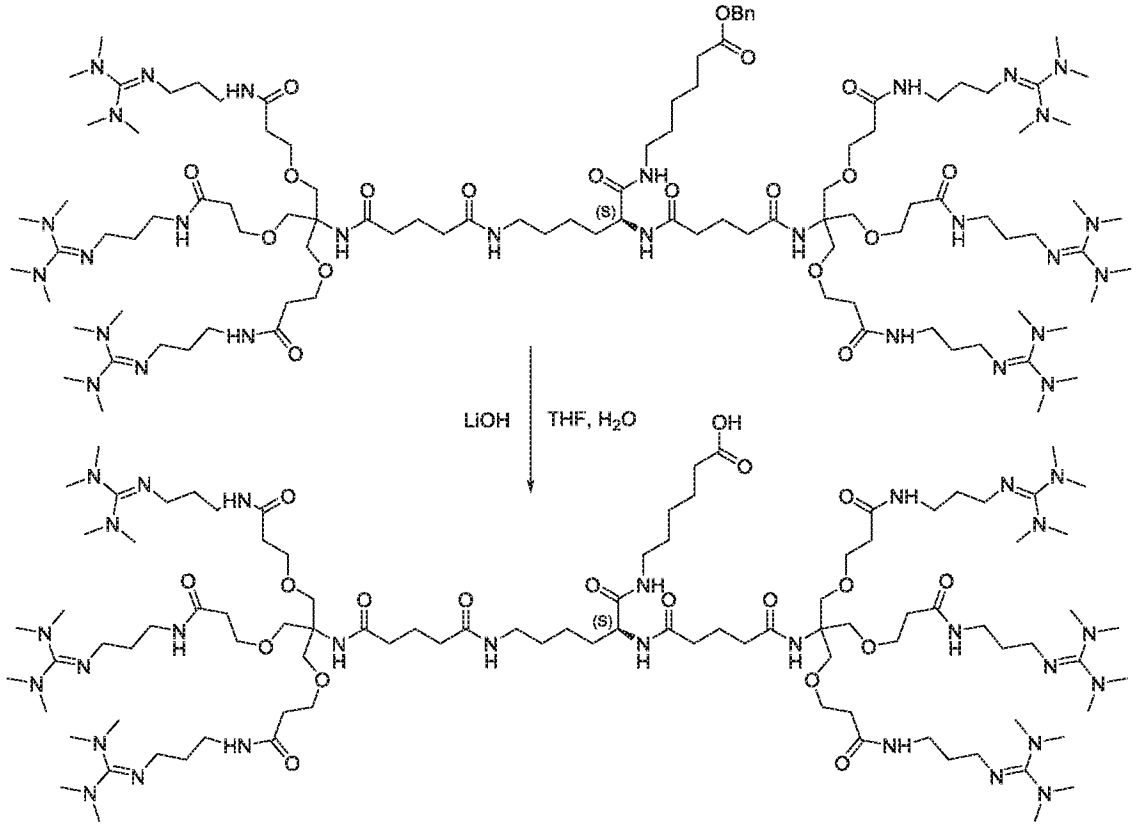
[001655] Step 1. To a solution of benzyl 15,15-bis(13,13-dimethyl-5,11-dioxo-2,12-dioxa-6,10-diazatetradecyl)-2,2-dimethyl-4,10,17-trioxo-3,13-dioxa-5,9,16-triazahenicosan-21-oate (5 g, 4.95 mmol, 1 *eq.*) in DCM (50 mL) was added TFA (16.93 g, 148.48 mmol, 10.99 mL, 30 *eq.*). The mixture was stirred at 0 - 25 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove solvent, then added ACN (50 mL), and MTBE (500 mL), filtered the viscous liquid. The crude benzyl 5-((1,19-diamino-10-((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate (5.21 g, crude, 3TFA) was obtained as a yellow oil. LCMS: ($M+H^+$): 710.6; ($M+Na^+$): 732.5.

[001656] Step 2. To a solution of benzyl 5-((1,19-diamino-10-((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate (3.86 g, 3.67 mmol, 1 *eq.*, 3TFA) in DCM (35.1 mL) was added DIEA (4.73 g, 36.63 mmol, 6.38 mL, 10 *eq.*) and [[(Z)-(1-cyano-2-ethoxy-2-oxo-ethylidene)amino]oxy-morpholino-methylene]-dimethylammonium;hexafluorophosphate (5.18 g, 12.09 mmol, 3.3 *eq.*). The mixture was stirred at 25 °C for 15 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude was dissolved by ACN (15 mL) then input it into the reversed-phase column. The crude product was purified by reversed-phase HPLC (0.75 % TFA in water, and acetonitrile). The crude compound benzyl (E)-2-methyl-14,14-bis((E)-2-methyl-3-morpholino-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-3-morpholino-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-oate (4.14 g, crude) was obtained as a yellow oil. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.43 - 7.24 (m, 5H), 3.78 (br s, 13H), 3.72 - 3.64 (m, 12H), 3.50 - 3.36 (m, 13H), 3.27 (br d, J = 8.6 Hz, 11H), 3.11 - 2.97 (m, 18H), 2.50 - 2.42 (m, 8H), 2.26 (t, J = 7.4 Hz, 2H), 1.93 - 1.78 (m, 8H).

[001657] Step 3. To a solution of benzyl (E)-2-methyl-14,14-bis((E)-2-methyl-3-morpholino-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-3-morpholino-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-oate (2 g, 1.77 mmol, 1 *eq.*) in THF (1 mL) and H_2O (0.2 mL) was added $LiOH.H_2O$ (519.71 mg, 12.38 mmol, 7 *eq.*). The mixture was stirred at 25 °C for 3 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (Phenomenex luna C18 250*50 mm *10 um; mobile phase: [water (0.1% TFA)-ACN];B%: 0%-20%, 20 min). The compound (E)-2-methyl-14,14-bis((E)-2-methyl-3-morpholino-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-3-morpholino-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-oic acid (1.2 g, 1.14 mmol, 64.65% yield, 99.16% purity) was obtained as a yellow gum. ^{1}H NMR (400MHz, DMSO-d6) δ = 7.99 (br s, 3H), 7.84 (br s, 3H), 7.06 (s, 1H), 3.67 (br s, 12H), 3.59 - 3.49 (m, 12H), 3.44 -3.25 (m, 12H), 3.11 (br s, 12H), 3.02 - 2.81 (m, 17H), 2.31 (br t, J = 6.1 Hz, 6H), 2.23 - 2.04 (m, 4H), 1.79 - 1.60 (m, 8H). LCMS: (M/2+H$^+$): 521.0; LCMS purity: 99.16%.

[001658] Synthesis of (S)-3-(dimethylamino)-26-(3-(dimethylamino)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-amido)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16,20,27-tetraoxo-12-oxa-2,4,8,15,21,28-hexaazatetratriacont-3-en-34-oic acid.



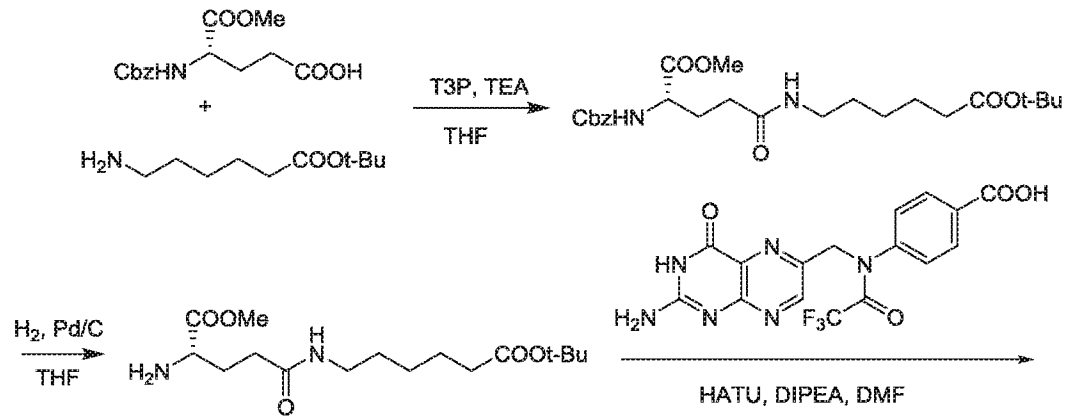


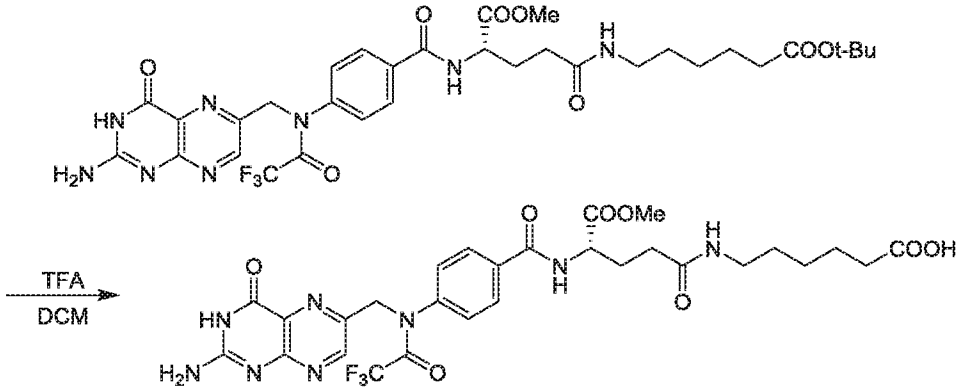
[001659] Step 1. To a solution of 3-(dimethylamino)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-oic acid (10 g, 10.94 mmol, 5 *eq.*) in DMF (100 mL) was added DIPEA (2.83 g, 21.88 mmol, 3.81 mL, 10 *eq.*) and followed by benzyl (S)-6-(2,6-diaminohexanamido)hexanoate (924.07 mg, 2.19 mmol, 1 *eq.*, 2HCl) and then to the mixture was dropwise added HATU (1.91 g, 5.03 mmol, 2.3 *eq.*) in DMF (10 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 12 hr. The mixture was concentrated in vacuo. The residue was purified by prep-HPLC (TFA condition). Column: Phenomenex luna C 18 250 * 50 mm * 10 um; mobile phase: [water (0.1%TFA)-ACN]; B% CH_3CN: 10%- 35%, 20min. Benzyl (S)-3-(dimethylamino)-26-(3-(dimethylamino)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-amido)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16,20,27-tetraoxo-12-oxa-2,4,8,15,21,28-hexaazatetratriacont-3-en-34-oate (3.7 g, crude) was obtained as a yellow oil. ^1H NMR (400MHz, CHLOROFORM-d) δ = 8.01 - 7.77 (m, 10H), 7.63 (br t, *J*=4.9 Hz, 6H), 7.40 - 7.29 (m, 5H), 7.07 (br d, *J*=16.5 Hz, 2H), 5.08 (s, 2H), 4.18 - 4.07 (m, 1H), 3.63 - 3.46 (m, 24H), 3.10 (br dd, *J*=3.2, 5.1 Hz, 25H), 3.00 - 2.78 (m, 79H), 2.39 - 2.23 (m, 18H), 2.15 - 1.98 (m, 20H), 1.72 - 1.13 (m, 31H). LCMS: $M/4+H^+$ = 536.5.

[001660] Step 2. To a solution of compound benzyl (S)-3-(dimethylamino)-26-(3-

(dimethylamino)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-amido)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16,20,27-tetraoxo-12-oxa-2,4,8,15,21,28-hexaazatetratriacont-3-en-34-oate (4.4 g, 2.05 mmol, 1 *eq.*) in THF (40 mL) and H_2O (8 mL) was added $LiOH.H_2O$ (603.45 mg, 14.38 mmol, 7 *eq.*). The mixture was stirred at 25 °C for 2 hr. The mixture was concentrated in vacuo. The residue was purified by prep-HPLC (TFA condition). Column: Phenomenex luna C 18 250 * 50 mm* 10 um; mobile phase: [water (0.1%TFA)-ACN]; B%: 2%- 30%, 20 min. Compound (S)-3-(dimethylamino)-26-(3-(dimethylamino)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-amido)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16,20,27-tetraoxo-12-oxa-2,4,8,15,21,28-hexaazatetratriacont-3-en-34-oic acid (1.4 g, 678.84 umol, 33.04% yield, 99.483% purity) was obtained as a yellow oil. ^1H NMR (400MHz, DMSO-d6) δ = 8.00 (br t, *J*=5.5 Hz, 6H), 7.91 (br t, *J*=5.6 Hz, 1H), 7.87 - 7.79 (m, 2H), 7.67 (br t, *J*=4.8 Hz, 5H), 7.15 - 7.01 (m, 2H), 4.17 - 4.10 (m, 1H), 3.70 - 3.43 (m, 24H), 3.16 - 3.06 (m, 24H), 3.05 - 2.75 (m, 76H), 2.30 (br t, *J*=6.4 Hz, 12H), 2.18 (t, *J*=7.4 Hz, 2H), 2.15 - 1.98 (m, 8H), 1.66 (quin, *J*=6.6 Hz, 17H), 1.48 (quin, *J*=7.4 Hz, 3H), 1.41 - 1.31 (m, 4H), 1.28 - 1.17 (m, 4H). ^{13}C NMR (101MHz, DMSO-d6) δ = 174.85, 172.67, 172.61, 172.40, 172.19, 170.87, 161.50, 158.77 (q, *J*=35.2 Hz, 1C), 118.06, 115.15, 68.72, 67.84, 60.03, 53.08, 42.36, 38.87, 38.78, 36.40, 35.95, 35.88, 35.81, 35.25, 34.91, 34.08, 29.85, 29.40, 29.19, 26.34, 24.63, 23.47, 22.14. LCMS: $M/3+H^+$ = 684.7, purity: 99.48%.

[001661] Synthesis of (S)-6-(4-(4-(N-((2-amino-4-oxo-3,4-dihydropteridin-6-yl)methyl)-2,2,2-trifluoroacetamido)benzamido)-5-methoxy-5-oxopentanamido)hexanoic acid.





[001662] Step 1. To a solution of (S)-4-(((benzyloxy)carbonyl)amino)-5-methoxy-5-oxopentanoic acid (14 g, 47.41 mmol, 1 *eq.*) in THF (150 mL) was added TEA (14.39 g, 142.23 mmol, 19.80 mL, 3 *eq.*), followed by tert-butyl 6-aminohexanoate 6-aminohexanoate (11.54 g, 61.63 mmol, 1.3 *eq.*) at 0 - 5°C and stirred for 0.5 hour. T3P (60.34 g, 94.82 mmol, 56.39 mL, 50% purity, 2 *eq.*) was added to the mixture at 0 - 5 °C and stirred at 20 – 25 °C for 12 hours. TLC (Petroleum ether/Ethyl acetate = 1:1, R_f = 0.35) showed that the starting material was consumed completely. The mixture was concentrated under reduced pressure to remove the solvent, and then re-dissolved with ethyl acetate (100 mL). The organic phase was washed by saturated aq. $NaHCO_3$ (50 mL×3) and dried over anhydrous Na_2SO_4. The crude product was purified by MPLC (SiO_2, Petroleum ether/Ethyl acetate = 1:1) to obtain tert-butyl (S)-6-(4-(((benzyloxy)carbonyl)amino)-5-methoxy-5-oxopentanamido)hexanoate (19.7 g, crude) as yellow oil.

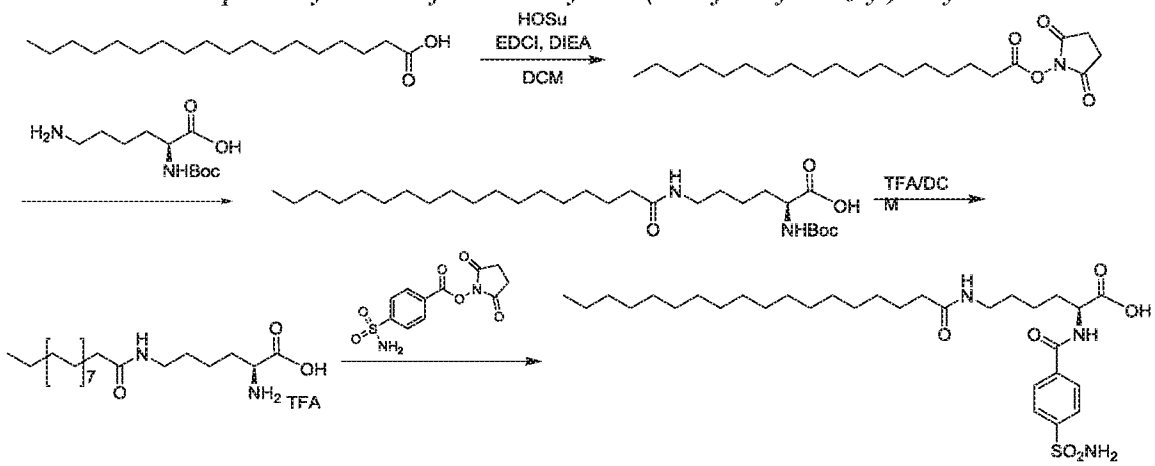
[001663] Step 2. A mixture of tert-butyl (S)-6-(4-(((benzyloxy)carbonyl)amino)-5-methoxy-5-oxopentanamido)hexanoate (15 g, 32.29 mmol, 1 *eq.*) and Pd/C (10 g, 10% purity) in THF (300 mL) was evacuated in vacuo and backfilled with H_2 (15 Psi) three times, then stirred at 20 - 25 °C for 6 hours. TLC (Petroleum ether/Ethyl acetate = 1:1, R_f = 0) showed that the starting material was consumed completely. The mixture was filtered and concentrated under reduced pressure to remove the most solvent. The crude product was used for the next step without any purification. tert-butyl (S)-6-(4-amino-5-methoxy-5-oxopentanamido)hexanoate (10.67 g, 31.42 mmol, 97.31% yield, 97.303% purity) was obtained as colorless liquid (in solvent). LCMS: M + H^+ = 331.2, purity: 97.70%.

[001664] Step 3. To a mixture of 4-(*N*-((2-Amino-4-oxo-3,4-dihydropteridin-6-yl)-methyl)-2,2,2-trifluoroacetamido)benzoic acid (8.28 g, 25.06 mmol, 1.1 *eq.*) and DIPEA (8.83 g, 68.33 mmol, 11.90 mL, 3 *eq.*) in DMSO (20 mL) was added HATU (8.66 g, 22.78 mmol, 1 *eq.*) and tert-butyl (S)-6-(4-amino-5-methoxy-5-oxopentanamido)hexanoate at 20 – 25 °C and stirred for 12 hours. The mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL×3). The organic phase was concentrated under reduced pressure to remove the solvent. The crude product was purified by MPLC (SiO_2, Methanol/Ethyl acetate = 2:5) to obtain tert-butyl (S)-6-(4-(4-(N-((2-amino-4-oxo-3,4-dihydropteridin-6-yl)methyl)-2,2,2-trifluoroacetamido)benzamido)-5-methoxy-5-

oxopentanamido)hexanoate (26.2 g, crude) as brown gum. LCMS: M + H^+ = 721.2.

[001665] Step 4. To a solution of tert-butyl (S)-6-(4-(4-(N-((2-amino-4-oxo-3,4-dihydropteridin-6-yl)methyl)-2,2,2-trifluoroacetamido)benzamido)-5-methoxy-5-oxopentanamido)hexanoate (13.1 g, 11.39 mmol, 1 *eq.*) in DCM (100 mL) was added TFA (7.79 g, 68.35 mmol, 5.06 mL, 6 *eq.*) at 0 – 5 °C and the mixture was stirred at 35 – 40 °C for 12 hours. The mixture was concentrated under reduced pressure to remove the solvent. The crude product was detected by HPLC and purified by prep-HPLC (column: Phenomenex luna C18 250*50 mm*10 um; mobile phase: [water (0.05% HCl)-ACN]; B%: 15%-35%, 20min) to obtain (S)-6-(4-(4-(N-((2-amino-4-oxo-3,4-dihydropteridin-6-yl)methyl)-2,2,2-trifluoroacetamido)benzamido)-5-methoxy-5-oxopentanamido)hexanoic acid (1.51 g, 1.88 mmol, 32.96% yield, 82.627% purity). ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.92 (br d, *J*=7.1 Hz, 1H), 8.74 (s, 1H), 7.93 (br d, *J*=8.4 Hz, 3H), 7.83 (br t, *J*=5.5 Hz, 1H), 7.66 (br d, *J*=8.3 Hz, 2H), 5.18 (s, 2H), 5.06 - 4.52 (m, 3H), 4.45 - 4.32 (m, 1H), 3.63 (s, 2H), 3.00 (q, *J*=6.2 Hz, 2H), 2.25 - 2.13 (m, 4H), 2.12 - 2.03 (m, 1H), 1.99 - 1.87 (m, 1H), 1.46 (quin, *J*=7.5 Hz, 2H), 1.35 (td, *J*=7.4, 14.9 Hz, 2H), 1.27 - 1.15 (m, 2H). ^{13}C NMR (101MHz, DMSO-d_6) δ = 174.91, 172.83, 171.50, 166.02, 159.47, 153.27, 149.15, 142.22, 134.71, 129.15, 128.99, 128.64, 54.27, 52.97, 52.38, 38.79, 34.05, 32.16, 29.29, 26.76, 26.40, 24.66. LCMS: M + H^+ = 665.2.

Example 5. Synthesis of N6-stearoyl-N2-(4-sulfamoylbenzoyl)-L-lysine



[001666] Step 1. To a solution of stearic acid (8.00 g, 28.12 mmol) in DCM (210 mL) was added 1-hydroxypyrrolidine-2,5-dione (3.24 g, 28.12 mmol) followed by EDCI (5.39 g, 28.12 mmol) at 15°C. The mixture was stirred at15 °C for 21 hr. TLC showed part of stearic acid remained. Additionally added 1-hydroxypyrrolidine-2,5-dione (0.32 g) and EDCI (1.07 g). Stirring was continued at 15 °C for 8 hr. TLC showed the reaction was completed. The solvent was evaporated under reduced pressure. The residue was dissolved in DCM (300 mL) and the solution washed with water (200 mL); the aqueous

phase was then back-extracted with DCM (2*100 mL). The combined organic phase was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to yield 2,5-dioxopyrrolidin-1-yl stearate as a white solid. No further purification. The crude product 2,5-dioxopyrrolidin-1-yl stearate (10.70 g, crude) was used into the next step without further purification. TLC (Petroleum ether : Ethyl acetate = 1:1) R_f = 0.79.

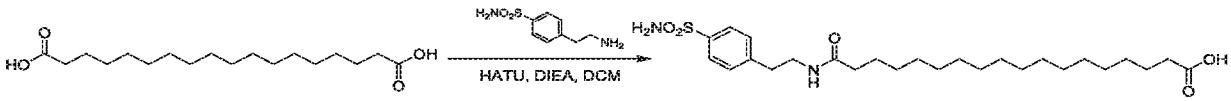
[001667] Step 2. To a solution of (tert-butoxycarbonyl)-L-lysine (4.49 g, 18.24 mmol) and 2,5-dioxopyrrolidin-1-yl stearate (5.80 g, 15.20 mmol) in DMF (20 mL) was added DIPEA (5.89 g, 45.60 mmol, 7.96 mL). The mixture was stirred at 20 °C for 20 hour. TLC and LCMS showed the reaction was completed. The resulting mixture was concentrated to dry under reduced pressure. The residue was combined with 9 g crude compound, partitioned between water (200 mL) and EtOAc (300 mL) and DCM (80 mL). The separated aqueous layer was extracted with EtOAc (300 mL*3). The combined organic layers were washed with water (100 mL*2), dried over anhydrous $MgSO_4$, filtered and concentrated to afford the product as a white solid (14.5 g). The crude product compound N^2-(tert-butoxycarbonyl)-N^6-stearoyl-L-lysine (7.70 g, crude) was used into the next step without further purification. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 11.29 (br s, 1H), 7.97 (s, 1H), 5.88 (br s, 1H), 5.24 (br d, *J*=7.3 Hz, 1H), 4.21 (br d, *J*=5.1 Hz, 1H), 3.17 (q, *J*=6.5 Hz, 2H), 2.11 (t, *J*=7.6 Hz, 2H), 1.79 (br s, 1H), 1.64 (dt, *J*=7.9, 14.0 Hz, 1H), 1.58 - 1.42 (m, 4H), 1.41 - 1.28 (m, 11H), 1.18 (br s, 29H), 0.81 (t, *J*=6.7 Hz, 3H); LCMS: ($M+Na^+$): 535.3; TLC (Petroleum ether : Ethyl acetate = 1:1) R_f = 0.01.

[001668] Step 3. To a solution of N^2-(tert-butoxycarbonyl)-N^6-stearoyl-L-lysine (12.50 g, 24.38 mmol) in DCM (120 mL) was added TFA (46.20 g, 405.20 mmol, 30 mL). The mixture was stirred at 15°C for 4.5 hr. LCMS showed the reaction was almost completed. The resulting mixture was concentrated under reduced pressure on a rotary evaporator with water pump to give a gray crude solid. The crude product compound N^6-stearoyl-L-lysine (12.80 g, crude, TFA salt) was used into the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.19 (br s, 3H), 7.77 - 7.65 (m, 1H), 3.88 (br d, *J*=4.9 Hz, 1H), 3.02 (br d, *J*=5.5 Hz, 2H), 2.03 (br t, *J*=7.3 Hz, 2H), 1.75 (br s, 2H), 1.56 - 1.34 (m, 6H), 1.24 (s, 28H), 0.86 (br t, *J*=6.4 Hz, 3H); LCMS: ($M+H^+$): 413.3.

[001669] Step 4. To a solution of compound N^6-stearoyl-L-lysine (5.00 g, 9.49 mmol, TFA salt) in DMF (150mL) was added compound 2,5-dioxopyrrolidin-1-yl 4-sulfamoylbenzoate (3.98 g, 13.34 mmol) followed by DIPEA (9.40 g, 72.73 mmol, 12.70 mL). The mixture was stirred at 80°C for 18hr. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure until 20 mL residue mixture left. To the residue was added DCM (80 mL) and petroleum ether (50 mL). After stood for 36 hr at 15°C, the precipitated solid was filtered and dried to give the product as a light yellow solid (1.9 g). The filtrate was concentrated to dry and triturated with ACN (100 mL), filtered and the filter cake was dried to give a crude (2.4 g). The filtrate was concentrated to give an oil messy crude. No

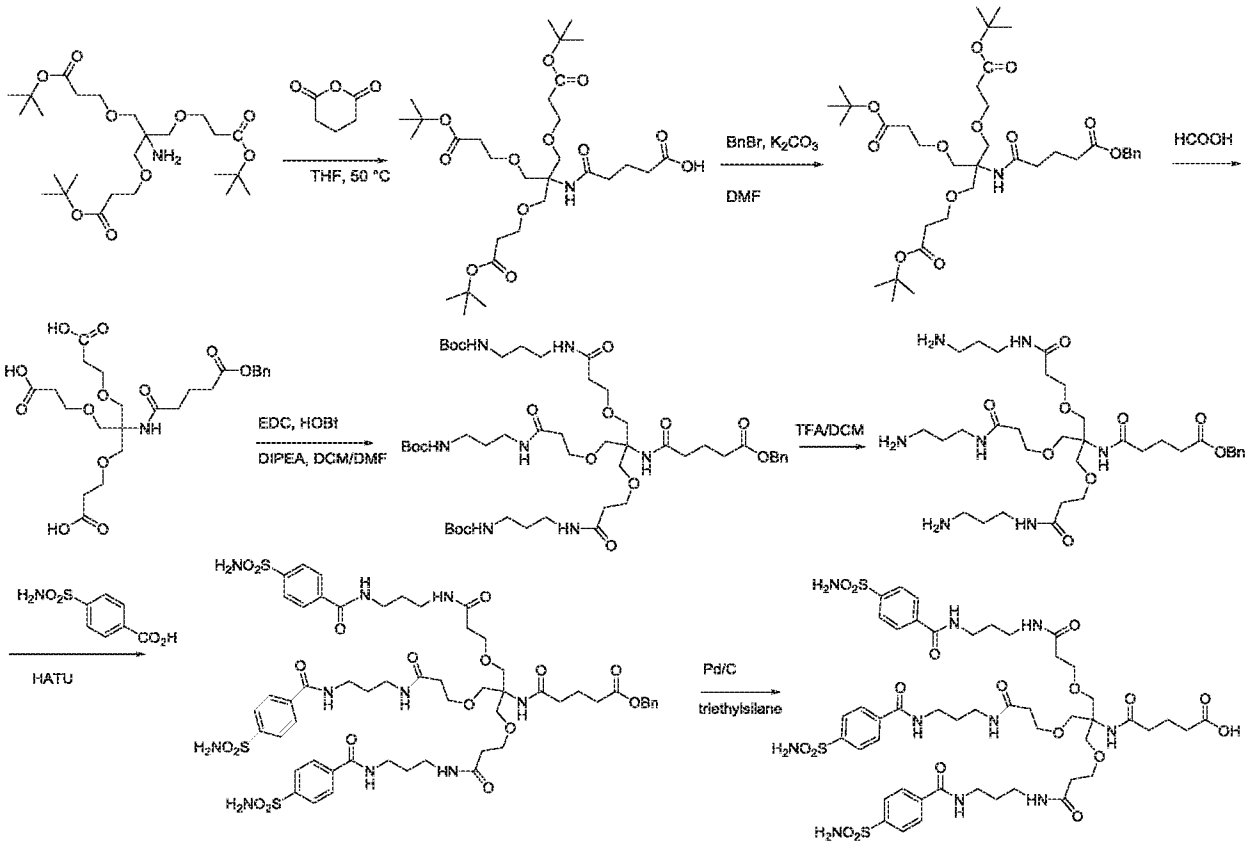
further purification. N^6-stearoyl-N2-(4-sulfamoylbenzoyl)-L-lysine (1.90 g, 33.60% yield) was obtained as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.19 - 11.82 (m, 1H), 8.74 (br d, J=5.7 Hz, 1H), 8.04 (br d, J=6.6 Hz, 2H), 7.91 (br d, J=7.1 Hz, 2H), 7.74 (br s, 1H), 7.49 (br s, 2H), 4.35 (br s, 1H), 3.02 (br s, 2H), 2.02 (br s, 2H), 1.80 (br s, 2H), 1.23 (br s, 31H), 0.86 (br s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.06, 172.39, 165.94, 146.85, 137.28, 128.54, 125.99, 53.24, 38.55, 35.88, 31.76, 30.69, 29.50, 29.41, 29.24, 29.18, 25.78, 23.72, 22.55, 14.39; LCMS: (M+H$^+$): 596.4, purity: 89.89%.

Example 6. Synthesis of 18-oxo-18-((4-sulfamoylphenethyl)amino)octadecanoic acid



[001670] To a solution of octadecanedioic acid (4.90 g, 15.58 mmol) and 4-(2-aminoethyl)benzenesulfonamide (3.12 g, 15.58 mmol) in DCM (50 mL) was added HATU (7.11 g, 18.70 mmol) and DIPEA (6.04 g, 46.74 mmol, 8.16 mL). The mixture was stirred at 10°C for 16 hours. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was washed by CH_3CN (100 mL*2) to give the crude product (11 g) as white solid. 1 g crude was dissolved by DMSO/DMF (V/V=3:1, 20 mL) purified by prep-HPLC (column: Phenomenex luna C18 250*50mm*10 um;mobile phase: [water(0.1%TFA)-ACN];B%: 45%-75%,20min) to give 40 mg product as a white solid. 10 g crude was added CH_3CN/H_2O (V/V=4:1, 100 mL) and stayed at ultrasonic instrument for 30 min, then filtered to give filter cake, filter cake was washed by petroleum ether (20 mL) and acetone (20 mL). Filter cake was concentrated under reduced pressure to give 6 g product as a yellow solid. Compound 18-oxo-18-((4-sulfamoylphenethyl)amino)octadecanoic acid (6.00 g, 77.53% yield) was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.86 (br t, *J*=5.3 Hz, 1H), 7.71 (d, *J*=8.2 Hz, 2H), 7.35 (d, *J*=7.9 Hz, 2H), 7.27 (s, 2H), 3.26 (q, *J*=6.6 Hz, 3H), 2.75 (br t, *J*=7.2 Hz, 2H), 2.15 (t, *J*=7.3 Hz, 1H), 2.00 (br t, *J*=7.3 Hz, 2H), 1.44 (br d, *J*=6.6 Hz, 4H), 1.21 (s, 23H), 1.06 (d, *J*=6.6 Hz, 3H). LCMS: (M+H$^+$): 497.3, purity 67.72%.

Example 7. Synthesis of 1,7,14-trioxo-12,12-bis((3-oxo-3-((3-(4-sulfamoylbenzamido)propyl)amino)propoxy)methyl)-1-(4-sulfamoylphenyl)-10-oxa-2,6,13-triazaoctadecan-18-oic acid



[001671] Step 1. A solution of di-tert-butyl 3,3'-((2-amino-2-((3-(tert-butoxy)-3-oxopropoxy)methyl)propane-1,3-diyl)bis(oxy))dipropanoate (4.0 g, 7.91 mmol) and dihydro-2H-pyran-2,6(3H)-dione (0.903 g, 7.91 mmol) in THF (40 mL) was stirred at 50 °C for 3 hrs and at rt for 3 hrs. LC-MS showed desired product. Solvent was evaporated to give 5-((9-((3-(tert-butoxy)-3-oxopropoxy)methyl)-2,2,16,16-tetramethyl-4,14-dioxo-3,7,11,15-tetraoxaheptadecan-9-yl)amino)-5-oxopentanoic acid, which was directly used for next step without purification.

[001672] Step 2. To a solution of 5-((9-((3-(tert-butoxy)-3-oxopropoxy)methyl)-2,2,16,16-tetramethyl-4,14-dioxo-3,7,11,15-tetraoxaheptadecan-9-yl)amino)-5-oxopentanoic acid (4.90 g, 7.91 mmol) and (bromomethyl)benzene (1.623 g, 9.49 mmol) in DMF was added anhydrous K_2CO_3 (3.27 g, 23.73 mmol). The mixture was stirred at 40 °C for 4 hrs and at room temperature for overnight. Solvent was evaporated under reduced pressure. The reaction mixture was diluted with EtOAc, washed with water, dried over anhydrous sodium sulfate, concentrated under reduced pressure to give a residue, which was purified by ISCO eluting with 10% EtOAc in hexane to 50% EtOAc in hexane to give di-tert-butyl 3,3'-((2-(5-(benzyloxy)-5-oxopentanamido)-2-((3-(tert-butoxy)-3-oxopropoxy)methyl)propane-1,3-diyl)bis(oxy))dipropanoate (5.43 g, 7.65 mmol, 97 % yield) as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.28 (m, 5H), 6.10 (s, 1H), 5.12 (s, 2H), 3.72 – 3.60 (m, 12H), 2.50 – 2.38 (m, 8H), 2.22 (t, *J* = 7.3 Hz, 2H), 1.95 (p, *J* = 7.4 Hz, 2H), 1.45 (s, 27H); MS (ESI), 710.5 $(M+H)^+$.

[001673] Step 3. A solution of di-tert-butyl 3,3'-((2-(5-(benzyloxy)-5-oxopentanamido)-2-((3-(tert-butoxy)-3-oxopropoxy)methyl)propane-1,3-diyl)bis(oxy))dipropanoate (5.43 g, 7.65 mmol) in formic acid (50 mL) was stirred at room temperature for 48 hrs. LC-MS showed the reaction was not complete. Solvent was evaporated under reduced pressure. The crude product was re-dissolved in formic acid (50 mL) and was stirred at room temperature for 6 hrs. LC-MS showed the reaction was complete. Solvent was evaporated under reduced pressure, co-evaporated with toluene (3X) under reduced pressure, and dried under vacuum to give 3,3'-((2-(5-(benzyloxy)-5-oxopentanamido)-2-((2-carboxyethoxy)methyl)propane-1,3-diyl)bis(oxy))dipropanoic acid (4.22 g, 7.79 mmol, 100 % yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.11 (s, 3H), 7.41 – 7.27 (m, 5H), 6.97 (s, 1H), 5.07 (s, 2H), 3.55 (d, J = 6.4 Hz, 6H), 2.40 (t, J = 6.3 Hz, 6H), 2.37 – 2.26 (m, 2H), 2.08 (t, J = 7.3 Hz, 2H), 1.70 (p, J = 7.4 Hz, 2H); MS (ESI), 542.3 $(M+H)^+$.

[001674] Step 4. A solution of 3,3'-((2-(5-(benzyloxy)-5-oxopentanamido)-2-((2-carboxyethoxy)methyl)propane-1,3-diyl)bis(oxy))dipropanoic acid (4.10 g, 7.57 mmol) and HOBt (4.60 g, 34.1 mmol) in DCM (60 mL) and DMF (15 mL) at 0 °C was added tert-butyl (3-aminopropyl)carbamate (5.94 g, 34.1 mmol), EDAC HCl salt (6.53 g, 34.1 mmol) and DIPEA (10.55 ml, 60.6 mmol). The reaction mixture was stirred at 0 °C for 15 minutes and at room temperature for 20 hrs. LC-MS showed the reaction was not complete. EDAC HCl salt (2.0 g) and tert-butyl (3-aminopropyl)carbamate (1.0 g) was added into the reaction mixture. The reaction mixture was stirred at room temperature for 4 hrs. Solvent was evaporated to give a residue, which was dissolved in EtOAc (300 mL), washed with water (1X), saturated sodium bicarbonate (2X), 10% citric acid (2X) and water, dried over sodium sulfate, and concentrated to give a residue which was purified by ISCO (80 g gold catridge) eluting with DCM to 30% MeOH in DCM to give benzyl 15,15-bis(13,13-dimethyl-5,11-dioxo-2,12-dioxa-6,10-diazatetradecyl)-2,2-dimethyl-4,10,17-trioxo-3,13-dioxa-5,9,16-triazahenicosan-21-oate **5** (6.99 g, 6.92 mmol, 91 % yield) as a white solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.35 (t, J = 4.7 Hz, 5H), 6.89 (s, 3H), 6.44 (s, 1H), 5.22 (d, J = 6.6 Hz, 3H), 5.12 (s, 2H), 3.71 – 3.62 (m, 12H), 3.29 (q, J = 6.2 Hz, 6H), 3.14 (q, J = 6.5 Hz, 6H), 2.43 (dt, J = 27.0, 6.7 Hz, 8H), 2.24 (t, J = 7.2 Hz, 2H), 1.96 (p, J = 7.5 Hz, 2H), 1.69 – 1.59 (m, 6H), 1.43 (d, J = 5.8 Hz, 27H); MS (ESI): 1011.5 (M+H)+.

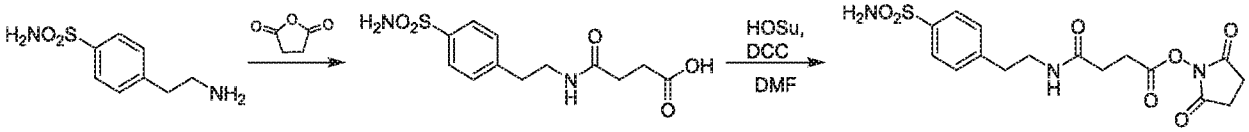
[001675] Step 5. A solution of benzyl 15,15-bis(13,13-dimethyl-5,11-dioxo-2,12-dioxa-6,10-diazatetradecyl)-2,2-dimethyl-4,10,17-trioxo-3,13-dioxa-5,9,16-triazahenicosan-21-oate (1.84 g, 1.821 mmol) in DCM (40 mL) was added 2,2,2-trifluoroacetic acid (7.02 ml, 91 mmol). The reaction mixture was stirred at room temperature for overnight. Solvent was evaporated to give benzyl 5-((1,19-diamino-10-((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate as a colorless oil. MS (ESI), 710.6 $(M+H)^+$.

[001676] Step 6. To a solution of 4-sulfamoylbenzoic acid (1.466 g, 7.28 mmol) and HATU (2.77

g, 7.28 mmol) in DCM (40 mL) followed by benzyl 5-((1,19-diamino-10-((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate (1.293 g, 1.821 mmol) in DMF (4.0 mL). The mixture was stirred at room temperature for 5 hrs. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO (40 g gold column) eluting with DCM to 50% MeOH in DCM to give benzyl 1,7,14-trioxo-12,12-bis((3-oxo-3-((3-(4-sulfamoylbenzamido)propyl)amino)-propoxy)methyl)-1-(4-sulfamoylphenyl)-10-oxa-2,6,13-triazaoctadecan-18-oate (0.36 g, 0.286 mmol, 16% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (t, J = 5.6 Hz, 3H), 7.96 – 7.81 (m, 15H), 7.44 (s, 6H), 7.35 – 7.23 (m, 5H), 7.04 (s, 1H), 5.02 (s, 2H), 3.50 (t, J = 6.9 Hz, 6H), 3.48 (s, 6 H), 3.23 (q, J = 6.6 Hz, 6H), 3.06 (q, J = 6.6 Hz, 6H),, 2.29 (t, J = 7.4 Hz, 2H), 2.24 (t, J = 6.5 Hz, 6H), 2.06 (t, J = 7.4 Hz, 2H), 1.69-1.57 (m, 8H).

[001677] Step 7. To a round bottom flask flushed with Ar was added 10% Pd/C (80 mg, 0.286 mmol) and EtOAc (15 mL). A solution of benzyl 1,7,14-trioxo-12,12-bis((3-oxo-3-((3-(4-sulfamoylbenzamido)propyl)amino)propoxy)methyl)-1-(4-sulfamoylphenyl)-10-oxa-2,6,13-triazaoctadecan-18-oate (360 mg) in methanol (15 mL) was added followed by diethyl(methyl)silane (0.585 g, 5.72 mmol) dropwise. The mixture was stirred at room temperature for 3 hrs. LC-MS showed the reaction was complete, diluted with EtOAc, and filtered through celite, washed with 20% MeOH in EtOAc, concentrated under reduced pressure to give 1,7,14-trioxo-12,12-bis((3-oxo-3-((3-(4-sulfamoylbenzamido)propyl)-amino)propoxy)methyl)-1-(4-sulfamoylphenyl)-10-oxa-2,6,13-triazaoctadecan-18-oic acid (360 mg, 100% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (t, J = 5.6 Hz, 3H), 7.94 – 7.81 (m, 15H), 7.44 (s, 6H), 7.04 (s, 1H), 3.50 (t, J = 6.9 Hz, 6H), 3.48 (s, 6 H), 3.23 (q, J = 6.6 Hz, 6H), 3.06 (q, J = 6.6 Hz, 6H),, 2.24 (t, J = 6.4 Hz, 6H), 2.14 (t, J = 7.5 Hz, 2H), 2.05 (t, J = 7.4 Hz, 2H), 1.66-1.57 (m, 8H); MS (ESI), 1170.4 $(M+H)^+$.

Example 8. Synthesis of 2,5-dioxopyrrolidin-1-yl 4-oxo-4-((4-sulfamoylphenethyl)amino)butanoate

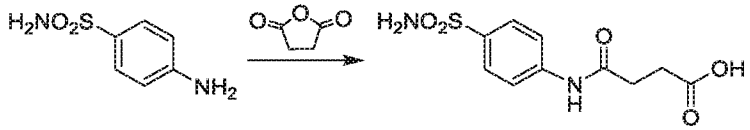


[001678] Step 1. A solution of 4-(2-aminoethyl)benzenesulfonamide (20 g, 99.87 mmol), tetrahydrofuran-2,5-dione (9.99 g, 99.87 mmol) in THF (200 mL) was stirred at 60 °C for 16 hr. The reaction mixture was diluted with HCl (aq., 1 M, 100 mL) and extracted with EtOAc (200 mL * 3). The combined organic layers were washed with brine (100 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 4-oxo-4-((4-sulfamoylphenethyl)amino)butanoic acid (17 g, 55.60 mmol, 55.67% yield, 98.228% purity) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.94 (t, J = 5.7 Hz, 1H), 7.72 (d, J = 7.9 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 3.30 - 3.20 (m, 2H), 2.75 (t, J = 7.2 Hz, 2H), 2.53 - 2.44 (m, 4H), 2.44 - 2.35 (m, 3H), 2.32 - 2.23 (m, 2H). LCMS: $(M+H^+)$:

301.1.

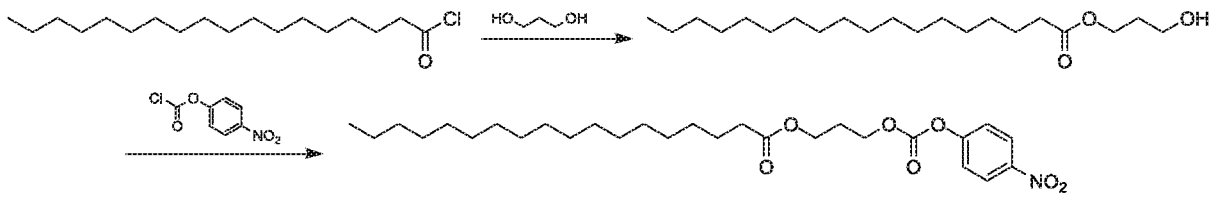
[001679] Step 2. To a solution of 4-oxo-4-((4-sulfamoylphenethyl)amino)butanoic acid (17 g, 56.60 mmol) and HOSu (10.42 g, 90.57 mmol) in DMF (200 mL) was added DCC (18.69 g, 90.57 mmol, 18.32 mL) at 0°C-5°C. The mixture was stirred at 0-5 °C for 16 hr. LCMS showed the reaction was not complete. The mixture was stirred at 15 °C for 16 hr. LCMS showed the reaction was complete and one main peak with desired MS was detected. The white suspension of N,N'-dicyclohexylurea (DCU) was filtered and removed white solid. The filtrate was concentrated to an oil. This crude product was washed with hot 2-propanol (60 mL*3), affording an off-white solid. The crude product was added THF (100 mL), and Petroleum ether (50 mL) and stirred for 30 min, then filtered to give 2,5-dioxopyrrolidin-1-yl 4-oxo-4-((4-sulfamoylphenethyl)amino)butanoate (8 g, 16.58 mmol, 29.29% yield, 82.36% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.12 - 7.96 (m, 1H), 7.71 (br d, *J*=7.9 Hz, 2H), 7.37 (br d, *J*=8.2 Hz, 2H), 3.58 (br t, *J*=6.7 Hz, 1H), 3.30 - 3.21 (m, 2H), 2.89 - 2.70 (m, 8H), 2.58 (s, 1H), 2.42 (br t, *J*=6.7 Hz, 2H); LCMS: (M+H$^+$)): 398.0, LCMS purity: 82.36%.

Example 9. Synthesis of 4-oxo-4-((4-sulfamoylphenyl)amino)butanoic acid



[001680] To a solid reagent of 4-aminobenezensulfonamide (2.0 g, 11.61 mmol) and tetrahydofuran-2,5-dione (1.16 g, 11.61 mmol) was added THF (30 mL). The reaction mixture was stirred at 60 °C for 4 hrs, and white solid precipitated out. The reaction mixture was cooled to room temperature, and filtered to give a white solid. The white solid was dried under vacuum to give 4-oxo-4-(4-sulfamoylanilino)butanoic acid (2.115 g, 67% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 7.74 (s, 4H), 7.23 (s, 2H), 2.65 – 2.51 (m, 4H).

Example 10. Synthesis of 3-(((4-nitrophenoxy)carbonyl)oxy)propyl stearate

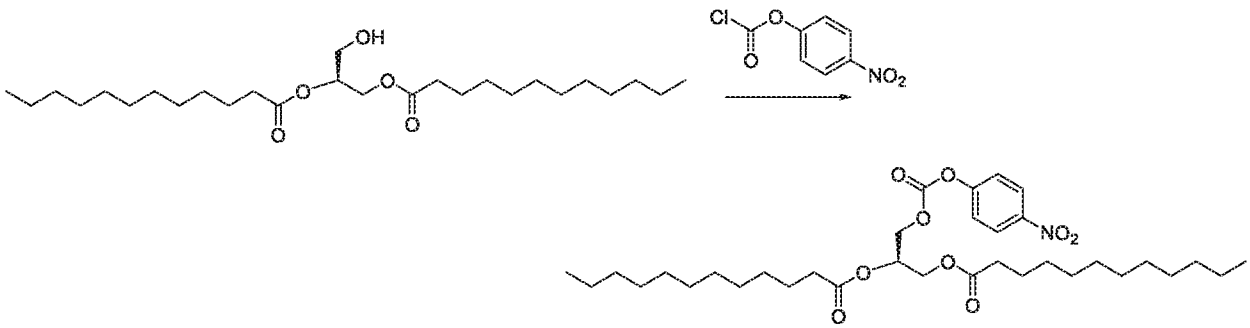


[001681] Step 1. A mixture of propane-1,3-diol (9.80 g, 128.75 mmol, 9.33 mL), Pyridine (2.61 g, 33.01 mmol, 2.66 mL) in $CHCl_3$ (50 mL) was degassed and purged with N_2 for 3 times, and then the mixture was dropwised stearoyl chloride (10 g, 33.01 mmol) in $CHCl_3$ (50 mL) at 0°C and stirred at 20°C for 20 hr under N_2 atmosphere. The mixture was extracted with EtOAc (50 mL * 2), and the combined

organic layers were washed with 1N HCl (50 mL * 2), *aq.* $NaHCO_3$ (50 mL * 2), H_2O (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Ethyl acetate/Petroleum ether = 2%, 12.5%) to afford 3-hydroxypropyl stearate (9 g) as a white gum. ^1H NMR (400 MHz, DMSO-d_6) δ = 4.24 (t, J = 6.06 Hz, 2H), 3.69 (t, J = 5.95 Hz, 2H), 2.31 (t, J = 7.50 Hz, 2H), 1.87 (q, J = 6.06 Hz, 2H), 1.56-1.68 (m, 2H), 1.22-1.31 (m, 24H), 0.88 (t, J = 6.73 Hz, 3H); TLC (Petroleum ether: Ethyl acetate = 3: 1) R_f = 0.54.

[001682] Step 2. A mixture of 3-hydroxypropyl stearate (9 g, 26.27 mmol), TEA (3.99 g, 39.41 mmol, 5.49 mL) in DCM (160 mL) was dropwised the solution of 4-nitrophenyl carbonochloridate (6.35 g, 31.53 mmol) in DCM (20 mL), then degassed and purged with N_2 for 3 times at 0°C, and then the mixture was stirred at 20°C for 16 hr under N_2 atmosphere. TLC indicated compound was consumed completely and many new spots formed. The reaction was clean according to TLC. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO_2, Ethyl acetate/Petroleum ether = 0%, 5%) to afford 3-(((4-nitrophenoxy)carbonyl)oxy)propyl stearate (5.73 g, 11.29 mmol, 42.96% yield) as an off-white solid. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 8.29 (d, J = 9.21 Hz, 2H), 7.39 (d, J = 9.21 Hz, 2H), 4.39 (t, J = 6.36 Hz, 2H), 4.24 (t, J = 6.14 Hz, 2H), 2.32 (t, J = 7.45 Hz, 2H), 2.11 (t, J = 6.36 Hz, 2H), 1.57 - 1.68 (m, 2H), 1.21 - 1.32 (m, 28H), 0.88 (t, J = 6.80 Hz, 3H); ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 173.73, 155.44, 152.40, 145.37, 125.30, 121.74, 66.00, 60.22, 34.21, 31.91, 29.68, 29.67, 29.64, 29.60, 29.30, 27.92, 24.91, 22.69, 14.12; TLC (Petroleum ether: Ethyl acetate = 3:1) R_f = 0.72.

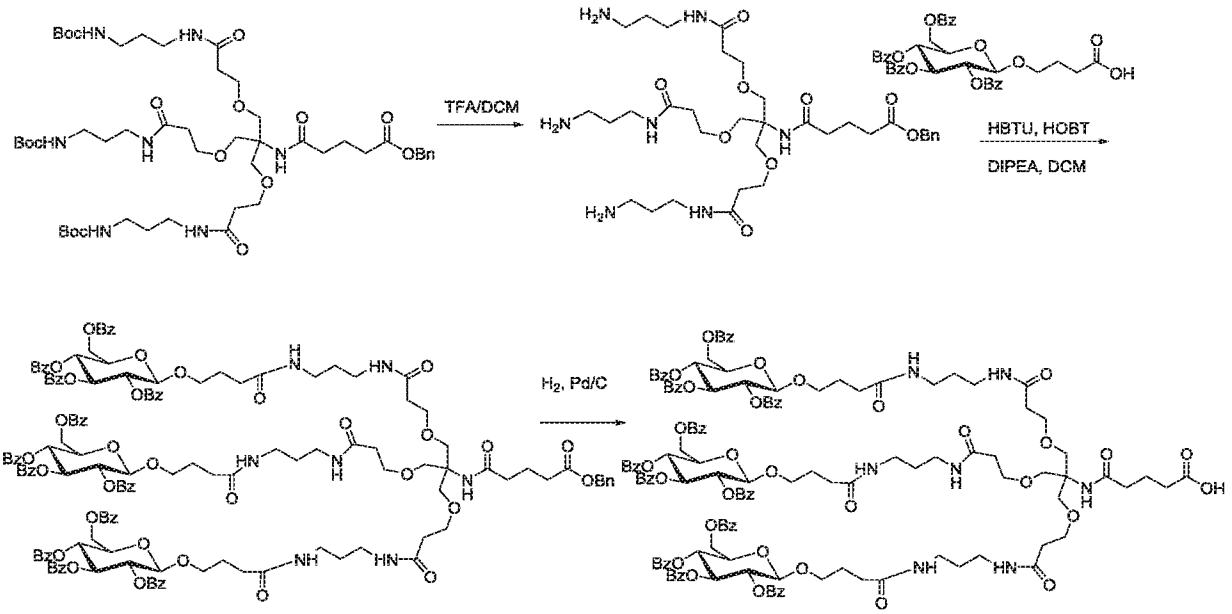
Example 11. Synthesis of (R)-3-(((4-nitrophenoxy)carbonyl)oxy)propane-1,2-diyl didodecanoate



[001683] To a solution of 4-nitrophenyl carbonochloridate (69.51 mg, 0.34 mmol) in THF (3.0 ml) at room temperature was added (S)-3-hydroxypropane-1,2-diyl didodecanoate (1,2-dilaurin) and DIPEA (0.11 ml, 0.66 mmol). The reaction mixture was stirred at room temperature for 3 hrs. Solvent was evaporated under reduced pressure, diluted with EtOAc, washed with water, dried over sodium sulfate, concentrated to give the desired product (R)-3-(((4-nitrophenoxy)carbonyl)oxy)propane-1,2-diyl

didodecanoate (204 mg, 100% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 (d, *J* = 8.9 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 2H), 5.32-.528 (m, 1 H), 4.34 – 4.09 (m, 4H), 2.31-2.23 (m, 4H), 1.58-0.79 (m, 42H).

Example 12. Synthesis of 4,10,17-trioxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-13-oxa-5,9,16-triazahenicosan-21-oic acid



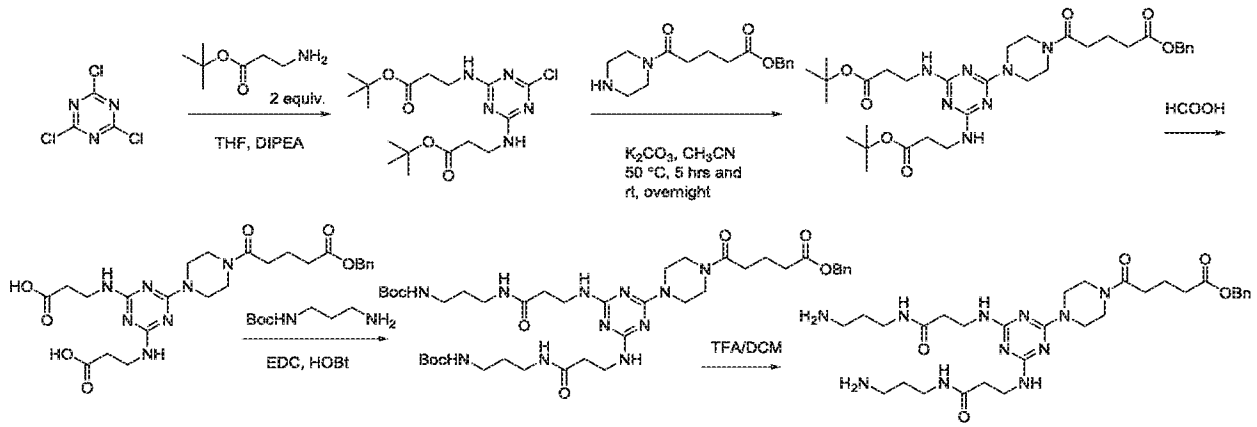
[001684] Step 1: To a solution of benzyl 15,15-bis(13,13-dimethyl-5,11-dioxo-2,12-dioxa-6,10-diazatetradecyl)-2,2-dimethyl-4,10,17-trioxo-3,13-dioxa-5,9,16-triazahenicosan-21-oate (0.95 g, 0.940 mmol) in DCM (5 mL) was added TFA (5 mL). The reaction mixture was stirred at room temperature for 4 hrs. LC-MS showed the reaction was completed. Solvent was evaporated under reduced pressure to give benzyl 5-((1,19-diamino-10-((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate as a colorless oil. Directly use for next step without purification.

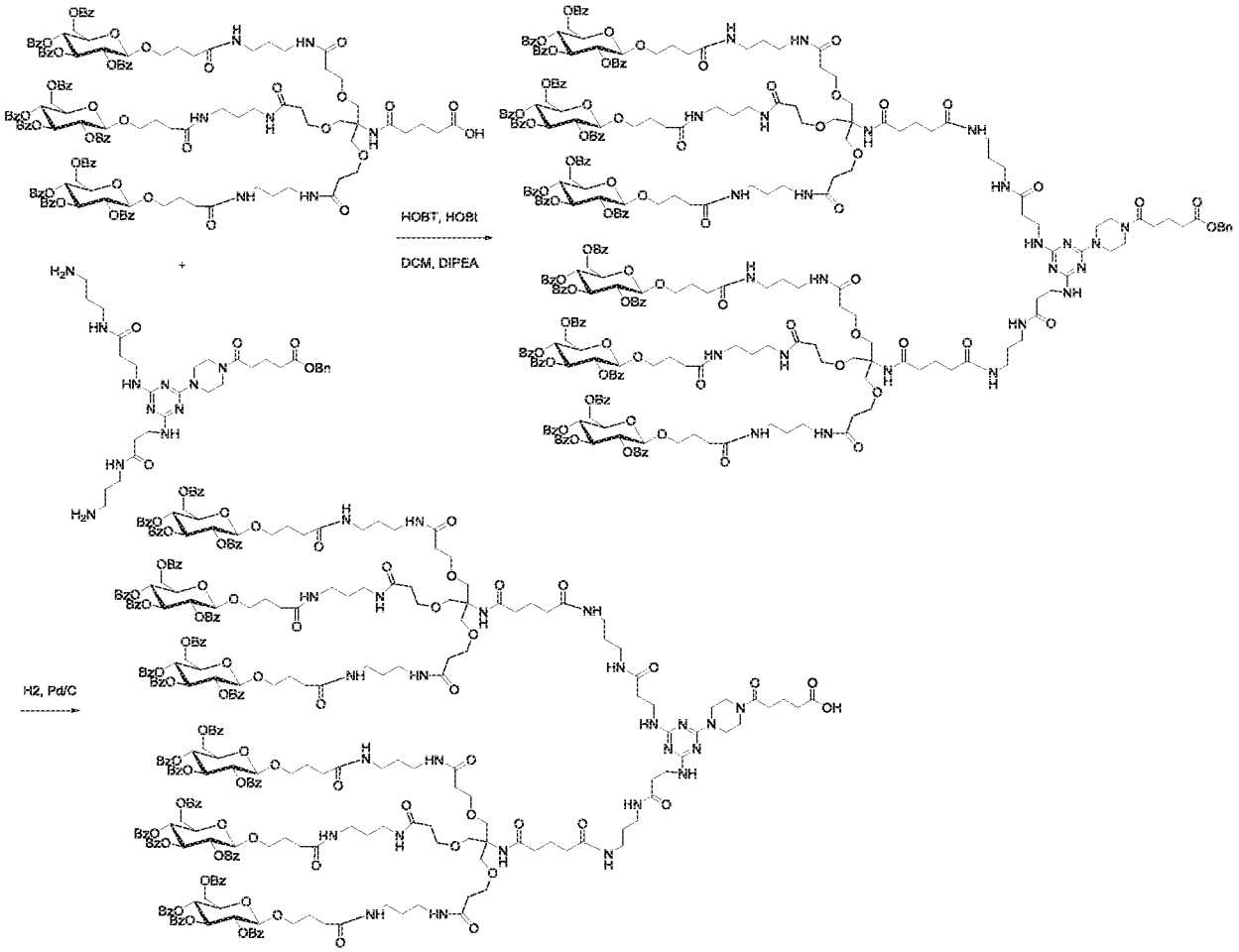
[001685] Step 2: To a solution of benzyl 5-((1,19-diamino-10-((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate (0.46 mmol) in DCM (6 mL) was added HOBt (62.16 mg, 0.46 mmol), HBTU (558.24 mg, 1.47 mmol), DIPEA (1.2 mL, 6.9 mmol) and a solution of 4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanoic acid (1.10 g, 1.61 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at rt for 3 hrs. Solvent was evaporated under reduced pressure to give a residue, which was diluted with EtOAc, washed with water, dried over anhydrous sodium sulfate to

give a residue, which was purified by ISCO (24g gold column) eluting with DCM to 20% MeOH in DCM to give 4,10,17-trioxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-13-oxa-5,9,16-triazahenicosan-21-anoic benzyl ester (1.14 g, 91.7%). MS (ESI), 1353.6 ((M/2+H)$^+$.

[001686] Step 3. To a solution of 4,10,17-trioxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-13-oxa-5,9,16-triazahenicosan-21-anoic benzyl ester (1.09 g, 0.400 mmol) in EtOAc (50 mL) was added 10% Pd-C (200 mg). The reaction mixture was stirred at rt for 4 hrs under hydrogen balloon. LC-MS showed the reaction was not completed. The reaction mixture was added another10% Pd-C (300 mg) and stirred at room temperature for 24 hrs under hydrogen balloon. The reaction mixture was filtered, washed with EtOAc/MeOH, concentrated to give 4,10,17-trioxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-13-oxa-5,9,16-triazahenicosan-21-oic acid (1.055 g, 100%). MS (ESI), 1308.1 ((M/2+H)$^+$.

Example 13. Synthesis of 5-(4-(4,6-bis((3,9,13,20,26-pentaoxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-29-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-17-oxa-4,8,14,21,25-pentaazanonacosyl)amino)-1,3,5-triazin-2-yl)piperazin-1-yl)-5-oxopentanoic acid





[001687] Step 1 to 2. To a solid reagent 2,4,6-trichloro-1,3,5-triazine (0.500 g, 2.71 mmol) in THF (30 mL) was added tert-butyl 3-aminopropanoate HCl salt (0.985 g, 5.42 mmol) and DIPEA (2.36 ml, 13.56 mmol). The reaction mixture was stirred at room temperature for 5 hrs. LC-MS showed the desired product; MS(ESI): 402.4 $(M+H)^+$. Solvent was evaporated under reduced pressure to give a residue, which was directly used for next step. To a solution of di-tert-butyl 3,3'-((6-chloro-1,3,5-triazine-2,4-diyl)bis(azanediyl))dipropionate (1.052 g, 2.71 mmol) in aceotnitrile (50 mL) was added benzyl 5-oxo-5-(piperazin-1-yl)pentanoate (1.103 g, 3.80 mmol) and K2CO3 (2.248 g, 16.27 mmol). The reaction mixture was stirred at room temperature for overnight and at 50 °C. Diluted with EtOAc, filtered and concentrated under reduced pressure to give a residue, which was purified by ISCO (40 g gold) eluting with 20% EtOAc in hexane to 50% EtOAc in hexane to give di-tert-butyl 3,3'-((6-(4-(5-(benzyloxy)-5-oxopentanoyl)piperazin-1-yl)-1,3,5-triazine-2,4-diyl)bis(azanediyl))dipropionate (1.13 g, 64%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.30 (m, 5 H), 5.15 (s, 2H), 3.75 (brs, 4H), 3.63 (brs, 6H), 3.43 (brs, 2H), 2.51 (q, *J* = 7.0, 6.5 Hz, 6H), 2.42 (t, *J* = 7.4 Hz, 2H), 2.09 – 1.96 (m, 2H), 1.48 (s, 18H); MS (ESI): 656.6 $(M+H)^+$.

[001688] Step 3. A solution of di-tert-butyl 3,3'-((6-(4-(5-(benzyloxy)-5-oxopentanoyl)piperazin-

1-yl)-1,3,5-triazine-2,4-diyl)bis(azanediyl))dipropionate (1.10 g, 1.68 mmol) in formic acid (20 mL) was stirred at room temperature for overnight. LC-MS showed the reaction was not completed and solvent was evaporated. Formic acid (20 mL) was added to the reaction mixture and the reaction mixture was stirred at room temperature for 5 hrs. LC-MS showed the reaction was complete. Solvent was concentrated, co-evaporated with toluene (2X) and dried under vacuum for overnight to give 3,3'-((6-(4-(5-(benzyloxy)-5-oxopentanoyl)piperazin-1-yl)-1,3,5-triazine-2,4-diyl)bis(azanediyl))dipropionic acid (0.91 g, 100 % yield) as a white solid. MS (ESI), 544.2 $(M+H)^+$.

[001689] Step 4. A solution of 3,3'-((6-(4-(5-(benzyloxy)-5-oxopentanoyl)piperazin-1-yl)-1,3,5-triazine-2,4-diyl)bis(azanediyl))dipropionic acid (0.91 g, 1.68 mmol) and HOBt (0.76 g, 4.36 mmol) in DCM (30 mL) and DMF (3 mL) at 0 °C was added tert-butyl (3-aminopropyl)carbamate (0.840 g, 4.36 mmol), EDC HCl salt (0.836 g, 4.36 mmol) and DIPEA (1.460 ml, 8.39 mmol). The reaction mixture was stirred at 0 °C for 15 minutes and at room temperature for 20 hrs. Solvent was evaporated to give a residue, which was dissolved in EtOAc (300 mL), washed with water (1X), saturated sodium bicarbonate (2X), 10% citric acid (2X) and water, dried over sodium sulfate, and concentrated to give a residue which was purified by ISCO (80 g gold catridge) eluting with DCM to 30% MeOH in DCM to give benzyl 5-(4-(4,6-bis((3-((3-((tert-butoxycarbonyl)amino)propyl)amino)-3-oxopropyl)amino)-1,3,5-triazin-2-yl)piperazin-1-yl)-5-oxopentanoate (1.11 g, 77 % yield) as a white solid. MS (ESI): 857.5 $(M+H)^+$.

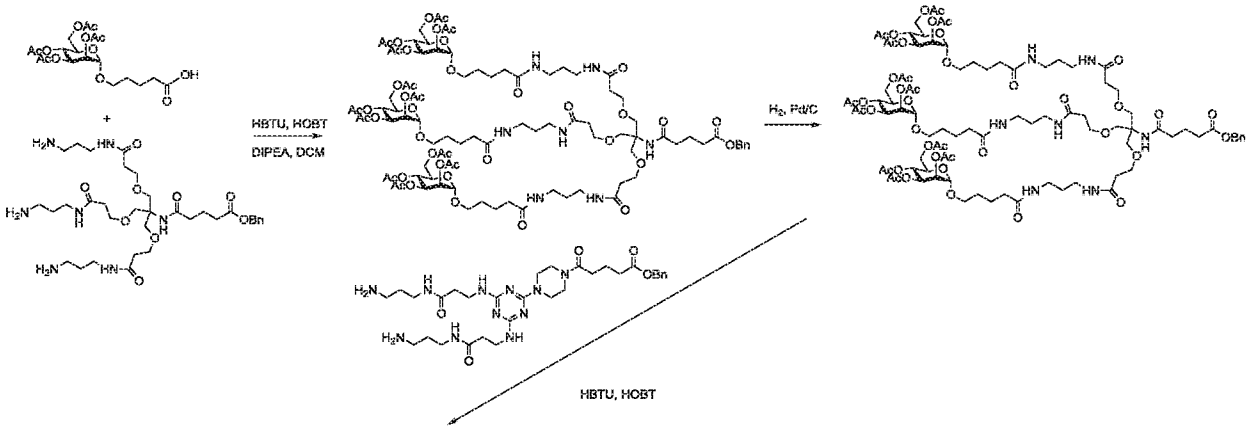
[001690] Step 5. A solution of benzyl 5-(4-(4,6-bis((3-((3-((tert-butoxycarbonyl)amino)propyl)amino)-3-oxopropyl)amino)-1,3,5-triazin-2-yl)piperazin-1-yl)-5-oxopentanoate (75.93 mg, 0.090 mmol) in DCM (3 mL) was added TFA (0.5 mL). The reaction mixture was stirred at room temperature for 3 hrs. Solvent was evaporated under reduced pressure, use directly for next step without purification. MS (ESI): 656.3 $(M+H)^+$.

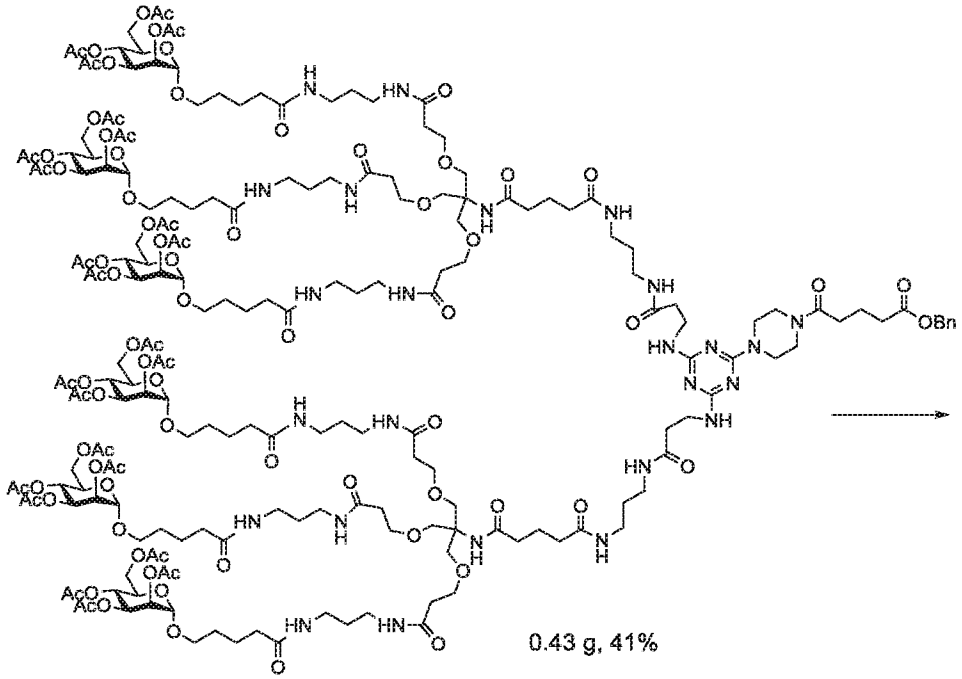
[001691] Step 6. To a solution of 4,10,17-trioxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-13-oxa-5,9,16-triazahenicosan-21-oic acid (580 mg, 0.222 mmol) in DCM (10 mL) was added HBTU (84.1 mg, 0.220 mmol), HOBt (11.99 mg, 0.09 mmol) and DIPEA (0.15 ml, 0.890 mmol). The reaction mixture was stirred at rt for 5 minutes and a solution of benzyl 5-(4-(4,6-bis((3-((3-aminopropyl)amino)-3-oxopropyl)amino)-1,3,5-triazin-2-yl)piperazin-1-yl)-5-oxopentanoate TFA salt (0.090 mmol) in acetonitrile was added to the reaction mixture. The reaction mixture was stirred at rt for overnight. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO (24 g gold) eluting with DCM to 40% MeOH in DCM to give 5-(4-(4,6-bis((3,9,13,20,26-pentaoxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-29-

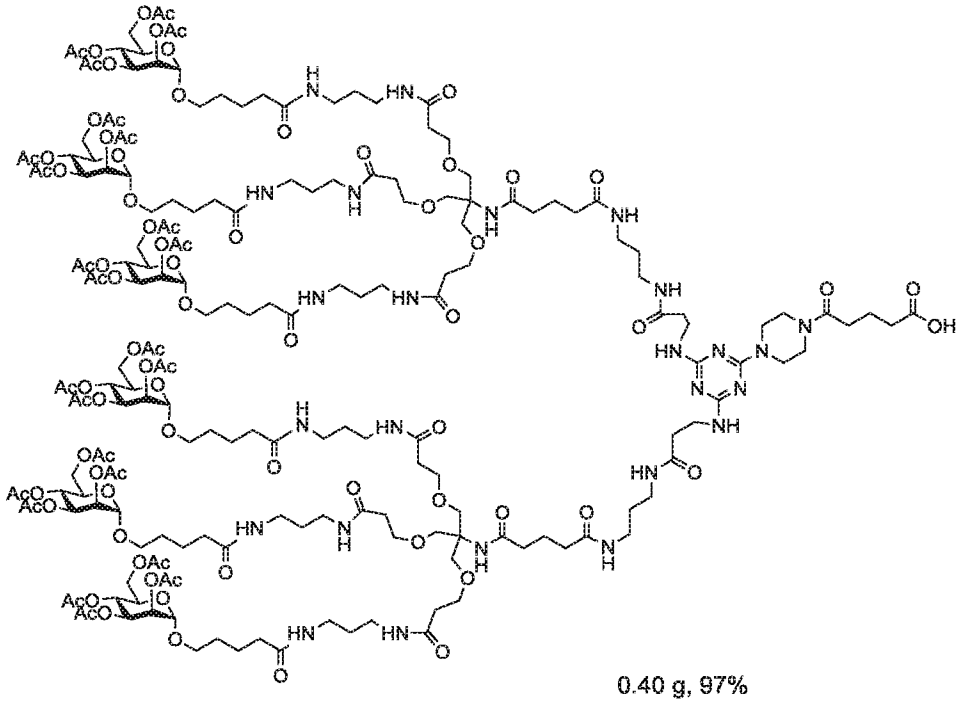
(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-17-oxa-4,8,14,21,25-pentaazanonacosyl)amino)-1,3,5-triazin-2-yl)piperazin-1-yl)-5-oxopentanoic benzyl ester (300 mg, 57.8%). MS (ESI), 1950.6 ((M/3+H)$^+$.

[001692] Step 7. To a solution of 5-(4-(4,6-bis((3,9,13,20,26-pentaoxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-29-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-17-oxa-4,8,14,21,25-pentaazanonacosyl)amino)-1,3,5-triazin-2-yl)piperazin-1-yl)-5-oxopentanoic benzyl ester (300 mg, 0.05 mmol) in EtOAc (10 ml) was added 10% Pd-C (100 mg). The reaction mixture was stirred at rt under hydrogen balloon for overnight. LC-MS showed the reaction was not complete. The reaction mixture was added MeOH (1 mL) and triethylsilane (2 mL). The reaction mixture was stirred at room temperature for 4 hrs. LC-MS showed the desired product. The reaction mixture was filtered, washed with EtOAc/MeOH, and concentrated under reduced pressure to give a residue, which was purified by ISCO (50 g C18 catridge) eluting with 1% TFA in water to 100% acetonitrile and lyophilized to give 5-(4-(4,6-bis((3,9,13,20,26-pentaoxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-29-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-17-oxa-4,8,14,21,25-pentaazanonacosyl)amino)-1,3,5-triazin-2-yl)piperazin-1-yl)-5-oxopentanoic acid (120 mg, 40.6% yield) as a white solid. MS (ESI), 1920 ((M/3+H)$^+$.

Example 14. Synthesis of 5-(4-(4,6-bis((3,9,13,20,26-pentaoxo-15,15-bis((3-oxo-3-((3-(5-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-30-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-17-oxa-4,8,14,21,25-pentaazatriacontyl)amino)-1,3,5-triazin-2-yl)piperazin-1-yl)-5-oxopentanoic acid







[001693] Step 1. To a solution of 5-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanoic acid (2.43 g, 5.43 mmol) in DCM was added HBTU (2.06 g, 5.43 mmol), HOBt (183.36 mg, 1.36 mmol) and DIPEA (4.73 ml, 27.14 mmol). The reaction mixture was stirred at room temperature for 10 minutes, and a solution of benzyl 5-((1,19-diamino-10-((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate TFA salt (1.36 mmol) in acetonitrile was added. The

reaction mixture was stirred at room temperature for 3 hrs. Solvent was concentrated under reduced pressure to give a residue, which was purified by ISCO (80 g gold catridge) eluting with 5% MeOH in DCM to 60% MeOH in DCM to give 5,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanoic benzyl ester (2.22 g, 81.8%). MS (ESI): 1002 $(M/2+H)^+$.

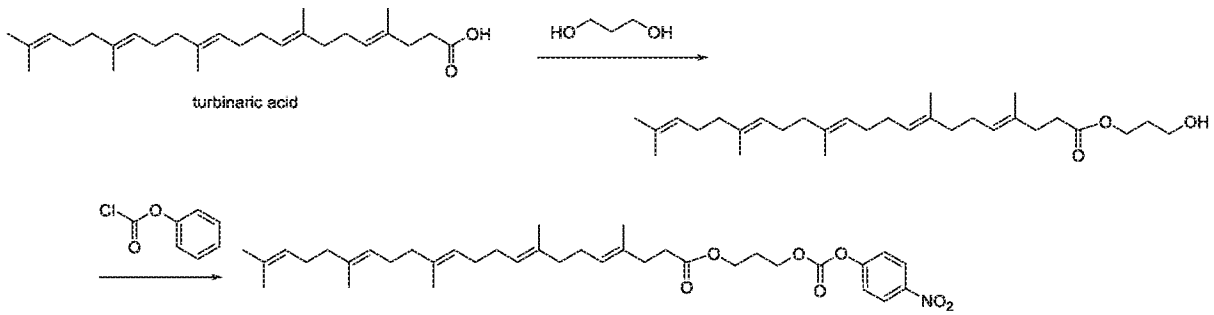
[001694] Step 2. To a solution of 5,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanoic benzyl ester (2.20 g, 1.1 mmol) in EtOAc (30 mL) and MeOH (3 mL) was added 10% Pd-C (300 mg) and triethylsilane (1.8 mL, 11.3 mmol) slowly. The reaction mixture was stirred at room temperature for 1 hr. The reaction mixture was filtered through celite and concentrated to give 5,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanoic acid. MS (ESI), 1912 $(M+H)^+$.

[001695] Step 3. To a solution of 5,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanoic acid (1911 mg, 0.580 mmol) in DCM (30 mL) was added HBTU (266 mg, 0.700 mmol), HOBt (31.56 mg, 0.23 mmol) and DIPEA (0.81 ml, 4.67 mmol). The reaction mixture was stirred at rt for 10 minutes and a solution of benzyl 5-(4-(4,6-bis((3-((3-aminopropyl)amino)-3-oxopropyl)amino)-1,3,5-triazin-2-yl)piperazin-1-yl)-5-oxopentanoate TFA salt (0.23 mmol) in acetonitrile (5 mL)was added to the reaction mixture. The reaction mixture was stirred at rt for 3 hrs. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO (24 g gold) eluting with DCM to 50% MeOH in DCM to give 5-(4-(4,6-bis((3,9,13,20,26-pentaoxo-15,15-bis((3-oxo-3-((3-(5-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-30-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-17-oxa-4,8,14,21,25-pentaazatriacontyl)amino)-1,3,5-triazin-2-yl)piperazin-1-yl)-5-oxopentanoic benzyl ester (430 mg, 41.4%). MS (ESI), 1482.1 $(M/3+H)^+$.

[001696] Step 4. A solution of 5-(4-(4,6-bis((3,9,13,20,26-pentaoxo-15,15-bis((3-oxo-3-((3-(5-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-

yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-30-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-17-oxa-4,8,14,21,25-pentaazatriacontyl)amino)-1,3,5-triazin-2-yl)piperazin-1-yl)-5-oxopentanoic benzyl ester (420 mg, 0.090 mmol) in EtOAc (15 mL) and MeOH (2 mL) was added 10% Pd-C (200 mg). The reaction mixture was stirred at room temperature under hydrogen balloon for overnight. The reaction mixture was filtered through celite, washed with 50% MeOH in EtOAc, and concentrated under reduced pressure to give 5-(4-(4,6-bis((3,9,13,20,26-pentaoxo-15,15-bis((3-oxo-3-((3-(5-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-30-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-17-oxa-4,8,14,21,25-pentaazatriacontyl)amino)-1,3,5-triazin-2-yl)piperazin-1-yl)-5-oxopentanoic acid. MS (ESI), 1452.0 $(M/3+H)^+$.

Example 15. Synthesis of 3-(((4-nitrophenoxy)carbonyl)oxy)propyl (4E,8E,12E,16E)-4,8,13,17,21-pentamethyldocosa-4,8,12,16,20-pentaenoate



[001697] Step 1. To the solution of turbinaric acid (2.00 g, 4.992mmol) in DCM (20 mL) was added 1,3-propanediol (1.8 mL, 24.96 mmol), EDC (1.91 g, 9.984 mmol) and DMAP (30.5 mg). The reaction mixture was stirred at rt for 5 hrs. LC-MS showed the reaction was complete. The reaction mixture was concentrated, diluted with EtOAc (100 mL), washed successively with 1N HC aq solution (20 ml), saturated $NaHCO_3$ aq solution (20 mL), water (10 mL), and brine (5 mL), dried over sodium sulfate, filtered, and concentrated to give a residue, which was purified by ISCO (40 g gold catridge) using 0-100% EtOAc in hexane as the gradient to give 3-hydroxypropyl (4E,8E,12E,16E)-4,8,13,17,21-pentamethyldocosa-4,8,12,16,20-pentaenoate (1.129g, 49% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 5.15 – 5.02 (m, 5H), 4.46 (t, J = 5.1 Hz, 1H), 4.06 (t, J = 6.6 Hz, 2H), 3.45 (td, J = 6.3, 5.1 Hz, 2H), 2.40 – 2.31 (m, 2H), 2.20 (t, J = 7.6 Hz, 2H), 2.08-1.90 (m, 16H), 1.70 (p, J = 6.4 Hz, 2H), 1.64 (d, J = 1.5 Hz, 3H), 1.56 (m, 15H); MS (ESI), 481.3 $(M+Na)^+$.

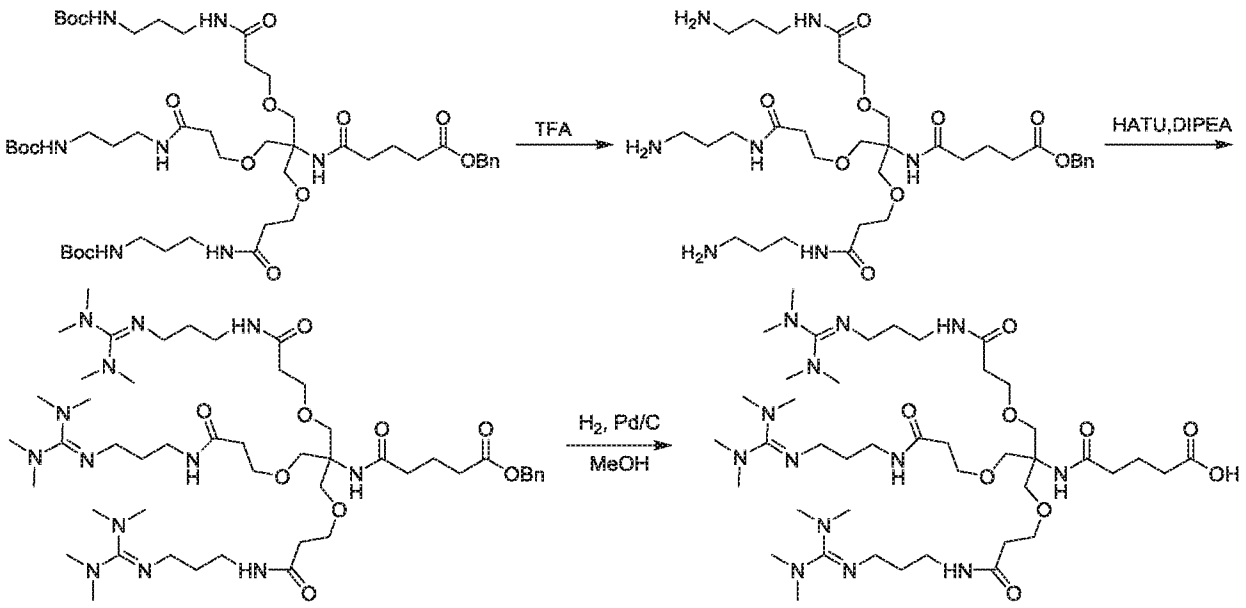
[001698] Step 2. To a solution of 3-hydroxypropyl (4E,8E,12E,16E)-4,8,13,17,21-pentamethyldocosa-4,8,12,16,20-pentaenoate (1.12g, 2.4416 mmol) in anhydrous DCM (12.5 mL) at 0 °C was added TEA (0.68 mL), and a solution of 4-nitrophenyl chloroformate (738mg) in anhydrous DCM (5 ml) slowly. The reaction mixture was stirred at 0°C for 40 min, and at room temperature for overnight.

The reaction mixture was concentrated to give a residue, which was purified by ISCO (40 gold catridge) eluting with using 0-50% EtOAc in hexane to give 3-(((4-nitrophenoxy)carbonyl)oxy)propyl (4E,8E,12E,16E)-4,8,13,17,21-pentamethyldocosa-4,8,12,16,20-pentaenoate (1.06 g, 70% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 – 8.29 (m, 2H), 7.58 – 7.51 (m, 2H), 5.13 – 5.01 (m, 5H), 4.32 (t, J = 6.3 Hz, 2H), 4.13 (t, J = 6.3 Hz, 2H), 2.44 – 2.34 (m, 2H), 2.21 (t, J = 7.6 Hz, 2H), 2.07 – 1.87 (m, 18H), 1.63 (d, J = 1.5 Hz, 3H), 1.55 (m, 15H).

Example 16. Preparation of certain chemical moieties and oligonucleotides comprising certain chemical moieties

[001699] In some embodiments, the present disclosure provides chemical moieties that can be incorporated into oligonucleotides. In some embodiments, a chemical moiety is a targeting moiety. In some embodiments, a chemical moiety is a carbohydrate moiety. In some embodiments, a chemical moiety is a lipid moiety. In some embodiments, chemical moieties may be incorporated into oligonucleotides to improve one or more properties, activities, and/or delivery. Certain chemical moieties, their preparation, and oligonucleotides comprising such moieties are described in the present example. Those skilled in the art appreciate that such chemical moieties may also be incorporated into oligonucleotides having other base sequences, modifications, etc.

[001700] **Synthesis of 3-(dimethylamino)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-oic acid**



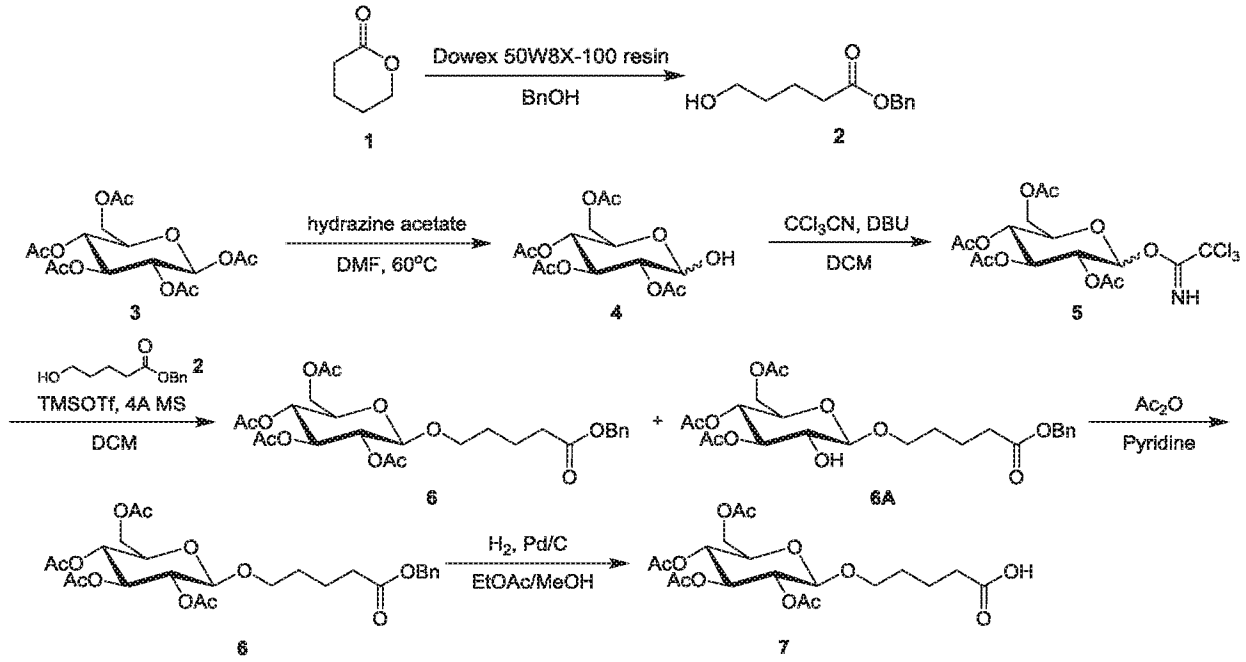
[001701] Step 1. To a solution of benzyl 15,15-bis(13,13-dimethyl-5,11-dioxo-2,12-dioxa-6,10-diazatetradecyl)-2,2-dimethyl-4,10,17-trioxo-3,13-dioxa-5,9,16-triazahenicosan-21-oate (9.0 g, 8.91 mmo) in DCM (100 mL) was added TFA (30.47 g, 267.27 mmol, 19.79 mL) at 0 °C. The mixture was stirred at 0-15 °C for 4 hr. The mixture was formed two phase. Lower phase was separated and

concentrated under reduced pressure to give a crude. benzyl 5-((1,19-diamino-10-((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate TFA salt (13 g) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, METHANOL-d4) Shift = 7.39 - 7.27 (m, 5H), 5.12 (s, 2H), 3.70 - 3.63 (m, 13H), 3.32 - 3.30 (m, 2H), 3.26 (s, 2H), 2.94 (t, J=7.3 Hz, 7H), 2.49 - 2.38 (m, 9H), 2.23 (t, J=7.4 Hz, 2H), 1.94 - 1.78 (m, 9H). **LCMS:** M+H$^+$= 710.2.

[001702] Step 2. To a solution of benzyl 5-((1,19-diamino-10-((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate TFA salt (13 g) in DCM (200 mL) was added DIPEA (15.97 g, 123.58 mmol, 21.53 mL) and HATU (15.51 g, 40.78 mmol). The mixture was stirred at 15 °C for 15 hr. LCMS showed compound **2** was consumed and desired MS was detected. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Agela innoval ods-2 250*80mm; mobile phase: [water (0.1%TFA)-ACN]; B%: 8%-38%, 20min) to give compound benzyl 3-(dimethylamino)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-oate (6.5 g, 52.37% yield) as a brown oil. **LCMS:** M/2+H$^+$= 503.1.

[001703] Step 3. To a solution of compound benzyl 3-(dimethylamino)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-oate (5.7 g, 5.68 mmol) in MeOH (30 mL) and H_2O (6 mL) was added LiOH.H_2O (1.67 g, 39.73 mmol). The mixture was stirred at 15 °C for 2 hr. LCMS showed compound **3** was consumed and desired MS was detected. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 250*50mm*10 um; mobile phase: [water (0.1%TFA)-ACN]; B%: 0%-25%, 20min). 3-(dimethylamino)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-oic acid (2.09 g, 2.25 mmol, 40% yield) was obtained as a yellow gum. **^{1}HNMR** (400 MHz, DMSO-d6) Shift = 8.07 (br t, J = 5.7 Hz, 3H), 7.75 (br t, J = 5.0 Hz, 3H), 7.08 (s, 1H), 3.63 - 3.45 (m, 12H), 3.09 (q, J = 6.1 Hz, 11H), 2.88 (br d, J = 15.3 Hz, 36H), 2.29 (br t, J = 6.4 Hz, 6H), 2.18 (t, J = 7.5 Hz, 2H), 2.12 - 2.06 (m, 2H), 1.65 (br t, J = 6.6 Hz, 8H). **^{13}CNMR** (101 MHz, DMSO-d6) Shift = 173.10, 170.88, 169.27, 159.88, 157.61, 157.27, 156.93, 156.58, 119.48, 116.56, 113.63, 110.70, 67.13, 66.27, 58.46, 40.77, 34.82, 34.34, 33.88, 31.87, 28.23, 19.66, 0.00. **LCMS:** M + H$^+$ = 915.7, purity: 98.265%.

[001704] **Synthesis of 5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanoic acid**



[001705] Step 1. A mixture of phenylmethanol (864.10 g, 7.99 mol), compound **1** (100 g, 998.85 mmol), and cation exchange resin (1.92 g, 998.85 mmol.) was stirred at 75°C with N_2 for 4 hr, and then the mixture was stirred at 20°C for 12 hr under N_2 atmosphere. TLC showed compound **1** was consumed completely and two main peaks were detected. The reaction mixture was filtered and then the residue was washed with DCM (500 mL). The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 10/1 to 3:1) to get compound **2** as a colorless oil (62 g, 29.81% yield). **^{1}HNMR (400 MHz, CHLOROFORM-d):** δ = 7.41 - 7.27 (m, 5H), 5.11 (s, 2H), 3.62 (t, *J* = 6.4 Hz, 2H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.77 - 1.70 (m, 2H), 1.65 - 1.51 (m, 2H); TLC (Petroleum ether / Ethyl acetate = 3:1) Rf = 0.20.

[001706] Step 2. To a solution of compound **3** (350 g, 896.66 mmol.) in DMF (2 L) was added acetic acid hydrazine (99.10 g, 1.08 mol). The mixture was stirred at 60°C for 5hr. TLC showed the starting material was consumed. The mixture was concentrated to move the most solvent and water (500 mL) was added, and the mixture was extracted with EtOAc (500 mL*3). The combined organic was dried over Na_2SO_4, filtered and concentrated to get the compound **4** as a brown oil (310 g, crude). **^{1}HNMR (400 MHz, CHLOROFORM-d):** δ = 5.49 (t, J = 9.9 Hz, 1H), 5.39 (d, J = 3.5 Hz, 1H), 5.06 - 4.99 (m, 1H), 4.84 (dd, J = 3.5, 10.1 Hz, 1H), 4.25 - 4.17 (m, 2H), 4.13 - 4.02 (m, 2H), 2.04 - 1.96 (m, 12H); TLC (Petroleum ether / Ethyl acetate = 1:1), Rf = 0.43.

[001707] Step 3. To a solution of compound **4** (310 g, 890.03 mmol.) in DCM (1.5 L) was added 2,2,2-trichloroacetonitrile (1.16 kg, 8.01 mol) at 0°C. The mixture was added drop-wise DBU (271.00 g, 1.78 mol) dissolved in DCM (1 L) at 0°C. The mixture was stirred at 20°C for 1h. TLC showed the

starting material was consumed. The mixture was concentrated to get the crude. The mixture was purified by silica gel chromatography (Petroleum ether / Ethyl acetate = 20:1, 10:1, 5:1) to get compound **5** as a yellow oil (90 g, 20.52% yield). **^{1}HNMR (400 MHz, $CDCl_3$):** δ = 8.70 (s, 1H), 6.56 (br d, J = 3.1 Hz, 1H), 5.57 (t, J = 9.8 Hz, 1H), 5.24 - 5.08 (m, 2H), 4.35 - 4.15 (m, 2H), 2.11 - 1.99 (m, 12H); TLC (Petroleum ether / Ethyl acetate = 1:1) Rf = 0.31.

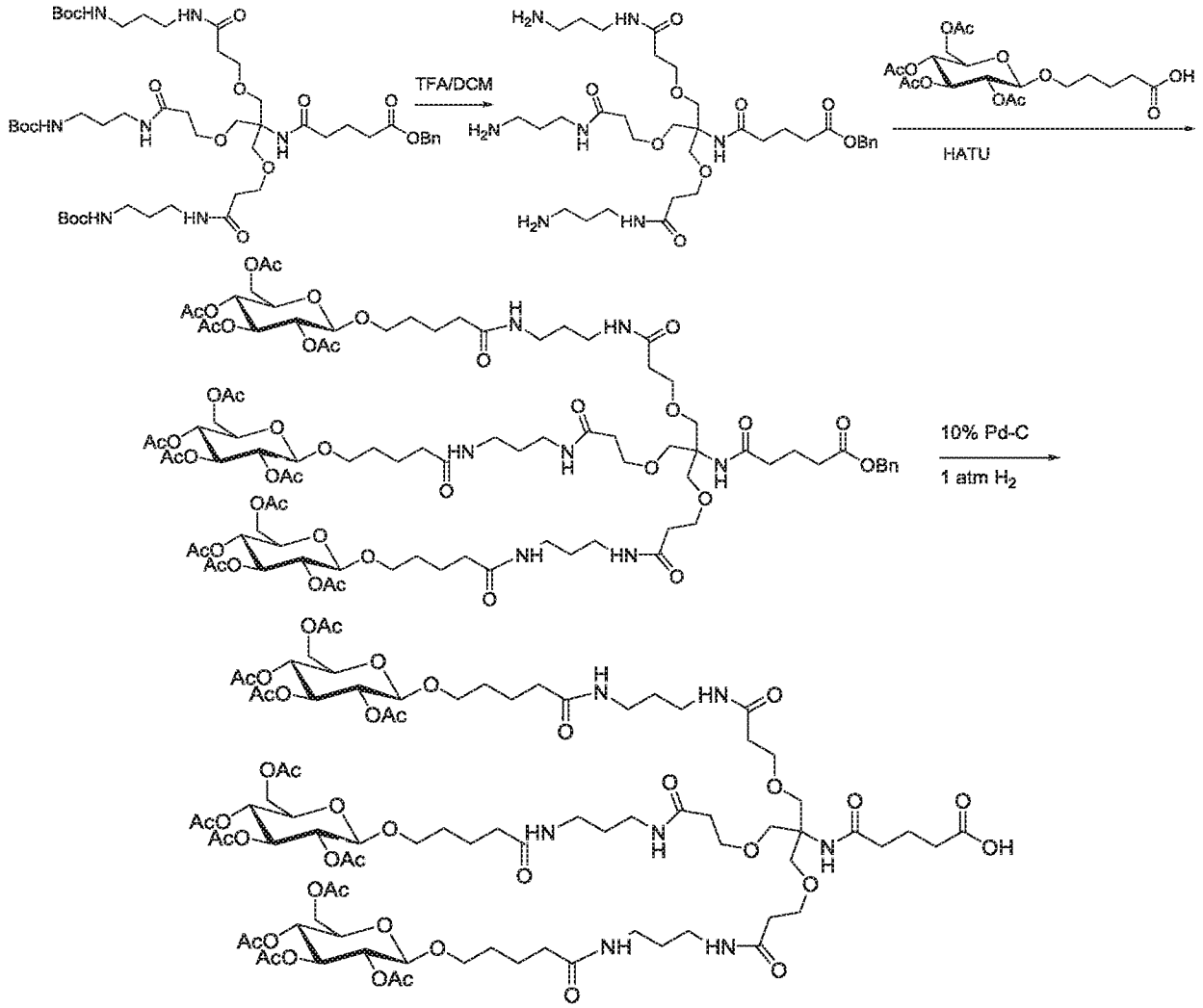
[001708] Step 4. To a solution compound **5** (89.5 g, 181.66 mmol) and compound **2** (75.66 g, 363.31 mmol) in DCM (800 mL) was added 4A MS (90 g), the mixture was stirred at -30°C for 30 min. TMSOTf (40.37 g, 181.66 mmol.) was added to the reaction and the mixture was stirred at 25°C for 3hr. LCMS and TLC showed the starting material was consumed and LCMS showed the de-Ac MS was found. Sat. $NaHCO_3$ (aq., 100 mL) was added and the mixture was extracted with DCM (150 mL*3). The combined organic was dried over Na_2SO_4, filtered and concentrated to get the crude. Totally got the mixture of benzyl compound **6** and compound **6A** (98 g) as a yellow oil, the mixture was used next step directly. TLC (Petroleum ether / Ethyl acetate = 2:1) Rf = 0.38.

[001709] Step 5. The mixture compound **6** and compound **6A** (98 g crude) was dissolved in the pyridine (150 mL) and then Ac_2O (150 mL) was added. The mixture was stirred at 20°C for 12h. TLC showed the starting material was consumed. The mixture was concentrated to get the crude. The mixture was purified by MPLC (silica, Petroleum ether / Ethyl acetate = 20:1, 10:1, 05:1) to get compound **6** as a yellow oil (41 g, 41.84% yield) and 12 g crude. **^{1}HNMR (400 MHz, $CDCl_3$):** δ = 7.39 - 7.31 (m, 5H), 5.23 - 4.93 (m, 3H), 4.48 (d, *J* = 7.9 Hz, 1H), 4.37 - 4.22 (m, 1H), 4.17 - 4.05 (m, 1H), 3.92 - 3.81 (m, 1H), 3.71 - 3.63 (m, 1H), 3.48 (td, *J* = 6.3, 9.8 Hz, 1H), 2.44 - 2.32 (m, 2H), 2.09 - 1.98 (m, 12H), 1.75 - 1.53 (m, 4H); **LCMS:** ($M+Na^+$): 561.0; **SFC:** de%: 100%; TLC (Petroleum ether / Ethyl acetate = 3:1) Rf = 0.14.

[001710] Step 6. To a solution of compound **7** (19.5 g, 36.21 mmol) in EtOAc (200 mL) was added Pd/C (4 g, 17.64 mmol, 10% purity) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (**25** Psi) at 20°C for 2 hr. LCMS and TLC showed the starting material was consumed. The mixture was filtered, the cake was washed with MeOH (50 mL*3) and the combined filter was concentrated to get the crude. The mixture was purified by silica gel chromatography (Petroleum ether / Ethyl acetate = 3:1, 1:1, 1:3) to get 5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanoic acid **7** as a white solid (23.9 g, 51.72 mmol, 71.41% yield, 97.03% LCMS purity). **^{1}HNMR (400 MHz, CHLOROFORM-d):** δ = 5.24 - 5.17 (m, 1H), 5.12 - 4.96 (m, 2H), 4.50 (d, J = 7.9 Hz, 1H), 4.26 (dd, J = 4.7, 12.3 Hz, 1H), 4.20 - 4.02 (m, 1H), 3.95 - 3.85 (m, 1H), 3.75 - 3.64 (m, 1H), 3.55 - 3.46 (m, 1H), 2.42 - 2.32 (m, 2H), 2.15 - 1.99 (m, 12H), 1.76 - 1.57 (m, 4H); **^{13}CNMR (101 MHz, CHLOROFORM-d):** δ = 178.85, 170.71, 170.30, 169.40, 169.35, 100.71, 72.81, 71.74, 71.25, 69.37, 68.42, 61.94, 33.36, 28.59, 21.09, 20.70, 20.56;

LCMS: (M-H+): 447.1, LCMS purity: 97.03%; TLC (Petroleum ether / Ethyl acetate = 1:1) Rf = 0.03.

[001711] **Synthesis of 5,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanoic acid**



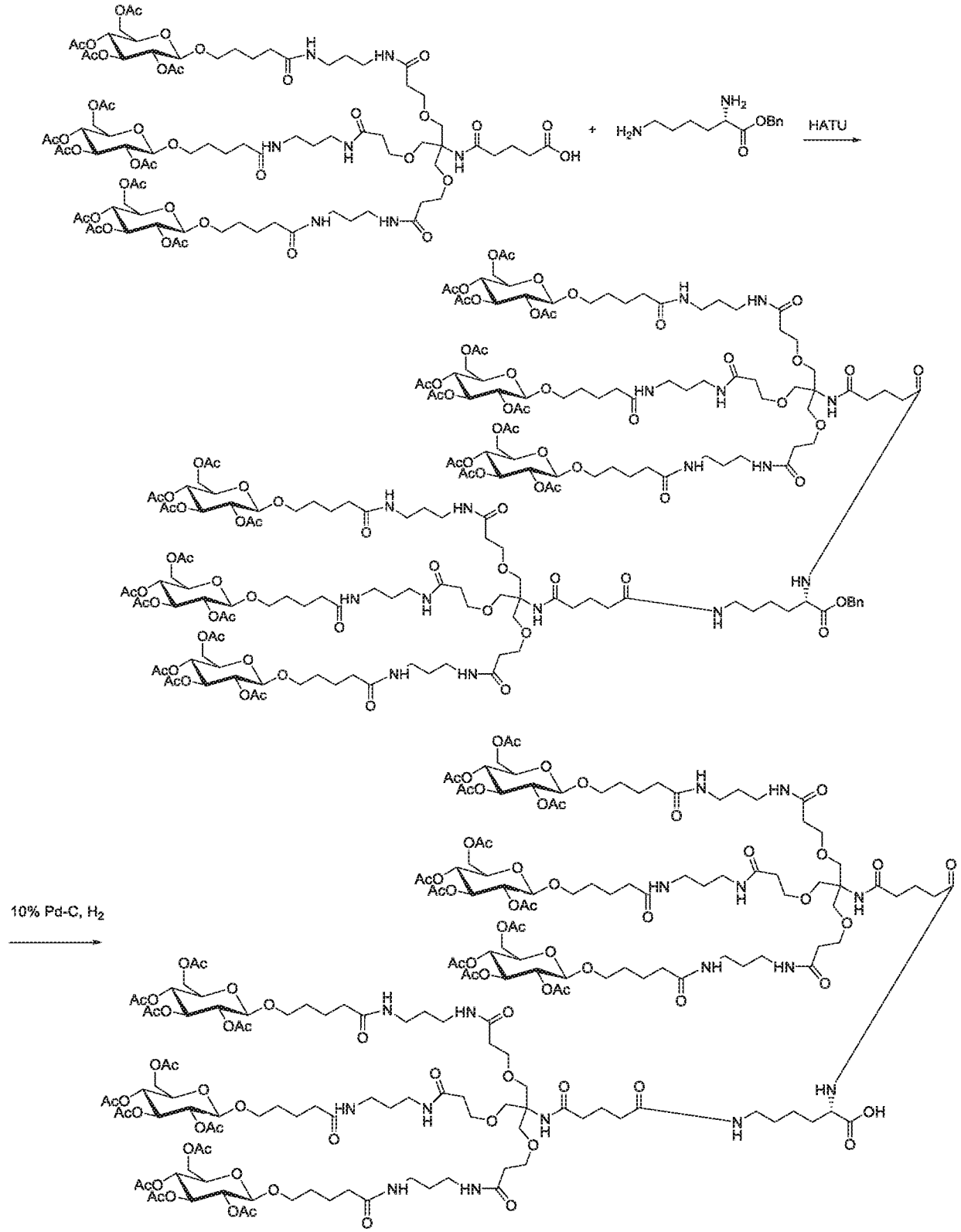
[001712] Step 1: To a solution of benzyl 15,15-bis(13,13-dimethyl-5,11-dioxo-2,12-dioxa-6,10-diazatetradecyl)-2,2-dimethyl-4,10,17-trioxo-3,13-dioxa-5,9,16-triazahenicosan-21-oate (2.15 g, 2.1282 mmol) in DCM (20 mL) was added TFA (5 mL). The reaction mixture was stirred at room temperature for 4 hrs. LC-MS showed the reaction was completed. Solvent was evaporated under reduced pressure to give benzyl 5-((1,19-diamino-10-((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate as a colorless oil. Directly use for next step without purification.

[001713] Step 2: To a solution of 5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-

(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanoic acid (3.817 g, 8.51 mmol) in DMF (20 mL) was added DIPEA (5.66 mL, 31.92 mmol) and HATU (2.824 g, 7.45 mmol) followed by benzyl 5-((1,19-diamino-10-((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate (2.1282 mmol). The reaction mixture was stirred at room temperature for 3 hrs. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO (120 g gold column) eluting with DCM to 50% MeOH in DCM to give 5,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanoic benzyl ester (5.08 g, 120%), which containing some impurities. MS (ESI), 1001.4 ((M/2+H)$^+$.

[001714] Step 3. To a solution of 5,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanoic benzyl ester (5.08 g) in EtOAc (100 mL) and MeOH (10 mL) was added 10% Pd-C (500 mg). The reaction mixture was stirred at rt for 4 hrs under hydrogen balloon. LC-MS showed the reaction was completed. The reaction mixture was filtered, washed with EtOAc/MeOH, concentrated to give 45,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanoic acid (4.60 g, 95%). MS (ESI), 1912 ((M+H)$^+$.

[001715] **Synthesis of (S)-5,11,18,22-tetraoxo-16,16-bis((3-oxo-3-((3-(5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-28-(5,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanamido)-14-oxa-6,10,17,23-tetraazanonacosan-29-oic acid**

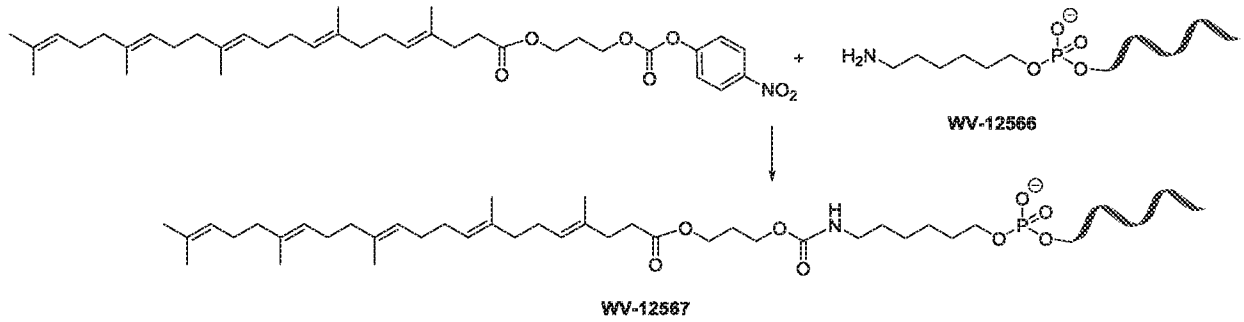


[001716] Step 1: To a solution of 5,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-

yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanoic acid (987 mg, 0.520 mmol) in acetonitrile (3 mL) and DCM (10 ml) was added DIPEA (0.27 mL, 1.55 mmol) and HATU (150 mg, 0.400 mmol) followed by L-lysine benzyl ester di-4-toluensulfonate salt (100 mg, 0.170 mmol). The reaction mixture was stirred at room temperature for overnight. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO (40 g gold column) eluting with DCM to 30% MeOH in DCM to give (S)-5,11,18,22-tetraoxo-16,16-bis((3-oxo-3-((3-(5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-28-(5,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanamido)-14-oxa-6,10,17,23-tetraazanonacosan-29-oic benzyl ester (433 mg, 63%), which containing some impurities. MS (ESI), 1342.0 $((M/3+H)^+$.

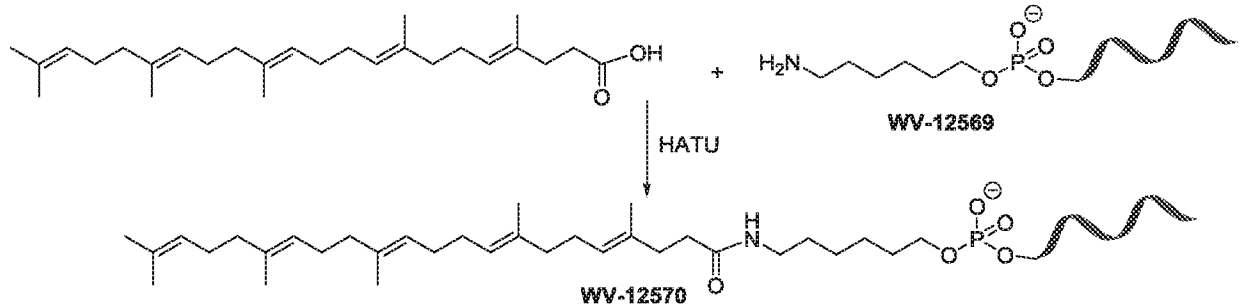
[001717] Step 3. To a solution of (S)-5,11,18,22-tetraoxo-16,16-bis((3-oxo-3-((3-(5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-28-(5,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanamido)-14-oxa-6,10,17,23-tetraazanonacosan-29-oic benzyl ester (430 mg) in EtOAc (15 mL) and MeOH (3 mL) was added 10% Pd-C (100 mg). The reaction mixture was stirred at rt for 4 hrs under hydrogen balloon. LC-MS showed the reaction was completed. The reaction mixture was filtered, washed with EtOAc/MeOH, concentrated to give (S)-5,11,18,22-tetraoxo-16,16-bis((3-oxo-3-((3-(5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-28-(5,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanamido)-14-oxa-6,10,17,23-tetraazanonacosan-29-oic acid (400 mg, 94%). MS (ESI), 1968 $((M/2+H)^+$.

[001718] **Synthesis of WV-12567**



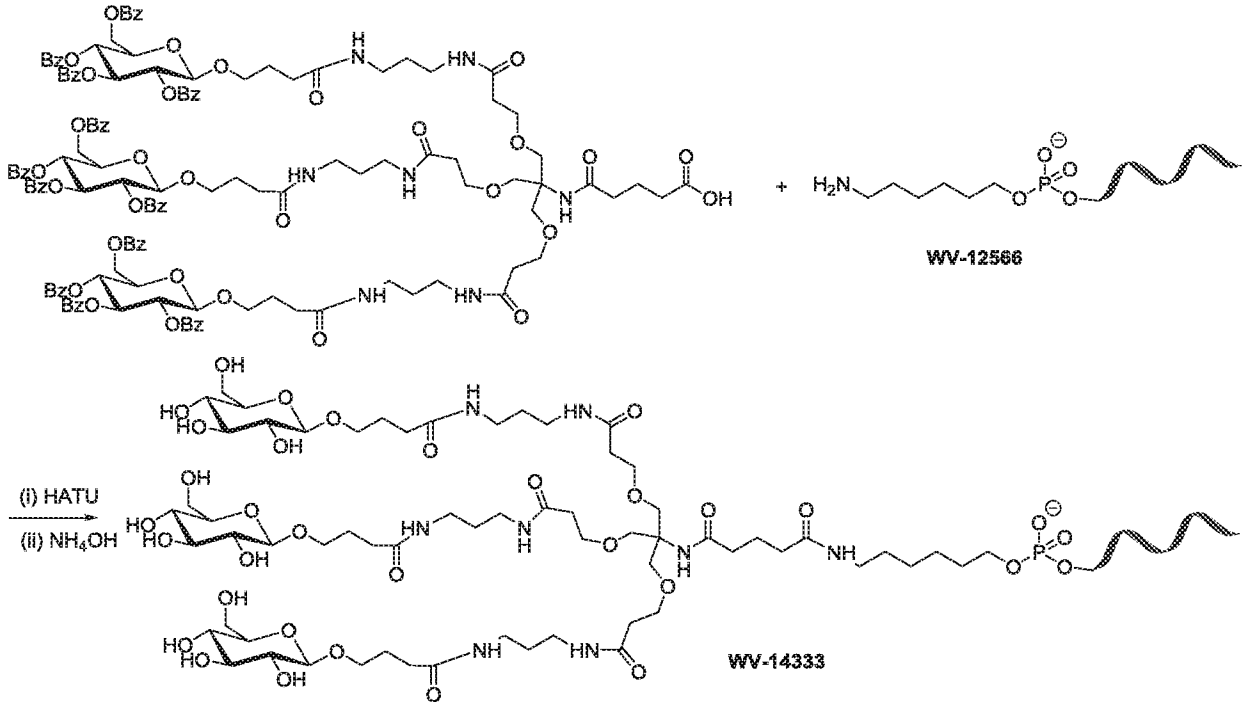
[001719] To a solution of WV-12566 in 0.4 ml NMP and 0.57 ml water was added DIPEA (20 µL) and a solution of 3-(((4-nitrophenoxy)carbonyl)oxy)propyl (4E,8E,12E,16E)-4,8,13,17,21-pentamethyldocosa-4,8,12,16,20-pentaenoate (20 mg) in NMP (0.40 mL). The reaction mixture was shaken for 12 hours at 35 °C. LC-MS showed the starting material was disappeared. The crude product was purified on RP HPLC (C8) using 50 mM TEAA in water and acetonitrile, and desalt to obtain 1.77 mg of the conjugate WV-12567. Deconvoluted mass: 7362; Calculated molecular weight: 7360.

[001720] **Synthesis of WV-12570**



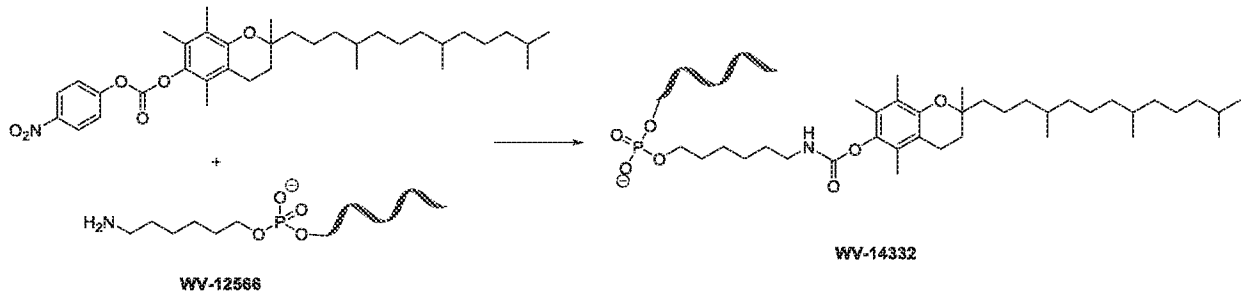
[001721] To a solution of (4E,8E,12E,16E)-4,8,13,17,21-pentamethyldocosa-4,8,12,16,20-pentaenoic acid (turbinaric acid) (6.4 mg, 16 µmol) and HATU (5.4 mg, 14.4 µmol) was added DIPEA (17µL). The mixture was shaken for 30 min at rt. The reaction mixture was added into a solution of WV 12569 (12.4 mg,1.6 µmol) in water (0.20 mL) and NMP (0.20 ml) and stirred for 2 hrs at 35 °C. LC-MS showed the starting material was disappeared. The crude product was purified on RP (C-8) HPLC using 50 mM TEAA in water and acetonitrile, and desalt to obtain 2.10 mg of the conjugate WV-12570. Deconvoluted mass: 8172; Calculated molecular weight: 8170.

[001722] **Synthesis of WV-14333**



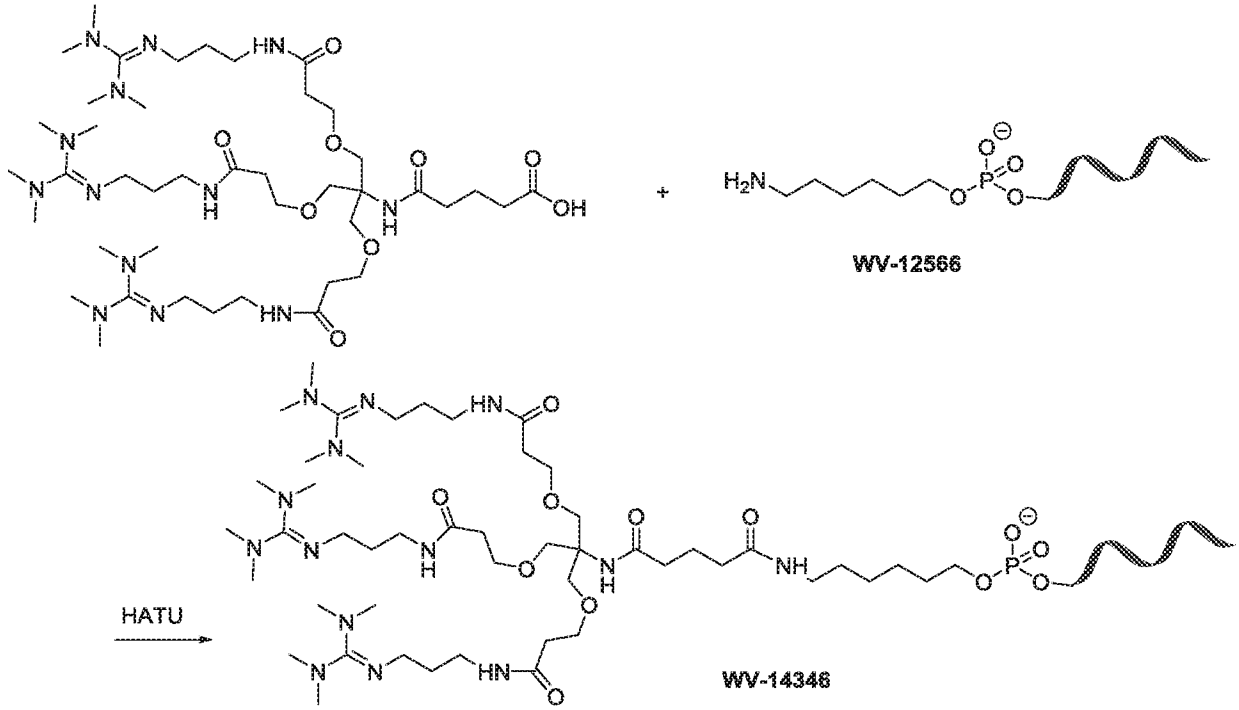
[001723] A solution of 4,10,17-trioxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-13-oxa-5,9,16-triazahenicosan-21-oic acid (25.4 mg, 9.72 μmol) in acetonitrile (0.50 mL) was added HATU (3.32 mg, 8.75 μmol) and DIPEA (8.5 μL). The reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was added into a solution of WV-12566 (16.7 mg, 2.43 μmol) in 0.5 mL water. The reaction mixture was stirred at 30 °C for 2 hrs, and LC-MS showed the reaction was complete. The reaction mixture was transferred to the pressure tube, and 4 ml 28-30% ammonium hydroxide was added. The reaction mixture was stirred at 35 °C for overnight. LC-MS showed the reaction was completely de-protected. The crude product was purified by ISCO via 30 g C18 Catridge eluting with 50 mM TEAA to acetonitrile, and desalt to obtain 12.8 mg of the conjugate WV-14333. Deconvoluted mass: 8224; Calculated molecular weight: 8221.

[001724] **Synthesis of WV-14332**



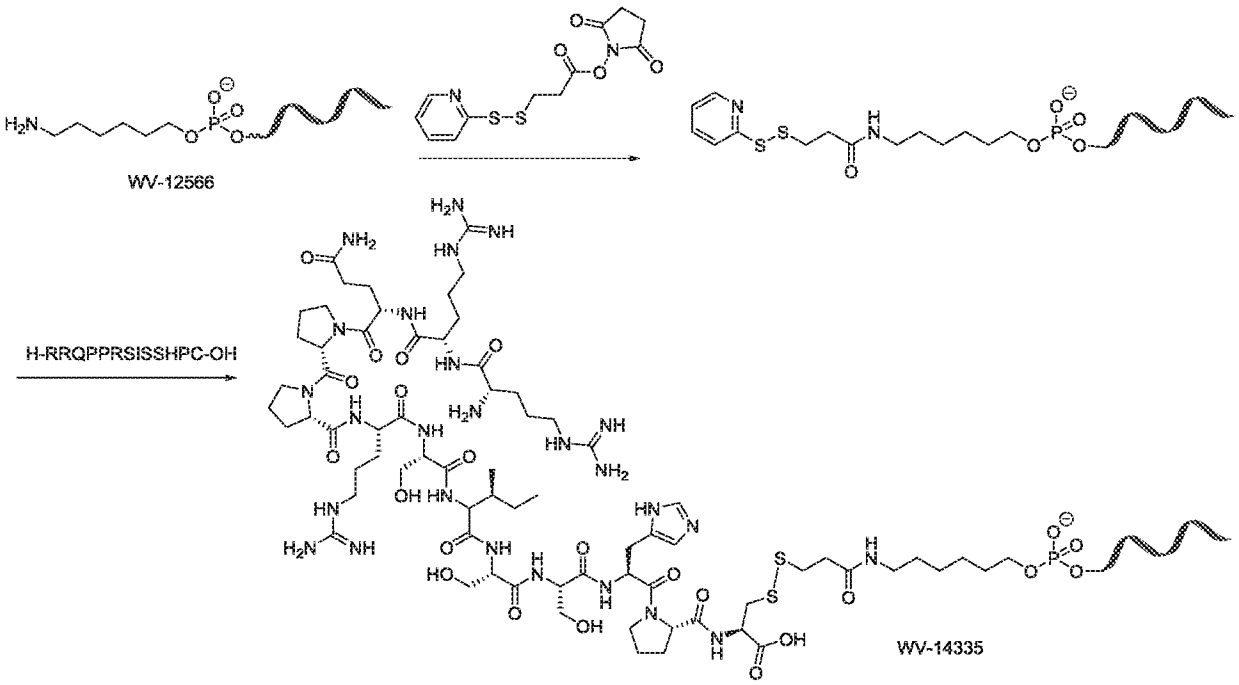
[001725] A solution of 4-nitrophenyl (2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl) carbonate (7.24 mg, 12.15 μmol) and DIPEA (8.50 μL) in NMP (0.20 ml) was added to a solution of WV-12566 (16.7 mg, 2.43 μmol) in 0.5 ml DMSO and 0.05 mL water. The reaction mixture was shaken for 3 hours at 40 °C. LC-MS showed the reaction was very clean. The crude product was lyophilized, purified on RP (C-8) HPLC using 50 mM TEAA in water and acetonitrile, and desalt to obtain 10 mg of the conjugate WV-14332. Deconvoluted mass: 7335; Calculated molecular weight: 7334.

[001726] **Synthesis of WV-14346**



[001727] A solution of 3-(dimethylamino)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-oic acid (75.26 mg, 82.34 μmol) in DMF (1.0 mL) was added DIPEA (123 μL, 0.823 mmol) and HATU (28.1 mg, 74.12 μmol). The reaction mixture was stirred at room temperature for 15 minutes. The reaction mixture was added to a solution of WV-12566 (113.22 mg, 16.47 μmol) in 1.50 ml DMSO and 0.50 mL water. The reaction mixture was shaken for 2 hours at rt. LC-MS showed the reaction was complete. The reaction mixture was diluted with water, and speed-vacuum to dry. The crude product was purified by RP-HPLC eluting with 50 mM TEAA in water to acetonitrile, and desalt to obtain 84.3 mg of the conjugate WV-14346. Deconvoluted mass: 7772; Calculated molecular weight: 7771.

[001728] **Synthesis of WV-14335**



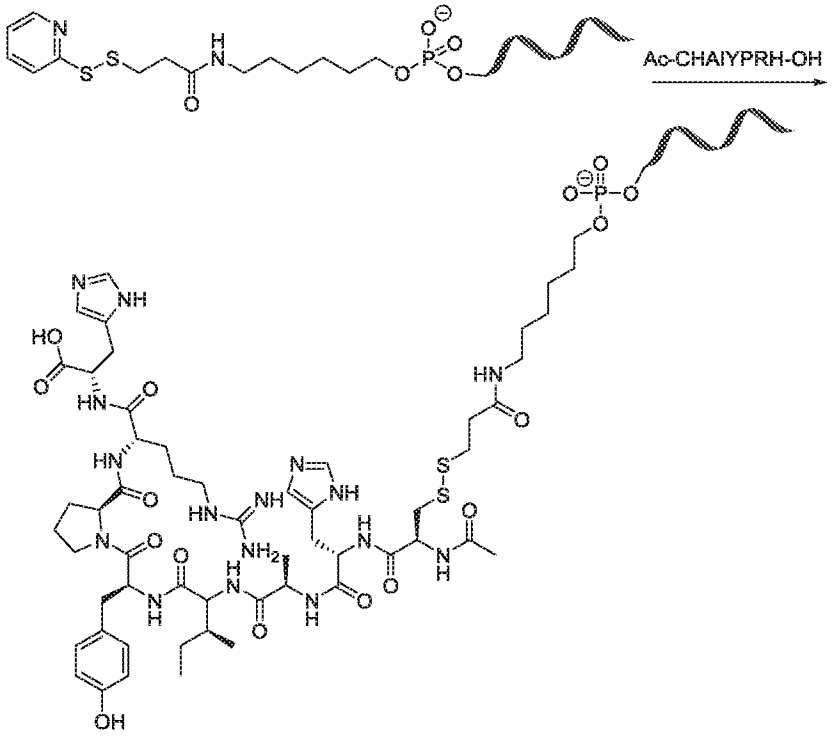
[001729] Step 1. A solution of 3-(2-Pyridyldithio)-propionic acid-OSu (9.08 mg) in DMF (1.0 mL) was added into a solution of WV-12566 (100 mg, 14.54 in 1.5 ml 0.5 M sodium phosphate buffer (pH = 8). The reaction mixture was stirred at room temperature for 1 hr. LC-MS showed that reaction was completed. Diluted with water, and lyophilized to give the desired product.

[001730] **Synthesis of WV-14335**

[001731] Step 1. A solution of 3-(2-Pyridyldithio)-propionic acid-OSu (9.08 mg) in DMF (1.0 mL) was added into a solution of WV-12566 (100 mg, 14.54 in 1.5 ml 0.5 M sodium phosphate buffer (pH = 8). The reaction mixture was stirred at room temperature for 1 hr. LC-MS showed that reaction was completed. Diluted with water, and lyophilized to give the desired product.

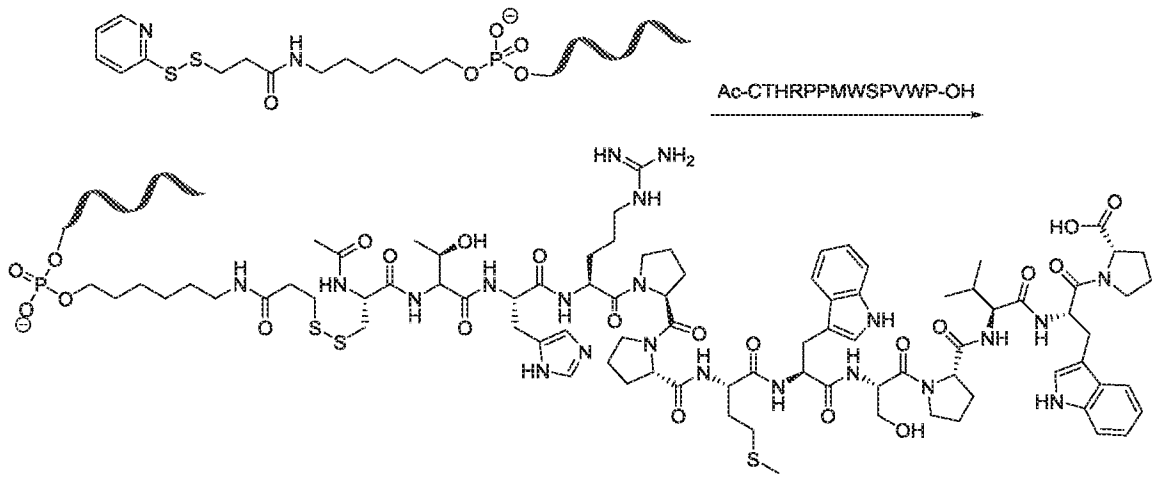
[001732] Step 2. A solution of H-RRQPPRSISSHPC-OH (5.47 mg, 3.6 umol) in DMF (0.85 ml) and 0.1 M sodium bicarbonate (0.15 ml) was added to the above product (step 1) (12 mg, 1.8 μmol) in 0.1 M sodium bicarbonate (0.50 mL). The reaction mixture was shaken for 1.5 hours at rt. LC-MS showed the reaction was complete. The reaction mixture was diluted with water, and speed-vacuum to dry. The crude product was purified by RP-HPLC eluting with 50 mM TEAA in water to acetonitrile, and desalt to obtain 3.0 mg of the conjugate WV-14335. Deconvoluted mass: 8485; Calculated molecular weight: 8482.

[001733] **Synthesis of WV-14347**



[001734] A solution of Ac-CHAIYPRH-OH (3.74 mg, 3.6 μmol) in DMF (0.85 mL) and 0.1 M $NaHCO_3$ (0.15 mL) was added to SPDP oligo (step 1 product of WV-14335) (12 mg, 1.8 μmol) in 0.10 M $NaHCO_3$ (0.50 mL). The reaction mixture was shaken for 1.5 hours at room temperature. LC-MS showed the reaction was complete. The reaction mixture was diluted with water, and speed-vacuum to dry. The crude product was purified by RP-HPLC eluting with 50 mM TEAA in water to acetonitrile, and desalt to obtain 8.8 mg of the conjugate WV-14347. Deconvoluted mass: 8003; Calculated molecular weight: 7999.

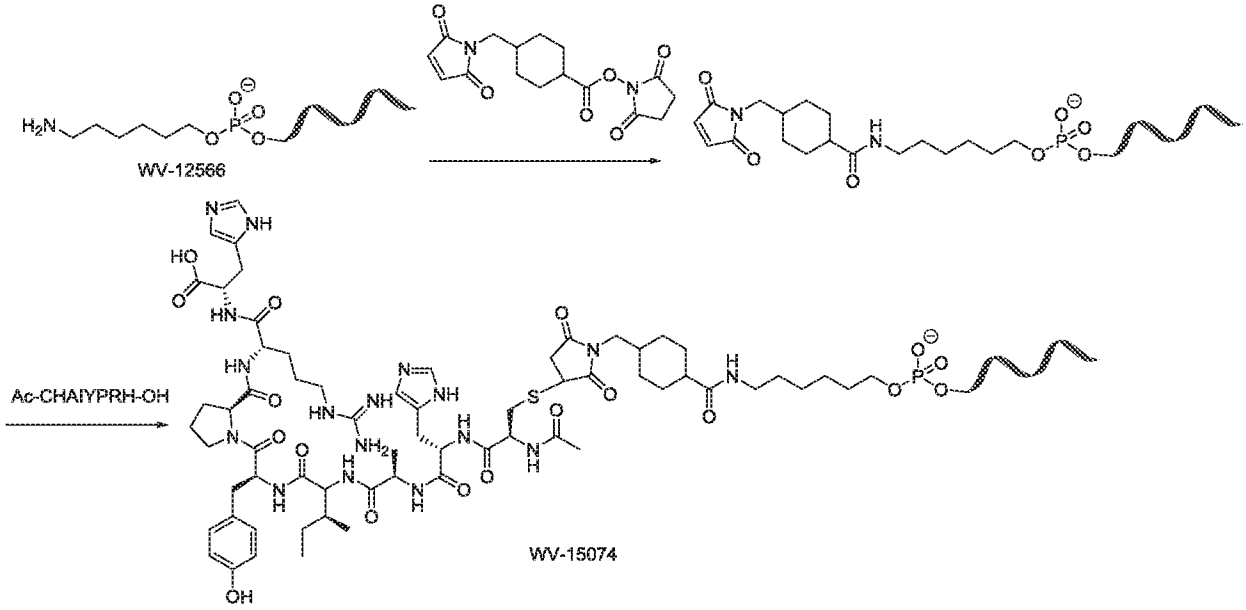
[001735] **Synthesis of WV-14348**



[001736] A solution of Ac-CTHRPPMWSPVWP-OH (5.88 mg, 3.6 μmol) in DMF (0.85 mL) and

0.1 M $NaHCO_3$ (0.15 mL) was added to SPDP oligo (step 1 product of WV-14335) (12 mg, 1.8 μmol) in 0.10 M $NaHCO_3$ (0.50 mL). The reaction mixture was shaken for 1.5 hours at room temperature. LC-MS showed the reaction was complete. The reaction mixture was diluted with water, and speed-vacuum to dry. The crude product was purified by RP-HPLC eluting with 50 mM TEAA in water to acetonitrile, and desalt to obtain 4.1 mg of the conjugate WV-14348. Deconvoluted mass: 8602; Calculated molecular weight: 8597.

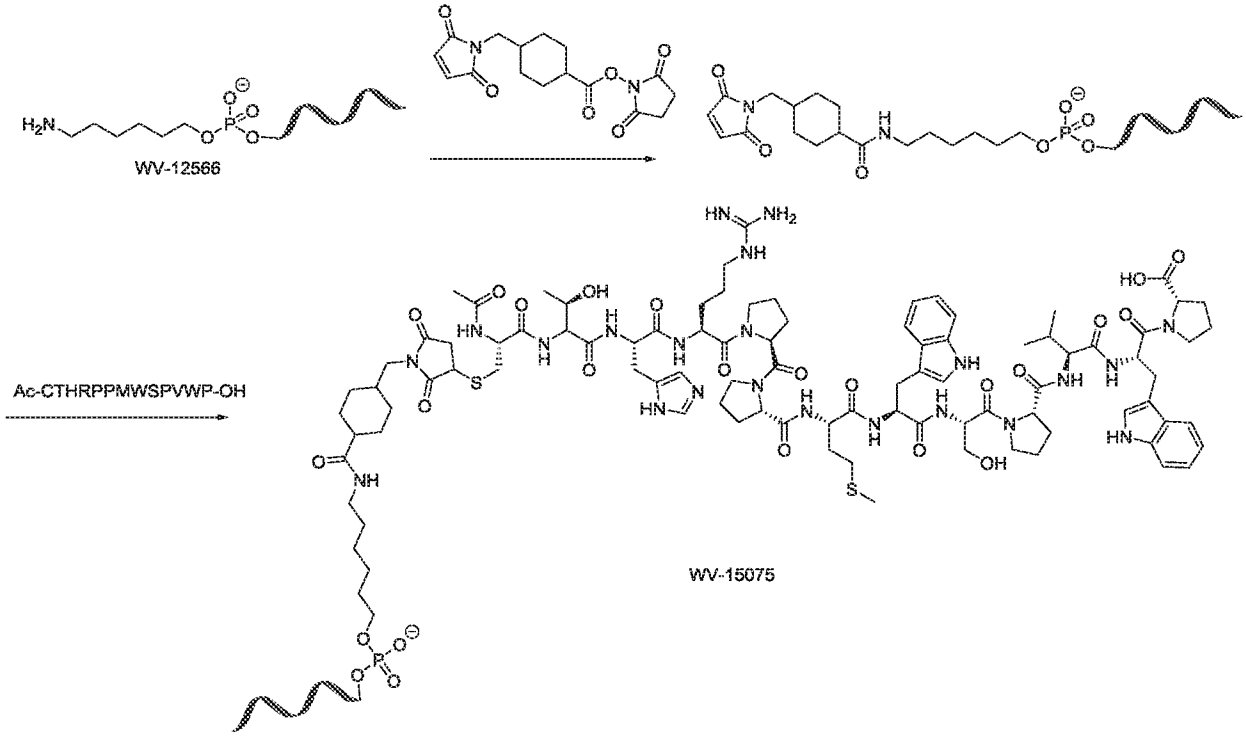
[001737] **Synthesis of WV-15074**



[001738] Step 1. A solution of 2,5-dioxopyrrolidin-1-yl 4-((2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)methyl)cyclohexane-1-carboxylate (8.25 mg, 24.71 μmol) in DMF (0.30 mL) was added to WV-12566 (113.22 mg, 16.47 μmol) and DIPEA (31 μL, 173 μmol) in DMSO (1.50 mL) and water (0.5 mL). The reaction mixture was stirred for 30 minutes at room temperature. LC-MS showed the reaction was almost complete.

[001739] Step 2. A solution of Ac-CHAIYPRH-OH (38.47 mg, 37.1 μmol) in DMF (0.50 mL) was added to the above reaction mixture. The reaction mixture was stirred at room temperature for 2 hr. LC_MS showed the reaction was complete. The reaction mixture was diluted with water, and speed-vacuum to dry. The crude product was purified by RP-HPLC eluting with 50 mM TEAA in water to acetonitrile, and desalt to obtain 66.0 mg of the conjugate WV-15074. Deconvoluted mass: 8133; Calculated molecular weight: 8132.

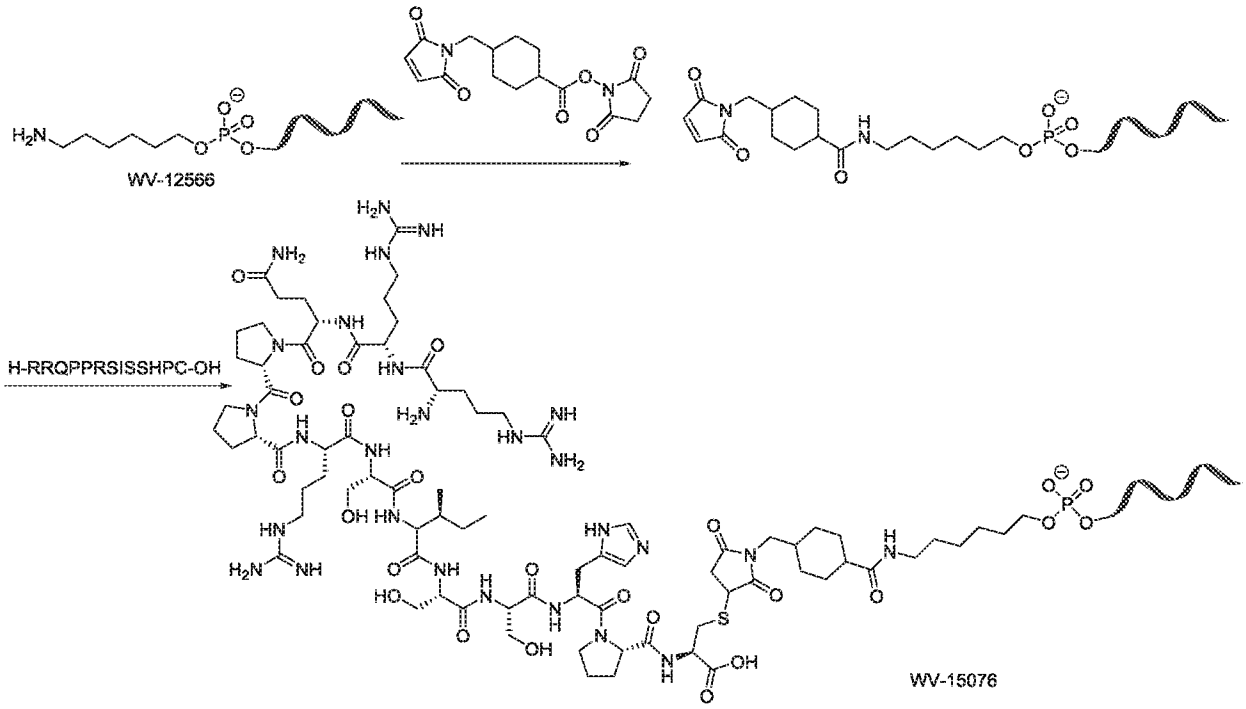
[001740] **Synthesis of WV-15075**



[001741] Step 1. A solution of 2,5-dioxopyrrolidin-1-yl 4-((2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)methyl)cyclohexane-1-carboxylate (1.3 mg, 3.99 μmol) in DMF (0.10 mL) was added to a solution of WV-12566 (16.7 mg, 2.49 μmol) and DIPEA (3.5 μL) in DMSO (0.30 mL) and water (0.10 mL). The reaction mixture was shaken for 1 hr at room temperature. LC-MS showed the reaction was almost complete.

[001742] Step 2. A solution of Ac-CTHRPPMWSPVWP-OH (9.8 mg, 6.0 μmol) in DMF (0.20 mL) was added to the above reaction mixture. The reaction mixture was stirred at room temperature for 3 hrs. LC_MS showed the reaction was complete. The reaction mixture was diluted with water, and speed-vacuum to dry. The crude product was purified by RP-HPLC eluting with 50 mM TEAA in water to acetonitrile, and desalt to obtain 8.9 mg of the conjugate WV-15075. Deconvoluted mass: 8735; Calculated molecular weight: 8730.

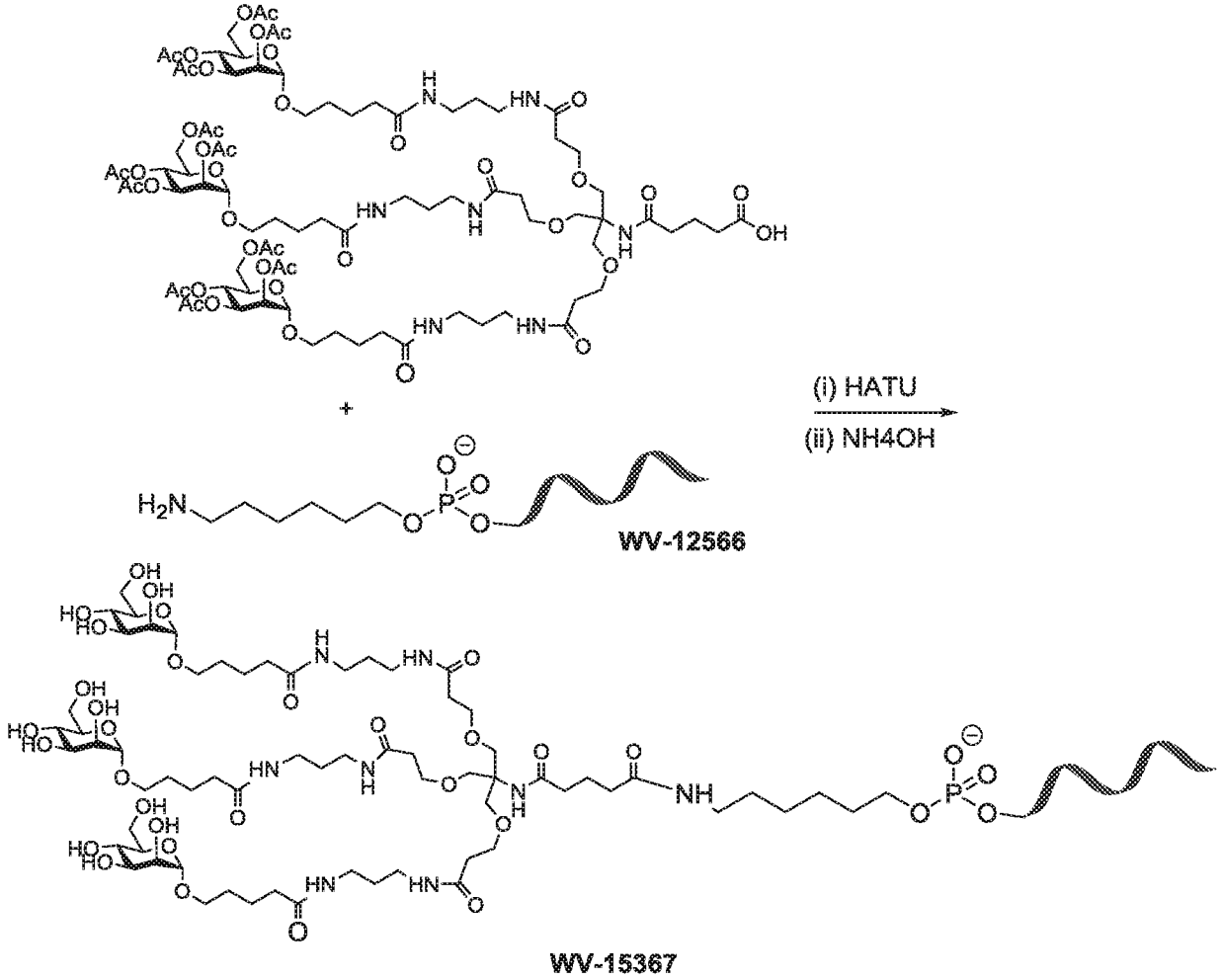
[001743] **Synthesis of WV-15076**



[001744] Step 1. A solution of 2,5-dioxopyrrolidin-1-yl 4-((2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)methyl)cyclohexane-1-carboxylate (1.3 mg, 3.99 umol) in DMF (0.10 mL) was added to a solution of WV-12566 (16.7 mg, 2.49 μmol) and DIPEA (3.5 μL) in DMSO (0.30 mL) and water (0.10 mL). The reaction mixture was shaken for 1 hr at room temperature. LC-MS showed the reaction was almost complete.

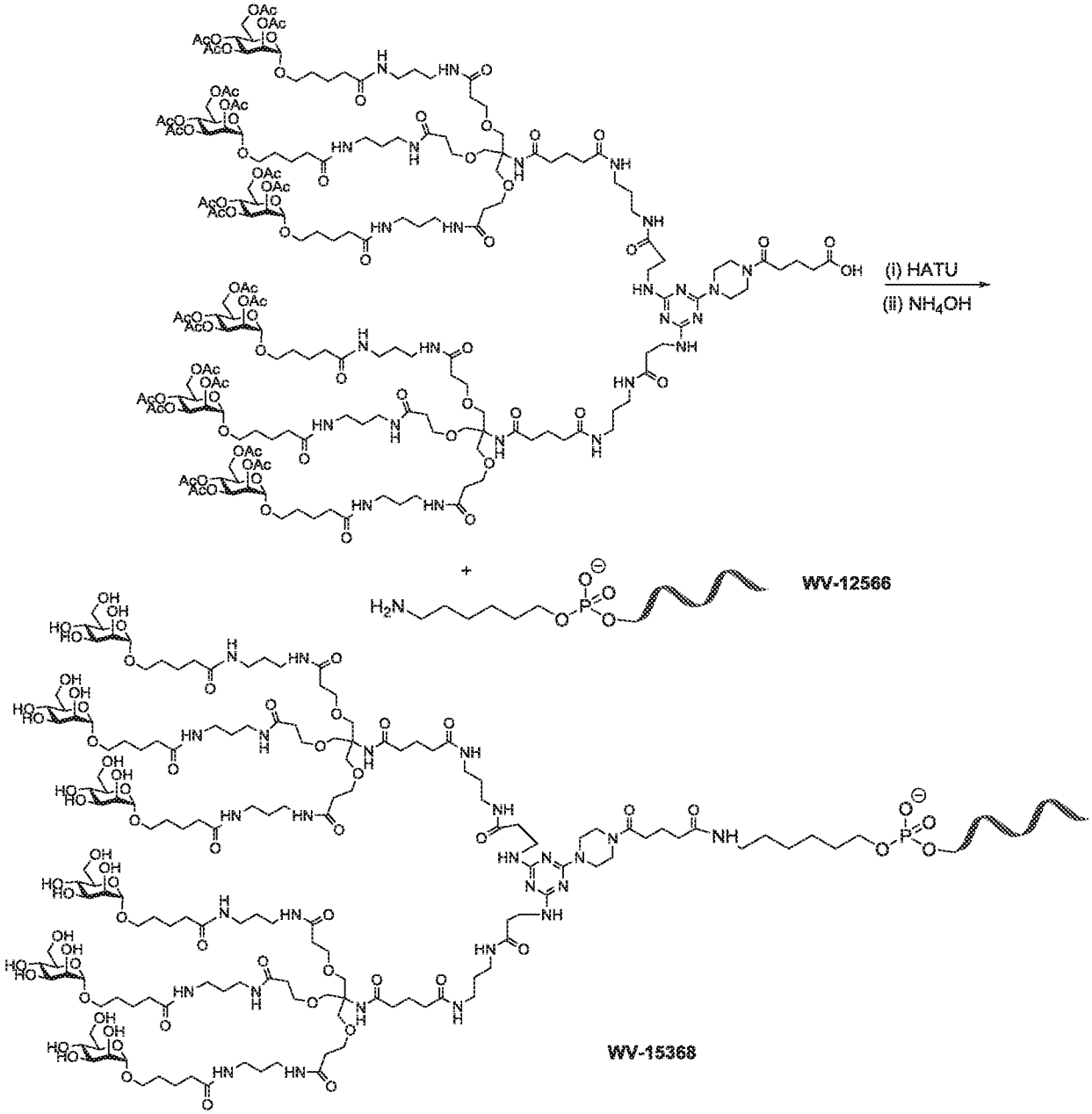
[001745] Step 2. A solution of H-RRQPPRSISSHPC-OH (9.1 mg, 6.0 μmol) in DMF (0.20 mL) was added to the above reaction mixture. The reaction mixture was stirred at room temperature for 3 hrs. LC_MS showed the reaction was complete. The reaction mixture was diluted with water, and speed-vacuum to dry. The crude product was purified by RP-HPLC eluting with 50 mM TEAA in water to acetonitrile, and desalt to obtain 4.7 mg of the conjugate WV-15076. Deconvoluted mass: 8735; Calculated molecular weight: 8730.

[001746] **Synthesis of WV-15367**



[001747] A solution of 5,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanoic acid (13.9 mg, 7.29 μmol) in DMF (0.50 mL) was added DIPEA (6.3 μL, 36.4 μmol) and HATU (2.3 mg, 6.0 μmol). The reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was added to a solution of WV-12566 (16.7 mg, 2.43 μmol) in 0.30 ml DMSO and 0.10 mL water. The reaction mixture was shaken for 2 hours at rt. LC_MS showed the reaction was complete. The reaction mixture was added 28-30% ammonium hydroxide, stirred at 40 °C for 3 hrs. LC_MS showed the reaction was complete. The reaction mixture was diluted with water, and speed-vacuum to dry. The crude product was purified by RP-HPLC eluting with 50 mM TEAA in water to acetonitrile, and desalt to obtain 9.2 mg of the conjugate WV-15367. Deconvoluted mass: 8269; Calculated molecular weight: 8263.

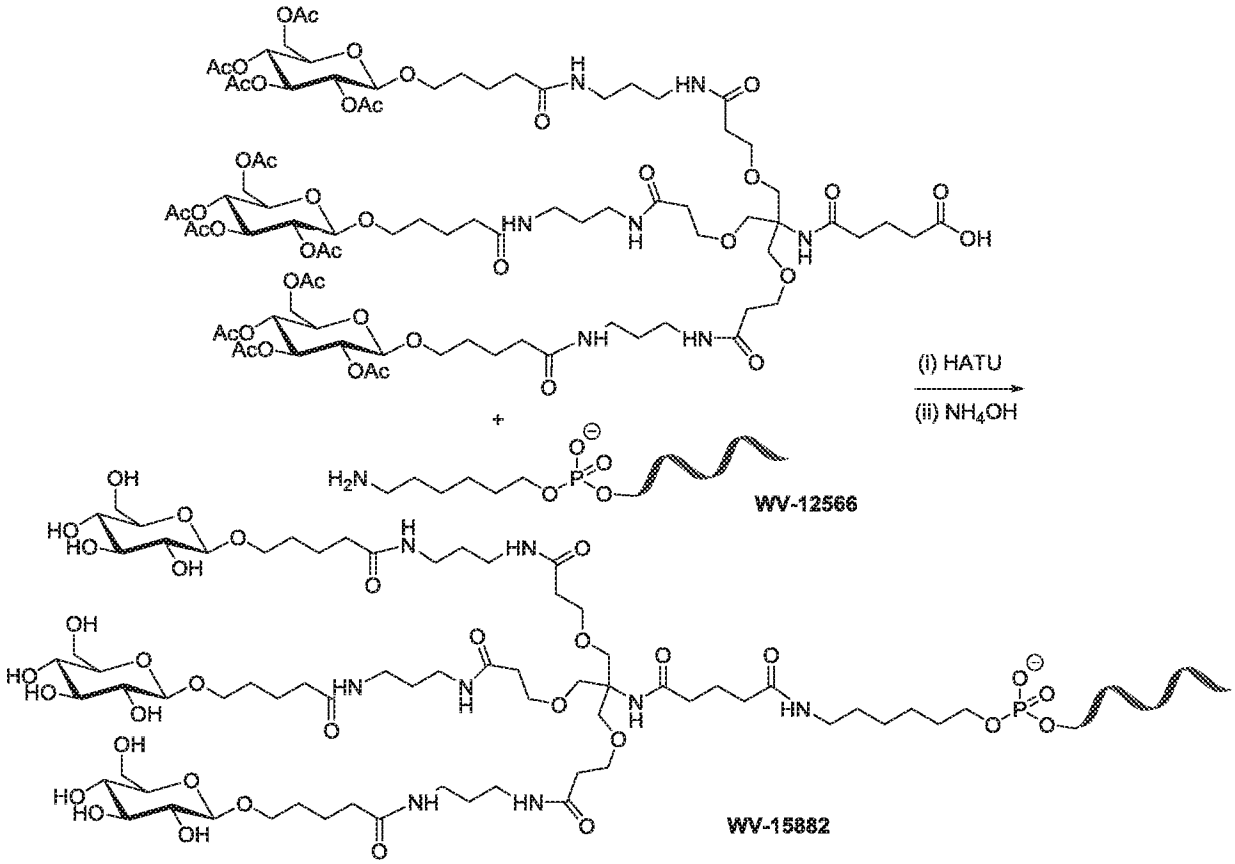
[001748] **Synthesis of WV-15368**



[001749] A solution of 5-(4-(4,6-bis((3,9,13,20,26-pentaoxo-15,15-bis((3-oxo-3-((3-(5-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-30-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-17-oxa-4,8,14,21,25-pentaazatriacontyl)amino)-1,3,5-triazin-2-yl)piperazin-1-yl)-5-oxopentanoic acid (31.7 mg, 7.29 μmol) in DMF (0.50 mL) was added DIPEA (6.3 μL 36.4 μmol) and HATU (2.3 mg, 6.0 μmol). The reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was added to a solution of WV-12566 (16.7 mg, 2.43 μmol) in 0.30 ml DMSO and 0.10 mL water. The reaction mixture was shaken for 2 hours at rt. LC_MS

showed the reaction was complete. The reaction mixture was added 28-30% ammonium hydroxide (1.0 mL), stirred at 40 °C for 5 hrs. LC_MS showed the reaction was complete. The reaction mixture was diluted with water, and speed-vacuum to dry. The crude product was purified by RP-HPLC eluting with 50 mM TEAA in water to acetonitrile, and desalt to obtain 7.5 mg of the conjugate WV-15368. Deconvoluted mass: 10206; Calculated molecular weight: 10200.

[001750] **Synthesis of WV-15882**



[001751] A solution of 5,12,18-trioxo-7,7-bis((3-oxo-3-((3-(5-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-22-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-9-oxa-6,13,17-triazadocosanoic acid (102 mg, 53.43 µmol) in DMF (1.0 mL) was added DIPEA (46.8 µL, 266.5 µmol) and HATU (13.5 mg, 35.68 µmol). The reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was added to a solution of WV-12566 (122.65 mg, 17.84 µmol) in 1.5 ml DMSO and 0.50 mL water. The reaction mixture was shaken for 1.5 hours at rt. LC_MS showed the reaction was completed. The reaction mixture was added 28-20% ammonium hydroxide (5.0 mL) and stirred at 35 °C for 1.5 hrs. LC_MS showed the reaction was complete. The reaction mixture was diluted with water, and speed-vacuum to dry. The crude product was purified by RP-HPLC eluting with 50 mM

TEAA in water to acetonitrile, and desalt to obtain 83.8 mg of the conjugate WV-15882. Deconvoluted mass: 8263; Calculated molecular weight: 8264.

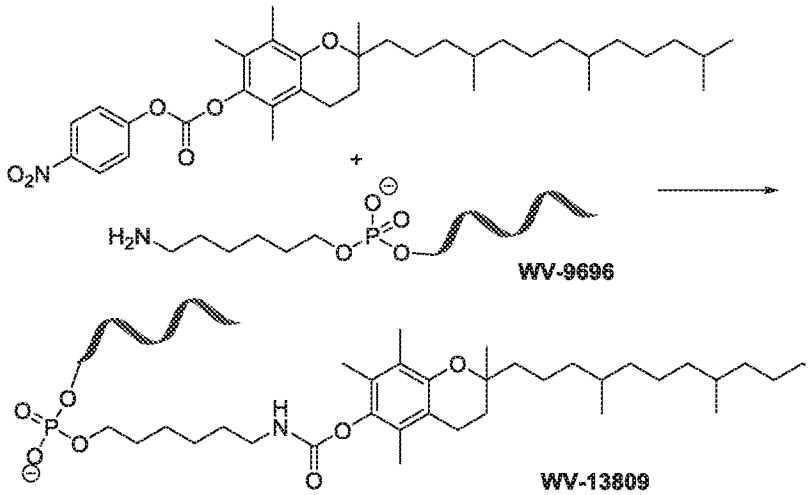
[001752] Some of the examples reference oligonucleotides which target Malat1. Some of these oligonucleotides are described elsewhere herein and/or below.

Oligo-nucleotide	Modified Sequence	Naked Sequence	Stereo-chemistry
WV-2809	L001 * Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTGC CAATGCTAG	XXXXXXXXXXX XXXXXXXXX
WV-3356	L001Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTGC CAATGCTAG	OXXXXXXXXXXX XXXXXXXX
WV-7430	Mod043L001Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTGC CAATGCTAG	OXXXXXXXXXXX XXXXXXXX
WV-7519	Mod009L001 * Geo * Geo * Geo * Teo * m5Ceo * A * G * C * T * G * C * C * A * A * T * Geo * m5Ceo * Teo * Aeo * Geo	GGGTCAGCTGC CAATGCTAG	XXXXXXXXXXX XXXXXXXXX
WV-7557	L001mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTG GTTATGACUC	OXXXXXXXXXXX XXXXXXXX
WV-7558	Mod027L001mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTG GTTATGACUC	OXXXXXXXXXXX XXXXXXXX
WV-7559	Mod028L001mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTG GTTATGACUC	OXXXXXXXXXXX XXXXXXXX
WV-7560	Mod007L001mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTG GTTATGACUC	OXXXXXXXXXXX XXXXXXXX
WV-8448	Mod059L001mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTG GTTATGACUC	OXXXXXXXXXXX XXXXXXXX
WV-8927	Mod053L001mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTG GTTATGACUC	OXXXXXXXXXXX XXXXXXXX
WV-8929	Mod057L001mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTG GTTATGACUC	OXXXXXXXXXXX XXXXXXXX
WV-8930	Mod058L001mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTG GTTATGACUC	OXXXXXXXXXXX XXXXXXXX
WV-8931	Mod009L001mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTG GTTATGACUC	OXXXXXXXXXXX XXXXXXXX
WV-8934	Mod050L001mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTG GTTATGACUC	OXXXXXXXXXXX XXXXXXXX

WV-9385	Mod066L001mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTG GTTATGACUC	OXXXXXXXXXXX XXXXXXXX
WV-9390	Mod074L001mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTG GTTATGACUC	OXXXXXXXXXXX XXXXXXXX
WV-13809	Mod097L001mU * SGeom5Ceom5CeomA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC	UGCCAGGCTG GTTATGACUC	OSOOOSSRS SRSSRSSSSSS
WV-27145	mU * SGCCmA * SG * SG * RC * STn001G * RG * ST * ST * RA * ST * SmG * SmA * SmC * SmU * SmC * SfU	UGCCAGGCTG GTTATGACUC U	SOOOSSRSnXR SSRSSSSSSS

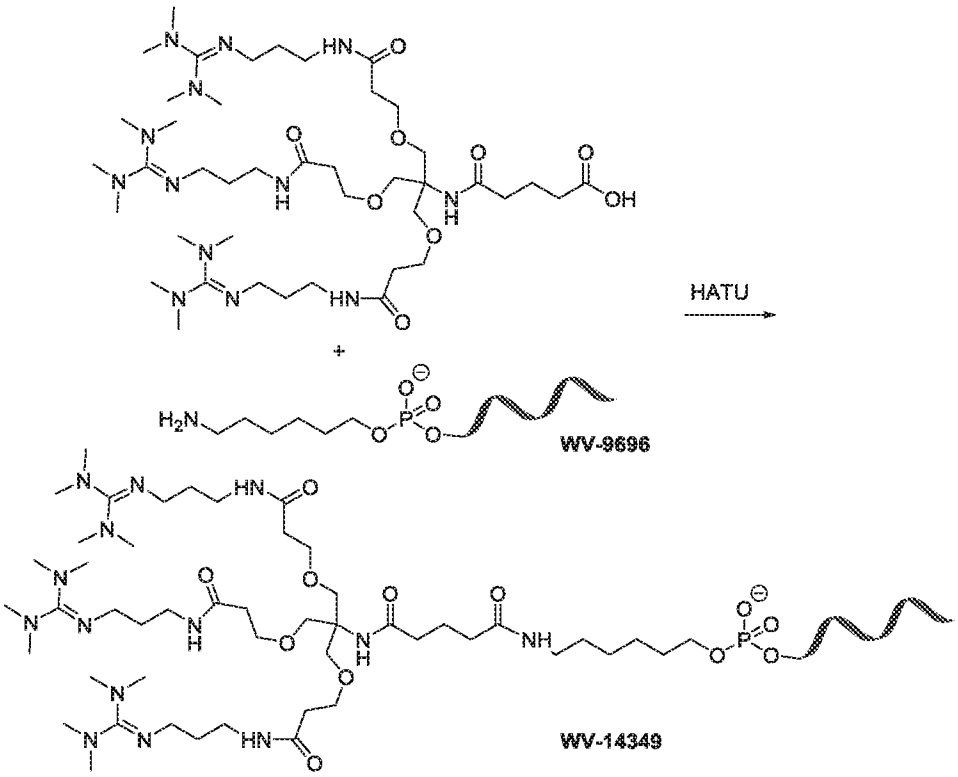
The Modifications (e.g., designated by Mod followed by a number, such as Mod097, Mod074, etc.) are described in the legend to Table A1 or elsewhere herein.

[001753] **Synthesis of WV-13809**



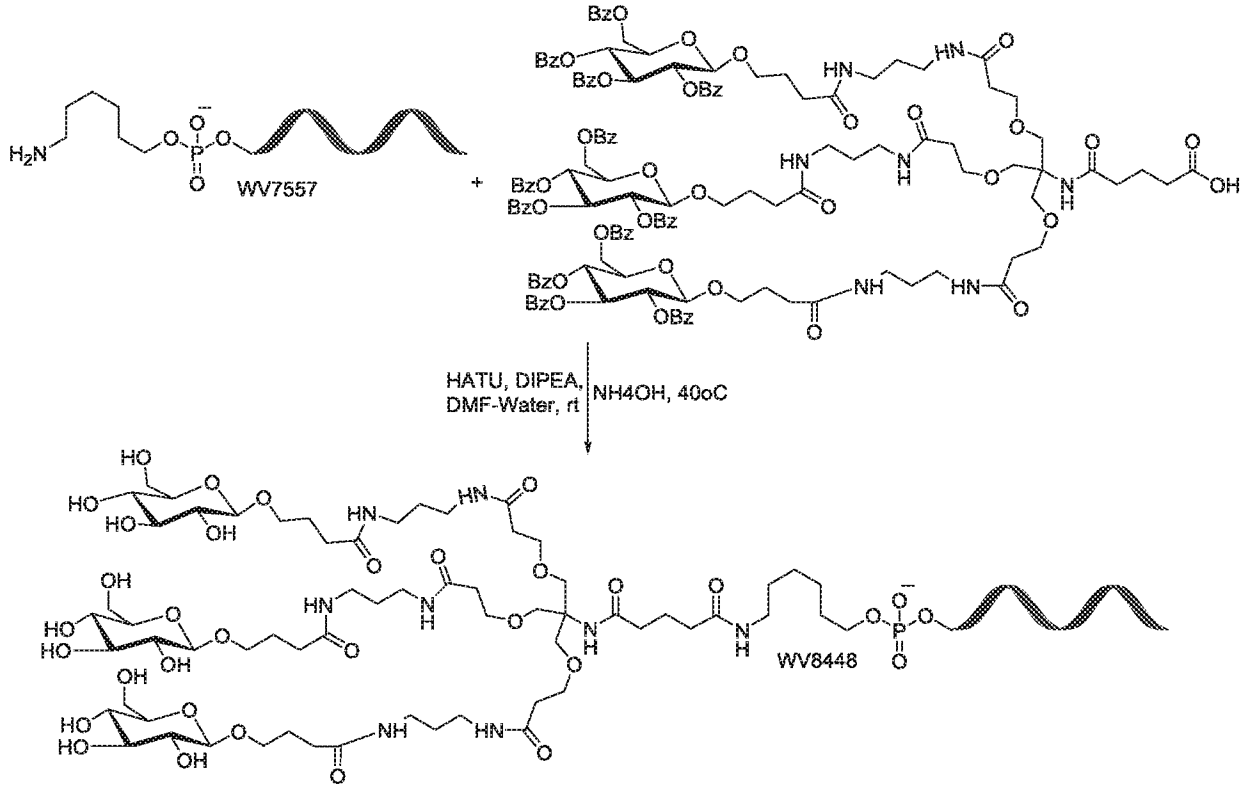
[001754] A solution of 4-nitrophenyl (2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl) carbonate (activated vitamin E) (15 mg, 25 µmol) and DIPEA (21 µL) in NMP (0.20 ml) was added to a solution of WV-9696 in 0.5 ml DMSO and 0.05 ml water. The reaction mixture was shaken for 2 hrs at 50 °C. LC-MS showed the reaction was completed. The crude product was lyophilized, purified on RP (C-8) HPLC using 50 mM TEAA in water and acetonitrile, and desalt to obtain 4.90 mg of the conjugate WV-13809. Deconvoluted mass: 7451; Calculated molecular weight: 7451.

[001755] **Synthesis of WV-14349**



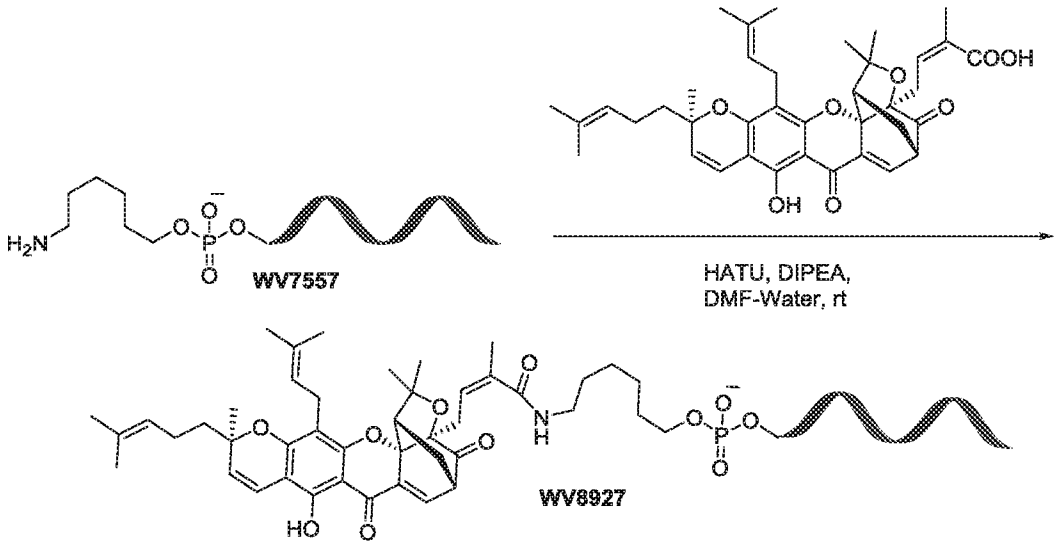
[001756] A solution of 3-(dimethylamino)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-oic acid (19.61 mg, 21.45 μmol) in DMF (0.30 mL) was added DIPEA (75 μL) and HATU (7.32 mg, 19.31 μmol). The reaction mixture was stirred at room temperature for 20 minutes. The reaction mixture was added to a solution of WV-9696 (30 mg, 4.29 μmol) in 0.4 ml DMSO and 0.10 mL water. The reaction mixture was shaken at rt for overnight. LC_MS showed the reaction was not complete. A solution of 3-(dimethylamino)-14,14-bis(3-(dimethylamino)-2-methyl-9-oxo-12-oxa-2,4,8-triazatridec-3-en-13-yl)-2-methyl-9,16-dioxo-12-oxa-2,4,8,15-tetraazaicos-3-en-20-oic acid (10 mg) in DMF (0.10 mL) was added DIPEA (38 μL) and HATU (3.7 mg). The reaction mixture was stirred at room temperature for 20 minutes. The reaction mixture was added into the above the reaction mixture with WV-9696. The reaction mixture was stirred at 30 °C for 2 hrs. LC_MS showed the reaction was completed. The reaction mixture was diluted with water, and speed-vacuum to dry. The crude product was purified by RP-HPLC eluting with 50 mM TEAA in water to acetonitrile, and desalt to obtain 9.1 mg of the conjugate WV-14349. Deconvoluted mass: 7893; Calculated molecular weight: 7889.

[001757] **Synthesis of WV8448**



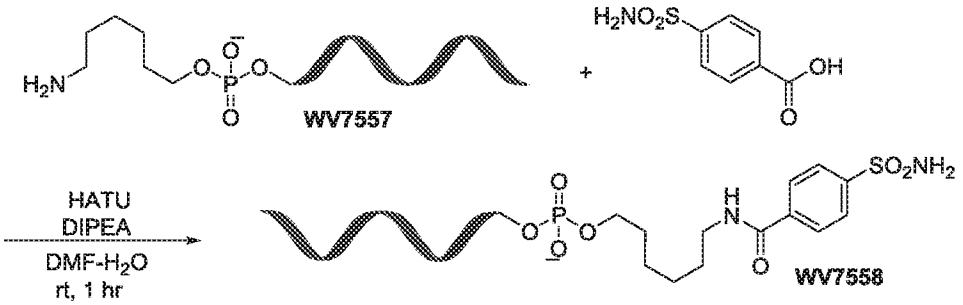
[001758] To a soluition of 4,10,17-trioxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-13-oxa-5,9,16-triazahenicosan-21-oic acid (57 mg, 21.8 µmol), HATU (7.5mg, 19.6 µmol) and DIPEA (14.6 mg, 109 µmol) in DMF (2.0 mL) was stirred at room temperature for 15 minutes. To this solution was added 75 mg (10.9 µmol) of WV7557 in 1 ml water. Reaction mixture was stirred for 60 minutes to obtain the desired product. This product was heated at 40°C with NH_4OH for 3 hrs. LC_MS showed the reaction was completed. The reaction mixture was diluted with water, and speed-vacuum to dry. The crude product was purified by RP-HPLC eluting with 50 mM TEAA in water to acetonitrile, and desalt to obtain 39.73 mg of the conjugate WV-8448. Deconvoluted mass: 8233; Calculated molecular weight: 8227.

[001759] **Synthesis of WV8927**



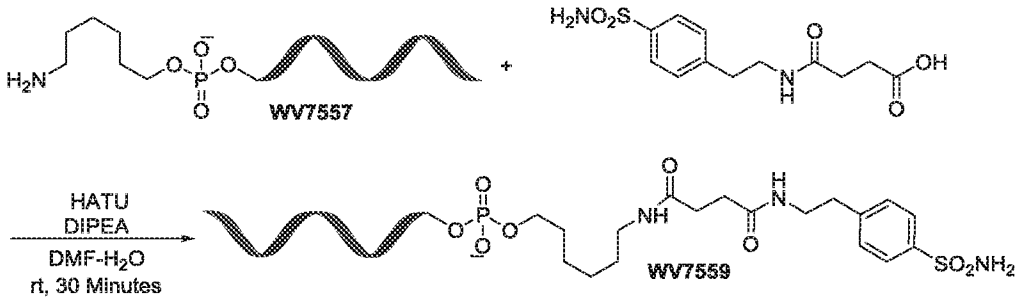
[001760] To a solution of gambogic acid (21 mg, 33.6 µmol) in 2 ml dry DMF was added HATU (11.5 mg, 30.2 µmol) and DIPEA (3.6 mg, 28 µmol) and vortexed well. This solution was added WV7557 (42 mg, 5.6 µmol) in water (1 ml) and shaken for 4 hours. LC-Analysis indicated product formation, but starting material remained. Another 6 six equivalents of Gambogic acid-HATU complex (same amount used initially) was added and shaken well for 2 hours. LC analysis indicated more product formation. The reaction mixture was diluted with water (10 ml). Excess gambogic acid precipitated out. This precipitate was filtered off and the crude product was purified by RP-HPLC eluting with 50 mM TEAA in water to acetonitrile, and desalt to obtain 19 mg of the conjugate WV-8927. Deconvoluted mass: 7496; Calculated molecular weight: 7492.

[001761] **Synthesis of WV-7558**

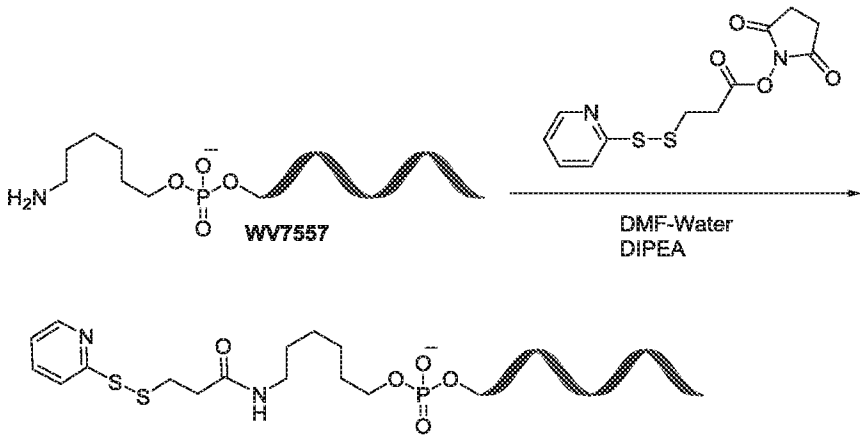


[001762] To a solution of 4-sulfamoylbenzoic acid (7.3 mg, 36 µmol) in DMF (2.0 mL) was added HATU (12.4 mg, 32.7 µmol) and DIPEA (46 mg, 360 µmol) and vortexed. After 2 minutes WV7557 (50 mg, 7.27 µmol) in 1 ml water was added and shaken well. After 60 minutes the reaction mixture was diluted with water (5 ml) and filtered. The filtrate was purified by RP column chromatography (C-18) and desalted to obtain the product (17 mg). Mass calculated: 7064; Deconvoluted Mass: 7068.

[001763] **Synthesis of WV-7559**

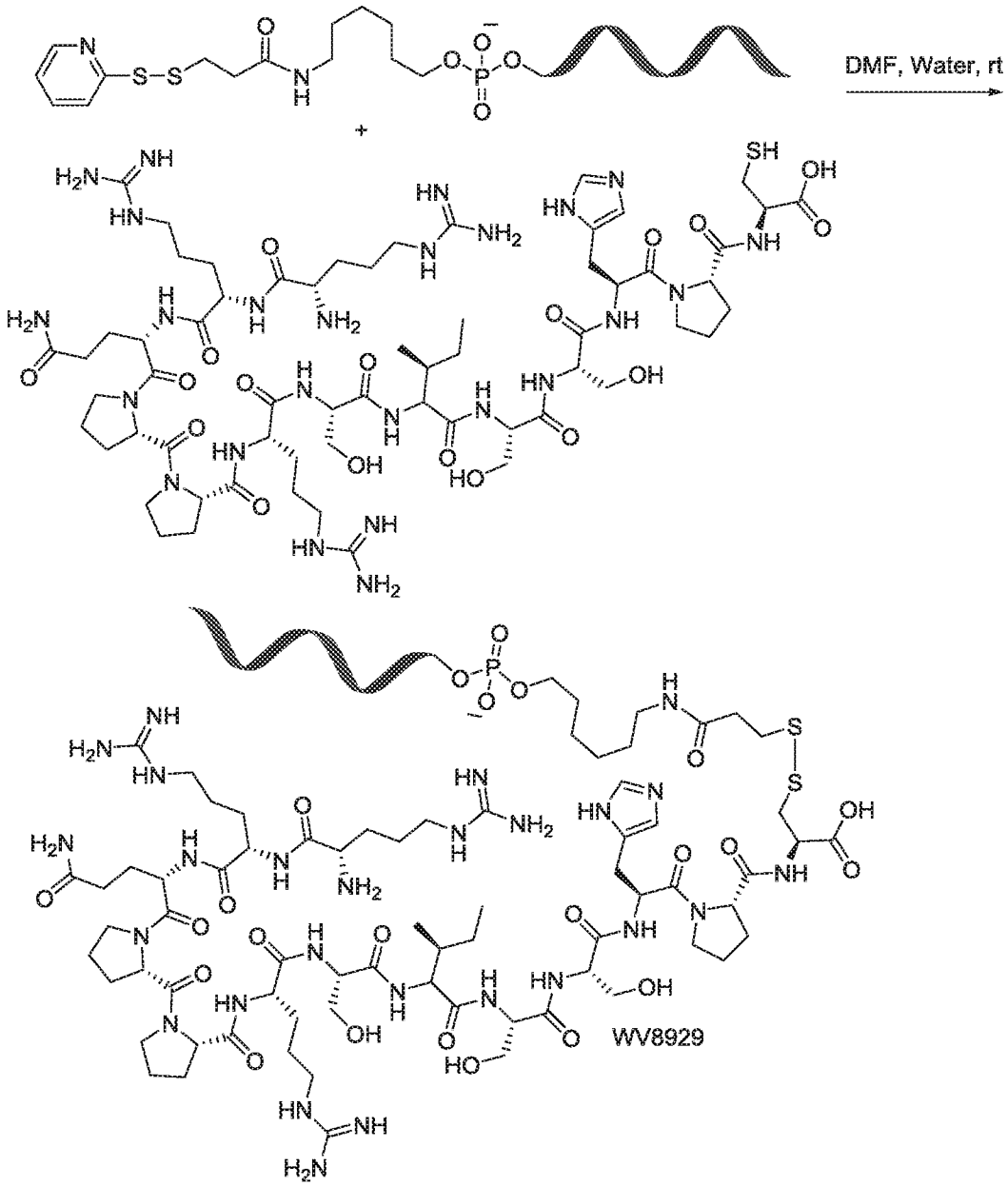


[001764] To a solution of 4-oxo-4-((4-sulfamoylphenethyl)amino)butanoic acid (8.7 mg, 29 µmol) in DMF (2.0 mL) was added HATU (9.9 mg, 26 µmol) and DIPEA (37 mg, 290 µmol) and vortexed. After 2 minutes WV7557 (40 mg, 5.81 µmol) in 1 ml water was added and shaken well. After 30 minutes the reaction mixture was diluted with water (5 ml) and filtered. The filtrate was purified by RP column chromatography (C-18) and desalted to obtain the product (13 mg). Mass calculated: 7163; Deconvoluted Mass: 7166.



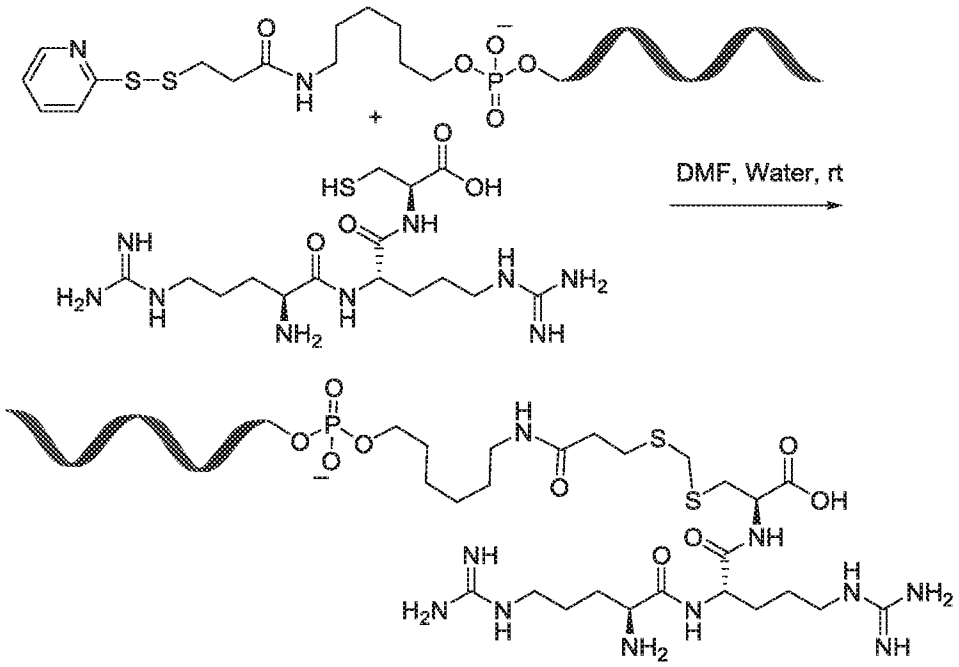
[001765] To a solution of WV7557 (62 mg, 9 µmol) in water (0.5 ml) and DMF (2.5 ml) was added DIPEA (11.6 mg, 90 µmol) and stirred well. To this solution was added 3-(2-Pyridyldithio)-propionic acid-OSu (4 mg, 12.6 µmol) and stirred well for 2h. The crude product was diluted with water and purified on ISCO (C18 column) using 50 mM TEAA and acetonitrile. Amount of product obtained: 46 mg.

[001766] **Synthesis of WV-8929**



[001767] To a solution of the oligo (WV7557 derivative, 23.5 mg, 3.3 µmol) in water-DMF (2 ml + 1 ml) mixture was added DIPEA (8.52 mg, 66 µmol), and vortexed for 5 minutes. To this solution was added H-RRQPPRSISSHPC-OH (10 mg, 6.6 µmol) and again vortexed for 5 minutes. After 12 hours, the reaction mixture was analyzed by LC-MS. LC_MS showed the reaction was completed. The reaction mixture was diluted with water, and speed-vacuum to dry. The crude product was purified by RP-HPLC eluting with 50 mM TEAA in water to acetonitrile, and desalt to obtain 14 mg of the conjugate WV-8929. Deconvoluted mass: 8496; Calculated molecular weight: 8490.

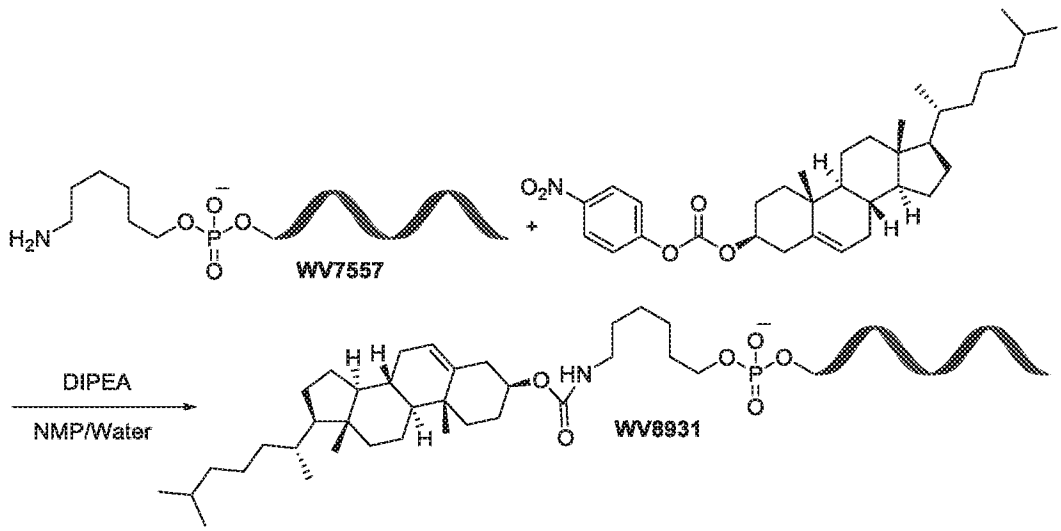
[001768] **Synthesis of WV-8930**



WV8930

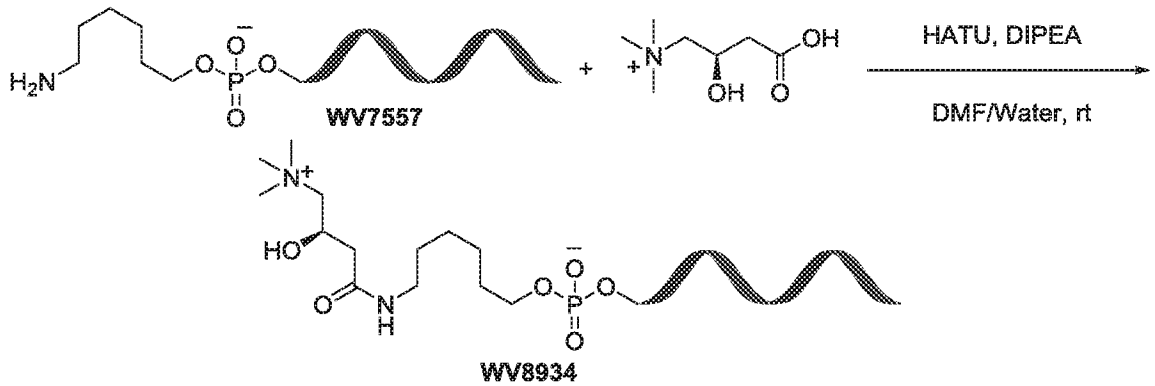
[001769] To a solution of the oligo (WV7557 derivative, 23.5 mg, 3.3 μmol) in water-DMF (2 ml + 1 ml) mixture was added DIPEA (8.52 mg, 66 μmol) and vortexed for 5 minutes. To this solution was added H-Arg-Arg-Cys-OH (4 mg, 10 μmol) and vortexed for 5 minutes. After 12 hours, the reaction mixture was analyzed by LC-MS. LC_MS showed the reaction was completed. The reaction mixture was diluted with water, and speed-vacuum to dry. The crude product was purified by RP-HPLC eluting with 50 mM TEAA in water to acetonitrile, and desalt to obtain 5 mg of the conjugate WV-8930. Deconvoluted mass: 7405; Calculated molecular weight: 7401.

[001770] **Synthesis of WV8931**



[001771] To a solution of WV7557 (20 mg, 2.91 μmol) in 0.47 ml water was treated with DIPEA (3.76 mg, 29.1 μmol) and vortexed well for 5 minutes. To this solution was added a solution of (3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl (4-nitrophenyl) carbonate (activated cholesterol derivative) (10.50 mg, 19 μmol) in NMP (1.0 ml). The solution turned slightly yellowish. It was shaken at 40 degrees for 12 hours. A bright yellow solution was obtained. LC-MS analysis indicated product formation. This solution was diluted to 10 ml using water, filtered and purified on a RP-HPLC using a C-8 column and desalted. Amount of product obtained: 18 mg; Deconvoluted mass: 7298; Calculated molecular weight: 7293.

[001772] **Synthesis of WV8934**

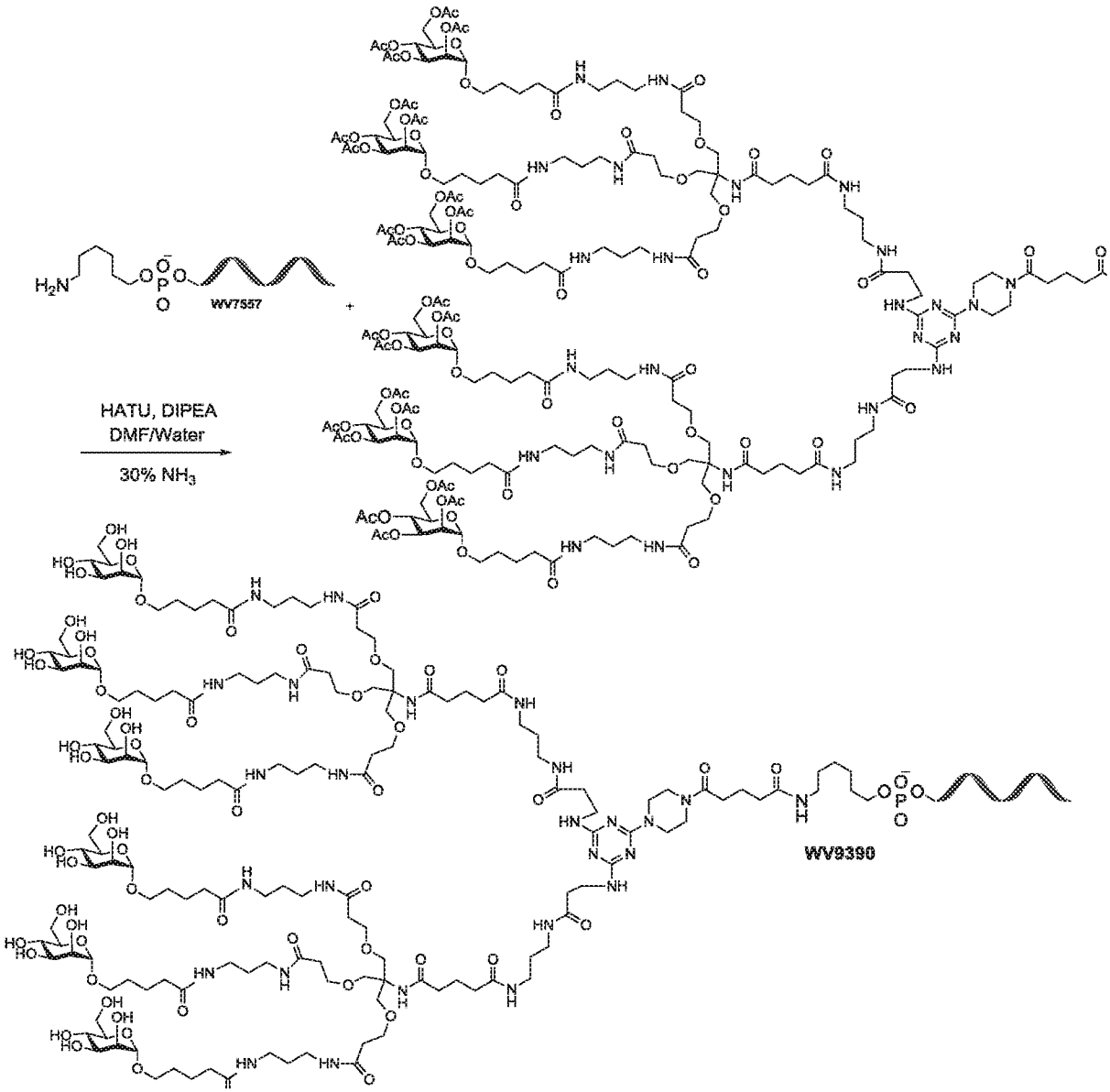


WV7557

WV8934

[001773] L-carnitine (3 mg, 17.5 μmol) and HATU (6 mg, 16 μmol) were mixed together and made in to a 1 ml solution in DMF. DIPEA (5.7 mg, 44 μmol) was added and stirred well for 3 minutes. To this solution was added a solution of WV-7557 (30 mg, 4.4 mmol) in 0.5 ml water and stirred well for 30 minutes. LC-MS analysis of the solution indicated product formation. But starting oligo was present in the reaction mixture. 4 equivalents more L-carnitine/HATU complex was added again and stirred well for 2h. The reaction mixture was diluted with water and the crude product was purified on a RP (C-18) column to obtain the product. Amount of product obtained: 12 mg, Calculated mass: 7025; De-convoluted mass: 7029.

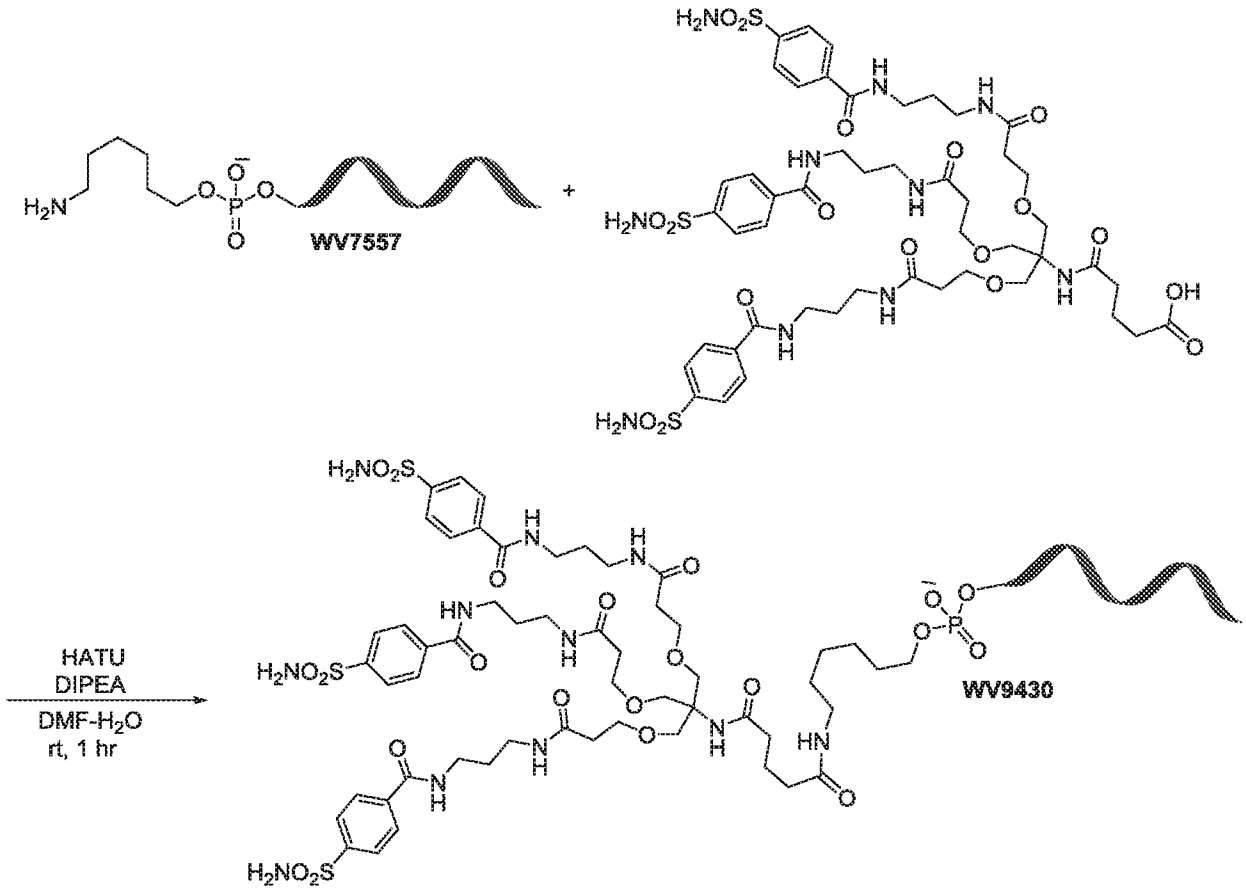
[001774] **Synthesis of WV-9390**



[001775] To a solution of 5-oxo-5-(4-(4-((2,8,12,19,25-pentaoxo-14,14-bis((3-oxo-3-((3-(5-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-29-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-16-oxa-3,7,13,20,24-pentaazanonacosyl)amino)-6-((3,9,13,20,26-pentaoxo-15,15-bis((3-oxo-3-((3-(5-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)propyl)amino)propoxy)methyl)-30-(((2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-17-oxa-4,8,14,21,25-pentaazatriacontyl)amino)-1,3,5-triazin-2-yl)piperazin-1-yl)pentanoic acid (15 mg, 3.5 μmol) and HATU (1.33 mg, 3.5 μmol) in DMF (1.0 ml) was added DIPEA (4.5 mg, 35 μmol) and vortexed for 2 minutes. To this solution was added WV7557 (12 mg, 1.74 μmol) in water (0.5 ml) and

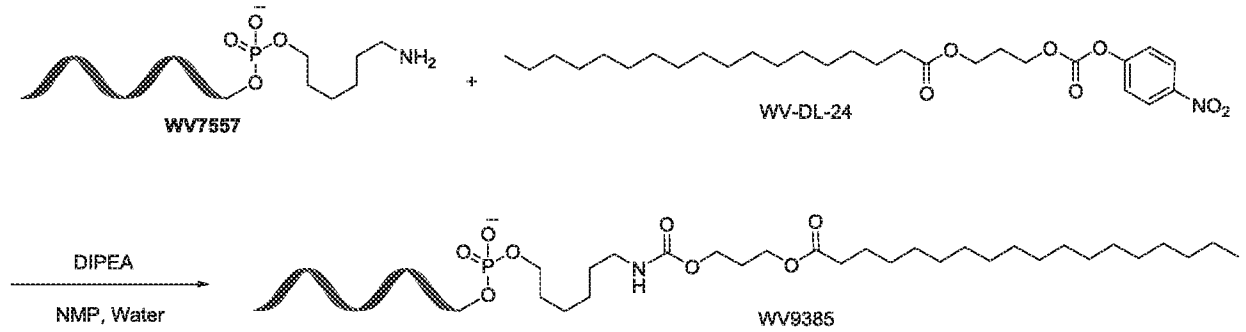
shaken for 60 minutes. 5 ml water was added to it and the solvent was removed under vacuum. The crude product was purified on a RP column (C-8) obtain acetylated product (Mass calculated: 10207, Deconvoluted mass: 10212). This product was dissolved in 5 ml 30% ammonium hydroxide solution and heated at 40 degrees Celsius for 6 hours. Solvent was removed under vacuum and the crude product was purified on a RP column (C-8) to obtain the product. Amount of product obtained (10 mg). Calculated Mass: 10205; Deconvoluted Mass obtained: 10205.

[001776] **Synthesis of WV 9430**



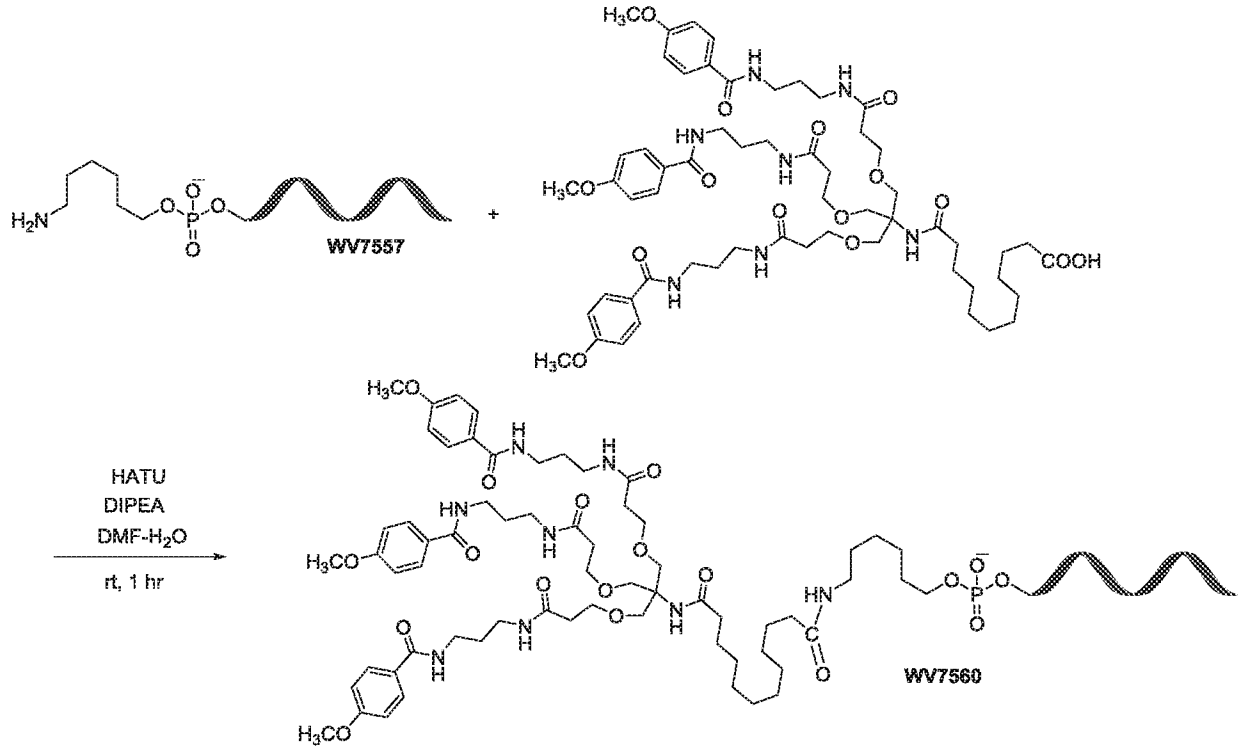
[001777] To a solution of 1,7,14-trioxo-12,12-bis((3-oxo-3-((3-(4-sulfamoylbenzamido)propyl)amino)propoxy)methyl)-1-(4-sulfamoylphenyl)-10-oxa-2,6,13-triazaoctadecan-18-oic acid (5.14 mg, 1.45 µmol) in DMF was added HATU (1.5 mg, 3.96 µmol) and DIPEA (2 mg, 15 µmol). The reaction mixture was stirred at room temperature for 2 minutes. A solution of WV7557 in 0.4 ml water was added and shaken well. After 30 minutes the reaction mixture was diluted with water (5 ml) and filtered. The filtrate was purified by RP column chromatography (C-18) and desalted to obtain the product WV-9430 (6 mg). Mass calculated: 8032; Deconvoluted Mass: 8031.

[001778] **Synthesis of WV-9385**



[001779] WV7557 (48 mg, 6.9 µmol) was dissolved in 1 ml NMP and 0.5 ml water. DIPEA (14 mg, 103.5 µmol) was added to this solution. Vortexed for 5 minutes. To this solution was added 3-(((4-nitrophenoxy)carbonyl)oxy)propyl stearate (14 mg, 27.6 µmol) in 1 ml NMP. The reaction mixture was filtered and the filtrate was purified by RP column chromatography (C-8) to obtain the product. The purified material was desalted and 11 mg of product was obtained. Mass calculated: 7250; Deconvoluted Mass: 7254.

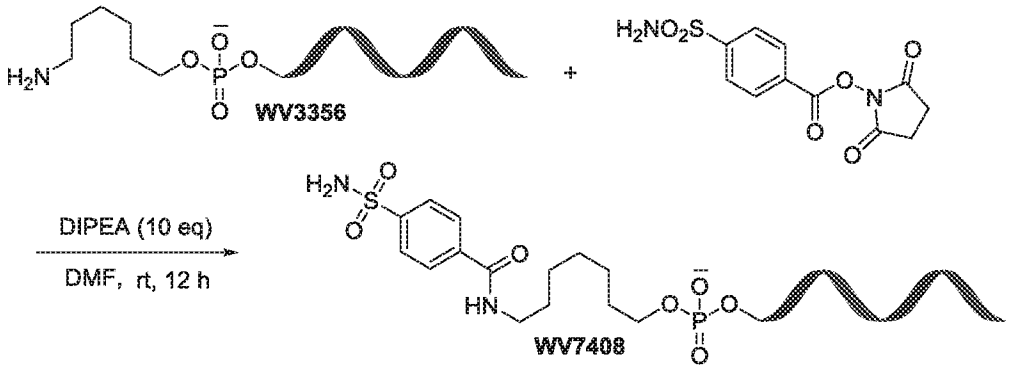
[001780] **Synthesis of WV-7560**



[001781] 12,12-bis((3-((3-(4-methoxybenzamido)propyl)amino)-3-oxopropoxy)methyl)-1-(4-methoxyphenyl)-1,7,14-trioxo-10-oxa-2,6,13-triazapentacosan-25-oic acid (triantennary anisamide) (32.5 mg, 29 µmol), HATU (10 mg, 26.1 µmol) and DIPEA (28 mg, 58 µmol) were dissolved in 2 ml DMF. After 2 minutes WV7557 (100 mg, 15 µmol) in 1 ml water was added and shaken well. After 60 minutes

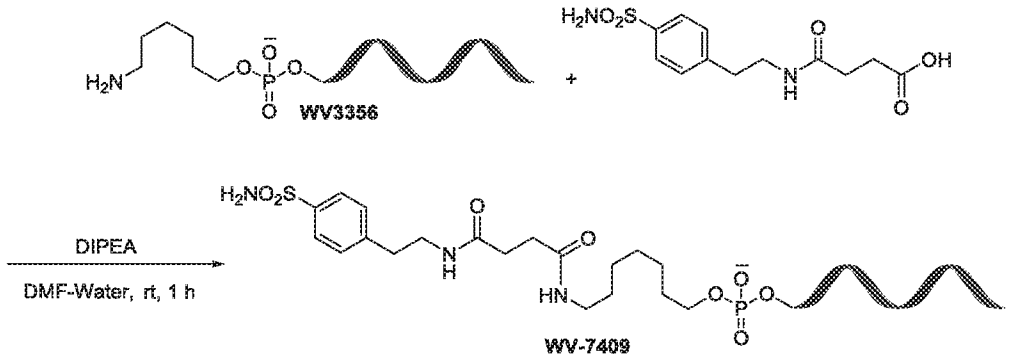
the reaction mixture was diluted with water (5 ml) and filtered. The filtrate was purified by RP column chromatography (C-8) and desalted to obtain the product (55 mg). Mass calculated: 7983; Deconvoluted Mass: 7987.

[001782] **Synthesis of WV-7408**



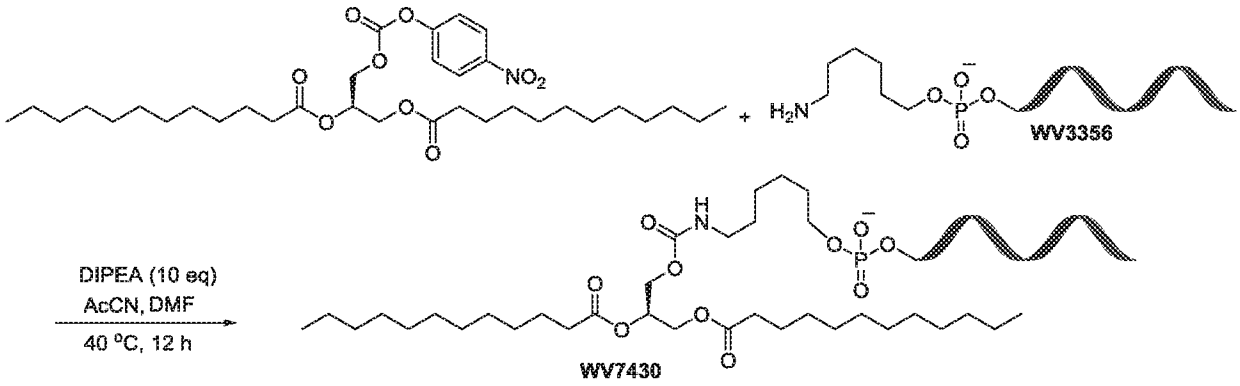
[001783] A suspension of WV 3356 (40 mg, 5.3 µmol) and DIPEA (7 mg, 53 µmol) in 2 ml DMF was vortexed for five minutes. To this suspension was added a solution of 2,5-dioxopyrrolidin-1-yl 4-sulfamoylbenzoate (8 mg, 26.5 µmol)] in 1 ml DMF. The reaction mixture was shaken for 12 hours. Afterwards, the reaction mixture was diluted with 5 ml water and filtered. The filtrate was purified by RP (C-18) column chromatography and desalted to obtain the product (20 mg). Mass calculated: 7596; Deconvoluted mass: 7594.

[001784] **Synthesis of WV7409**



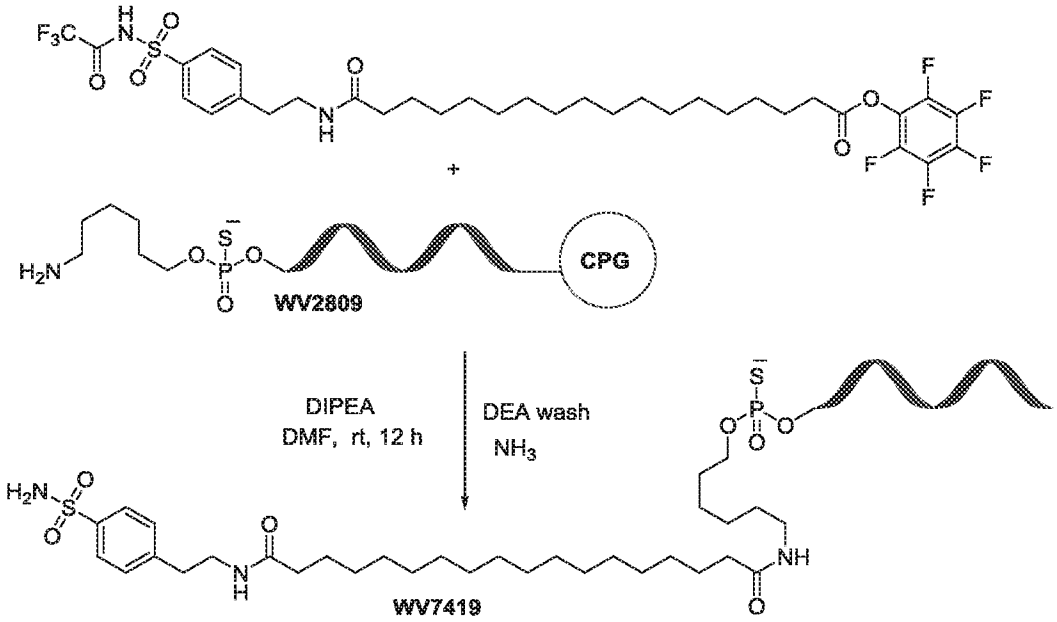
[001785] To a solution of 4-oxo-4-((4-sulfamoylphenethyl)amino)butanoic acid (2.16 mg, 7.2 µmol), HATU (2.32 mg, 6.1 µmol) and DIPEA (3.1 mg, 24 µmol) were dissolved in 1 ml DMF and vortexed. After 2 minutes WV3356 (18 mg, 2.4 µmol) in 0.5 ml water was added and shaken well. After 60 minutes the reaction mixture was diluted with water (5 ml) and filtered. The filtrate was purified by RP column chromatography (C-18) and desalted to obtain the product (9 mg). Mass calculated: 7694; Deconvoluted Mass: 7695.

[001786] **Synthesis of WV-7430**



[001787] To a solution of WV3356 (32 mg, 4.3 µmol) in DMF (2.0 mL) was added DIPEA (5.8 mg, 43 µmol) was added a solution of (R)-3-(((4-nitrophenoxy)carbonyl)oxy)propane-1,2-diyl didodecanoate (11 mg, 17.6 µmol) in acetonitrile (1.0 mL). Reaction mixture was shaken at 40°C for 12 hours. LC-MS analysis indicated formation of product. The reaction mixture was diluted with water and filtered. The filtrate was purified by RP column chromatography (C-8) to obtain the product. The purified material was desalted and 11 mg of product was obtained. Mass calculated:7895, Deconvoluted Mass:7896.

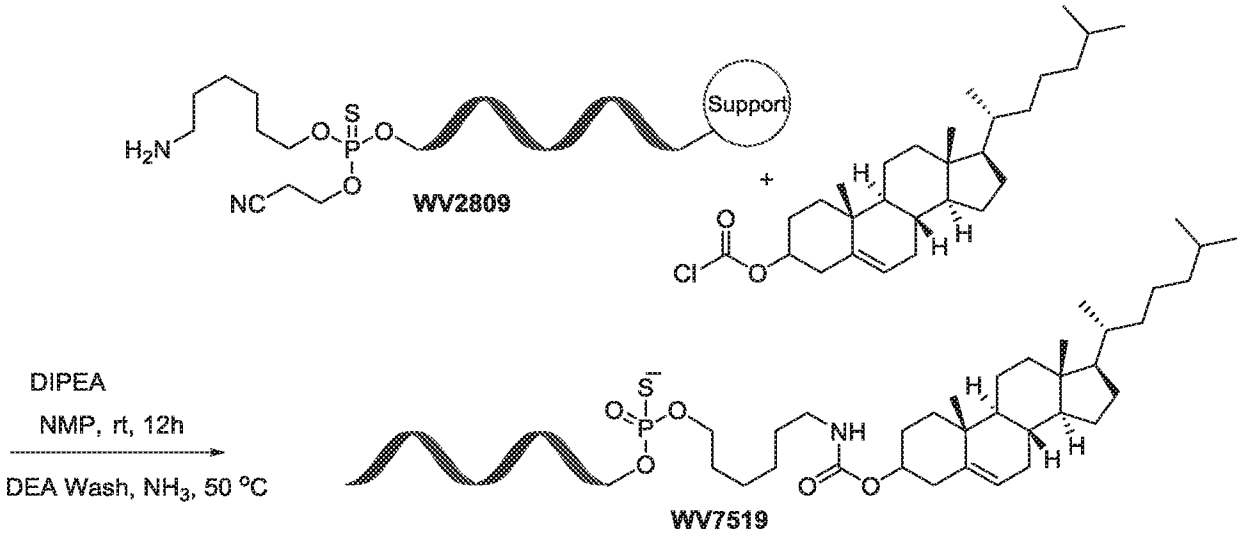
[001788] **Synthesis of WV-7419**



[001789] To a suspension of WV-2809 (56 mg, 7.5 µmol, 125 mg support) in DMF (2.0 mL) was added DIPEA (19.3 mg, 150 µmol) and vortexed well for 5 minutes. To this suspension was added perfluorophenyl 18-oxo-18-((4-(N-(2,2,2-trifluoroacetyl)sulfamoyl)phenethyl)amino)octadecanoate (12 mg, 15 µmol) and shaken for 12 hours at room temperature. The solid support was washed with acetonitrile (20 ml X 3) and dried. This support was treated with 20% DEA in acetonitrile (1 ml) for 10

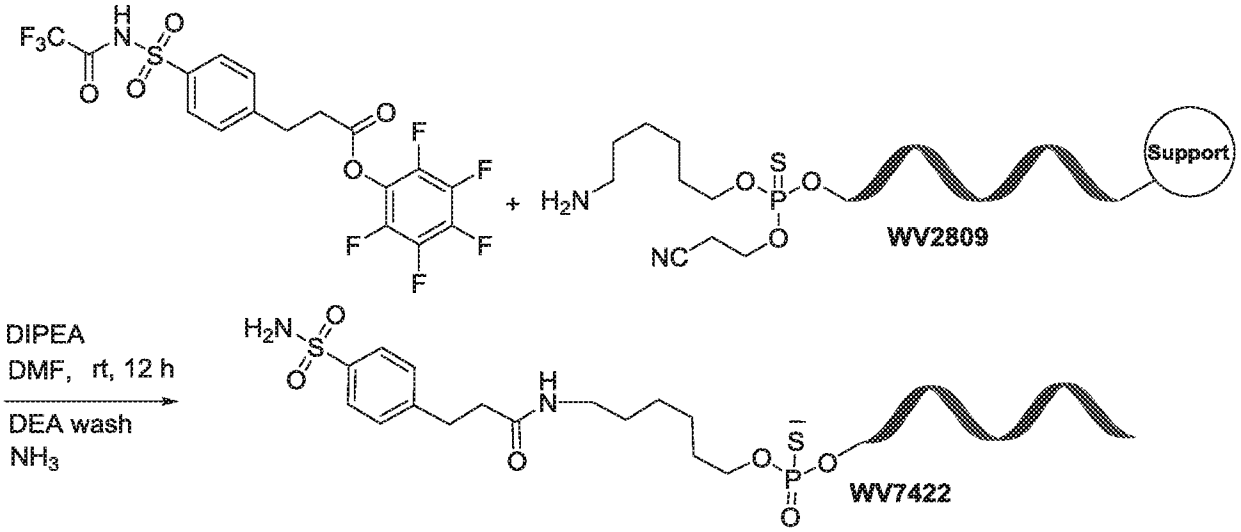
minutes. The DEA solution was removed by filtration. The solid support was washed with acetonitrile (20 ml X 3) and dried. The solid support was heated with 2 ml of 30% ammonium hydroxide for 12 hours. The support was filtered off and the filtrate was lyophilized to remove the solvent. The crude product was purified by RP column chromatography (C-8) and desalted to obtain the product (7 mg). Mass calculated:7906, Deconvoluted Mass:7909.

[001790] **Synthesis of WV-7519**



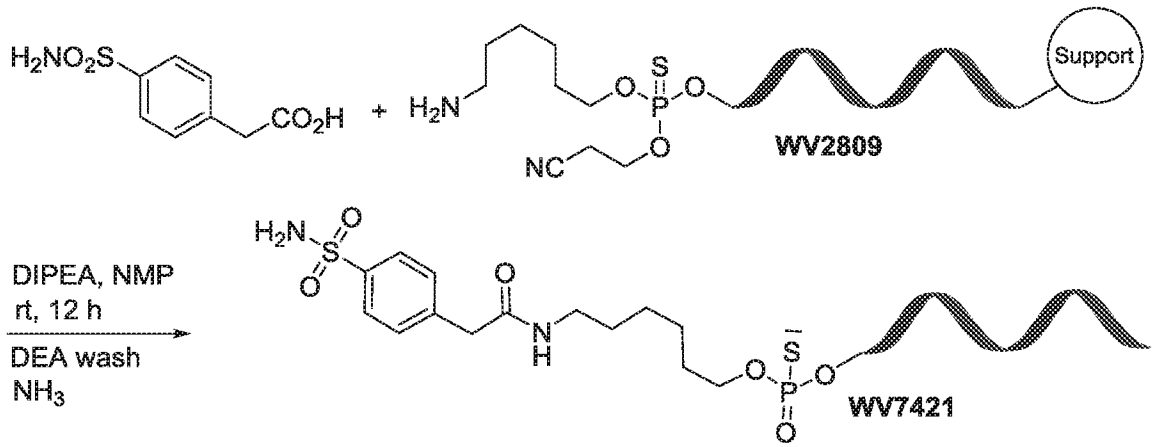
[001791] To a suspension of WV2809 (60 mg, 8 µmol, 150 mg support) in 2 ml NMP was added DIPEA (11 mg, 80 µmol) and vortexed well for 5 minutes. To this suspension was added (8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl carbonochloridate (15 mg, 33 µmol) and shaken for 12 hours at room temperature. The solid support was washed with acetonitrile (20 ml X 3) and dried. This support was treated with 20% DEA in acetonitrile (1 ml) for 10 minutes. The DEA solution was removed by filtration. The solid support was washed with acetonitrile (20 ml X 3) and dried. The solid support was heated at 50 °C with 2 ml of 30% ammonium hydroxide for 12 hours. The support was filtered off and the filtrate was lyophilized to remove the solvent. The crude product was purified by RP column chromatography (C-8) and desalted to obtain the product (20 mg). Mass calculated:7840, Deconvoluted mass: 7841.

[001792] **Synthesis of WV-7422**



[001793] To a suspension of WV2809 (56 mg, 7.5 µmol, 125 mg support) in 2 ml DMF was added DIPEA (19.3 mg, 150 µmol) and vortexed well for 5 minutes. To this suspension was added perfluorophenyl 3-(4-(N-(2,2,2-trifluoroacetyl)sulfamoyl)phenyl)propanoate (37 mg, 75 µmol) and shaken for 12 hours at room temperature. The solid support was washed with acetonitrile (20 ml X 3) and dried. This support was treated with 20% DEA in acetonitrile (1 ml) for 10 minutes. The DEA solution was removed by filtration. The solid support was washed with acetonitrile (20 ml X 3) and dried. The solid support was heated at 50 °C with 2 ml of 30% ammonium hydroxide for 12 hours. The support was filtered off and the filtrate was lyophilized to remove the solvent. The crude product was purified by RP column chromatography (C-8) and desalted to obtain the product (18 mg). Mass calculated:7638, Deconvoluted Mass:7641.

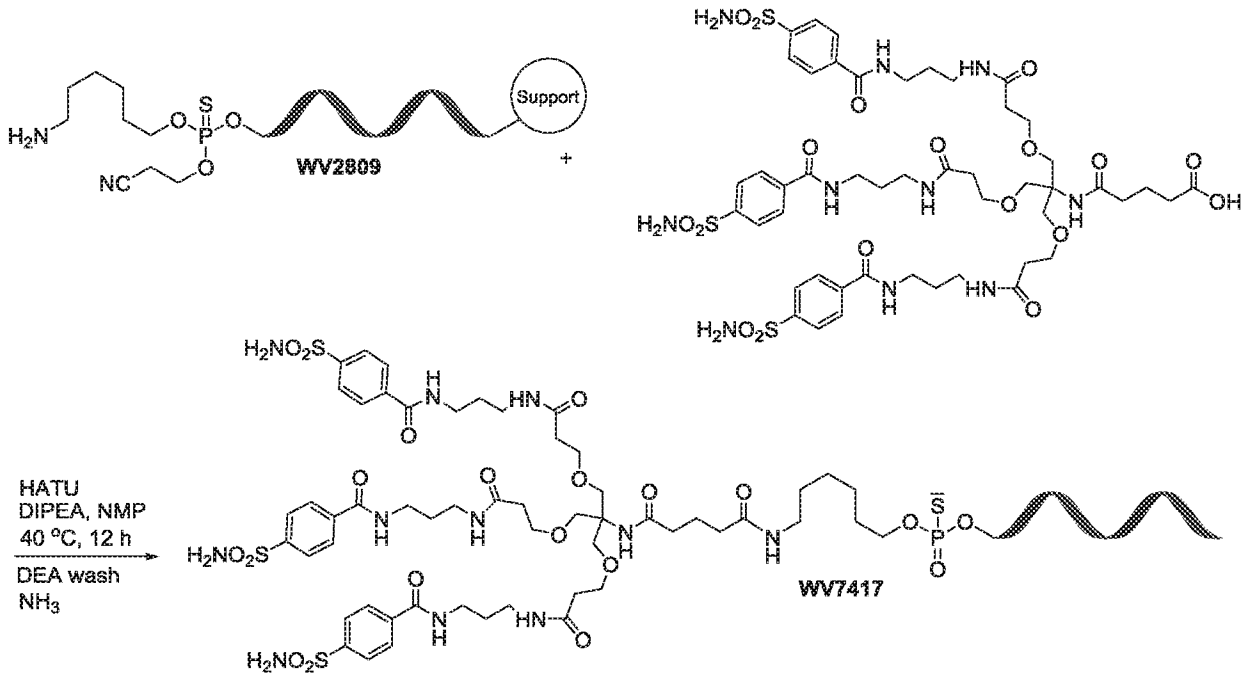
[001794] **Synthesis of WV-7421**



[001795] 2-(4-sulfamoylphenyl)acetic acid (17.2 mg, 80 µmol), HATU (28 mg, 76 molµ) and DIPEA (20.6 mg, 160 µmol) in 2 ml NMP was vortexed well for 2 minutes. To this suspension was added WV2809 (60 mg, 8 µmol, 150 mg support) and shaken well for 12 hours at room temperature. The

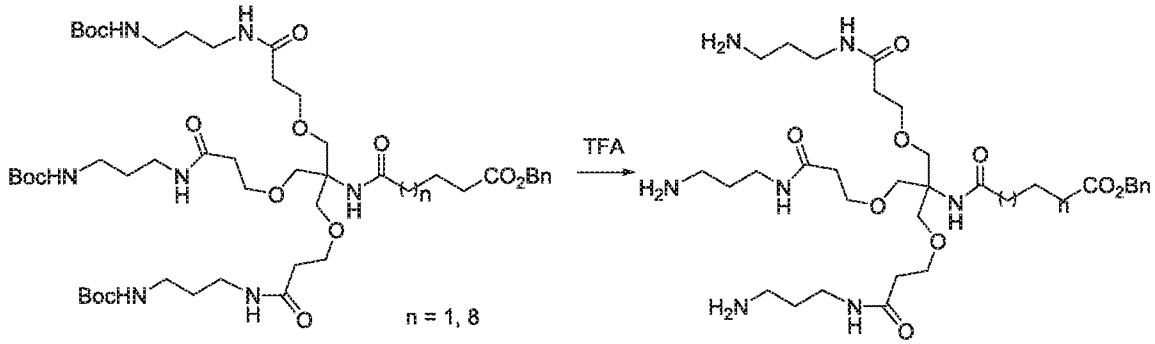
solid support was washed with acetonitrile (20 ml X 3) and dried. This support was treated with 20% DEA in acetonitrile (1 ml) for 10 minutes. The DEA solution was removed by filtration. The solid support was washed with acetonitrile (20 ml X 3) and dried. The solid support was heated at 50°C with 2 ml of 30% ammonium hydroxide for 12 hours. The support was filtered off and the filtrate was lyophilized to remove the solvent. The crude product was purified by RP column chromatography (C-18) and desalted to obtain the product (20 mg). Mass calculated:7624, Deconvoluted Mass:7627.

[001796] **Synthesis of WV-7417**



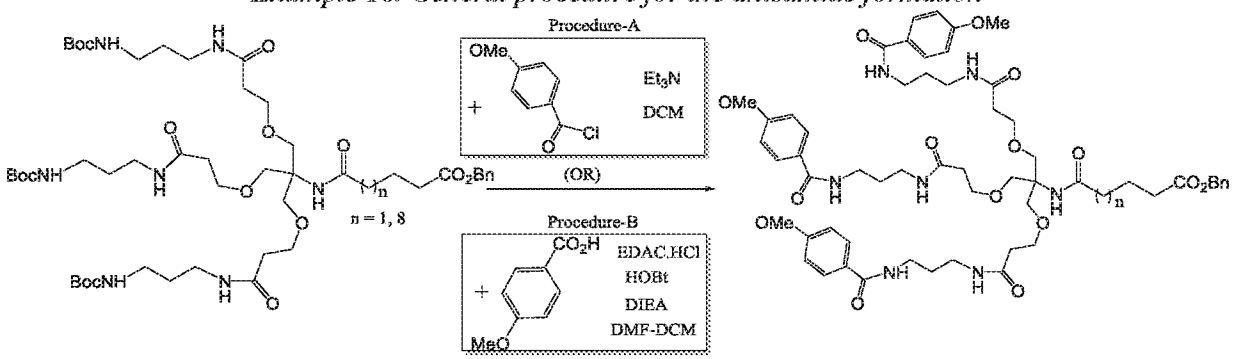
[001797] A suspension of 1,7,14-trioxo-12,12-bis((3-oxo-3-((3-(4-sulfamoylbenzamido)propyl)amino)propoxy)methyl)-1-(4-sulfamoylphenyl)-10-oxa-2,6,13-triazaoctadecan-18-oic acid (40 mg, 34 μmol), HATU (12 mg, 76 μmol) and DIPEA (44 mg, 340 μmol) in 2 ml NMP was vortexed well for 3 minutes. To this suspension was added WV2809 (60 mg, 8 μmol, 150 mg support) and shaken well for 12 hours at 40 °C. The solid support was washed with acetonitrile (20 ml X 3) and dried. This support was treated with 20% DEA in acetonitrile (1 ml) for 10 minutes. The DEA solution was removed by filtration. The solid support was washed with acetonitrile (20 ml X 3) and dried. The solid support was heated at 50°C with 2 ml of 30% ammonium hydroxide for 12 hours. The support was filtered off and the filtrate was lyophilized to remove the solvent. The crude product was purified by RP column chromatography (C-18) and desalted to obtain the product (10 mg). Mass calculated:8579, Deconvoluted Mass:8577.

Example 17. General procedure for the deprotection of amine



[001798] 15.2 g of NHBoc amine was dissolved in dry DCM (100 ml) then TFA (50 ml) was added dropwise at RT. Reaction mixture was stirred at RT overnight. Solvents were removed under reduced pressure then co-evaporated with toluene (2 x 50 mL) then used for the next step without any further purification. NMR in CD_3OD confirmed the NHBoc deprotection.

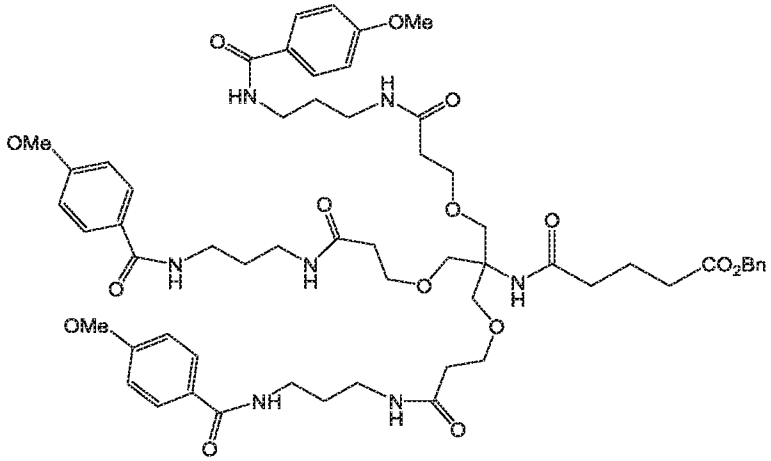
Example 18. General procedure for the anisamide formation



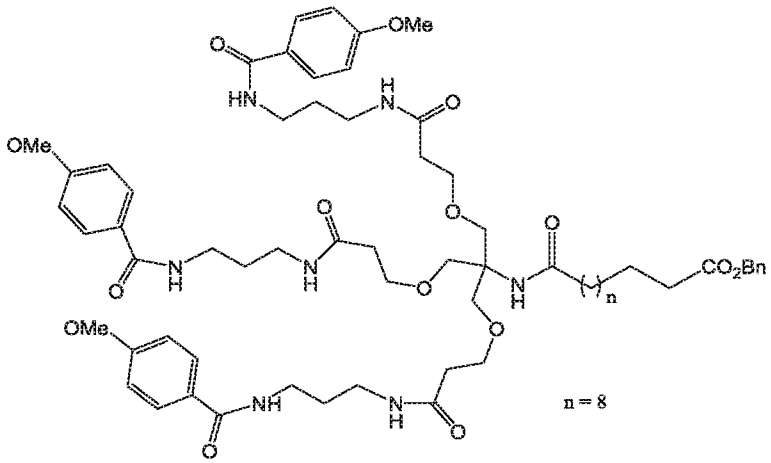
[001799] **Procedure-A:** The crude amine from the previous step was dissolved in a mixture of DCM (100 ml) and Et_3N (10 equ.) at RT. During this process, the reaction mixture was cooled with a water bath. Then 4-Methoxybenzoyl chloride (4 equ) was added dropwise to the reaction mixture under argon atmosphere at RT, stirring continued for 3 h. Reaction mixture was diluted with water and extracted with DCM. Organic layer was extracted with aq. $NaHCO_3$, 1N HCl, brine then dried with magnesium sulfate evaporated to dryness. The crude product was purified by silica column chromatography using DCM-MeOH as eluent.

[001800] **Procedure-B:** The crude amine (0.27 equ), acid and HOBt (1 equ) were dissolved in a mixture of DCM and DMF (2:1) in an appropriate sized RBF under argon. EDAC.HCl (1.25 equ) was added portion wise to the reaction mixture under constant stirring. After 15 mins, the reaction mixture was cooled to ~10 °C then DIEA (2.7 equ) was added over a period of 5 mins. Slowly warmed the reaction mixture to ambient temperature and stirred under argon for overnight. TLC indicated completion of the reaction TLC condition, DCM: MeOH (9.5:0.5). Solvents were removed under reduced pressure, then water was added to the residue, and a gummy solid separated out. The clear solution was decanted,

and the solid residue was dissolved in EtOAc and washed successively with water, 10% aqueous citric acid, aq. $NaHCO_3$, followed by saturated brine. The organic layer was separated and dried over magnesium sulfate. Solvent was removed under reduced pressure then the crude product was purified with silica column to get the pure product.

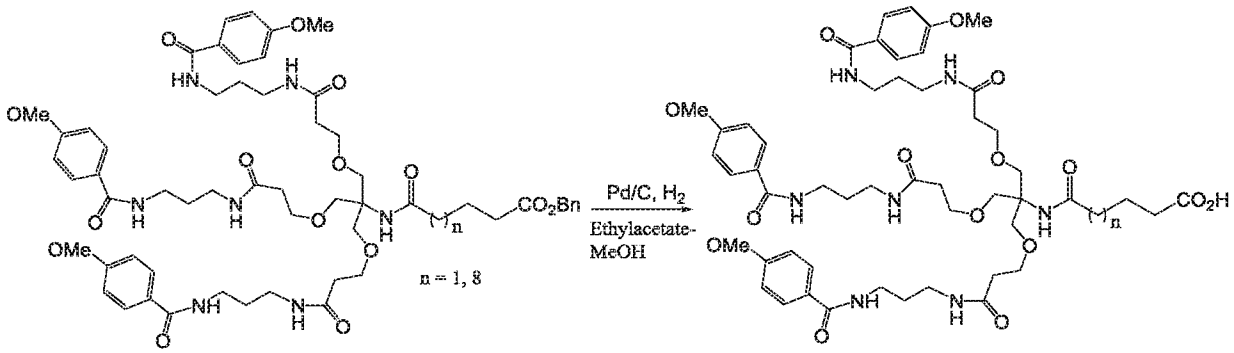


[001801] Anisamide was obtained from the amine in 32% yield over 2 steps using the above procedure-B: ^1H NMR ($CDCl_3$): δ = 7.74 (d, 6H), 7.44 (t, 2H), 7.34 (t, 1H), 7.26 (m, 5H), 7.05 (m, 3H), 6.83 (d, 6H), 6.46 (s, 1H), 5.01 (s, 2H), 3.75 (s, 9H), 3.57 (m, 12H), 3.37 (m, 6H), 3.25 (m, 6H), 2.31 (m, 8H), 2.11 (m, 2H), 1.84 (m, 2H), 1.62 (m, 6H) ppm.

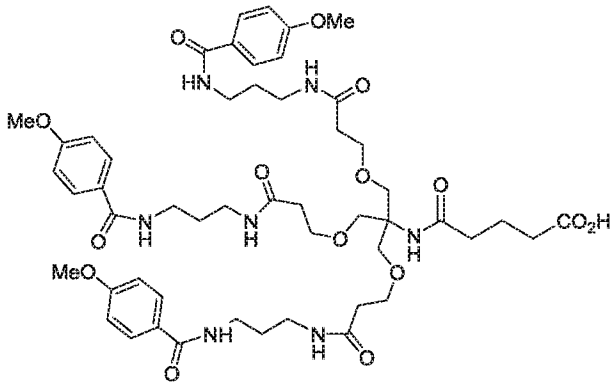


[001802] Anisamide was obtained from the amine in 57% yield over 2 steps using the above procedure-A: ^1H NMR ($CDCl_3$): δ = 7.75 (m, 3H), 7.73 (d, 6H), 7.43 (t, 3H), 7.25 (m, 5H), 6.80 (d, 6H), 6.51 (brs, 1H), 5.01 (s, 2H), 3.72 (s, 9H), 3.58 (m, 6H), 3.21 (m, 12H), 2.33 (t, 3H), 2.25 (t, 2H), 2.02 (t, 2H), 1.64 (q, 6H), 1.52 (p, 2H), 1.41 (q, 2H), 1.12 (m, 12H) ppm.

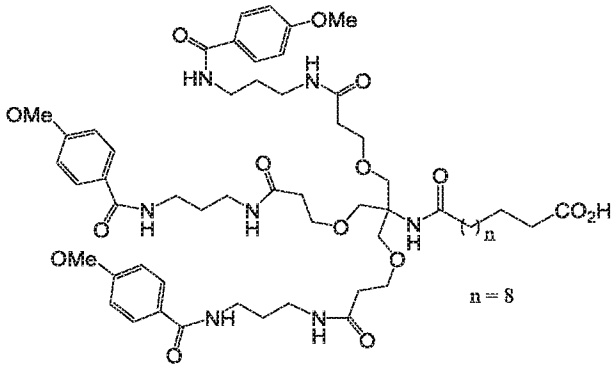
[001803] General procedure for debenzylation.



[001804] The benzyl ester (10 g) was dissolved in a mixture of ethyl acetate (100 ml) and methanol (25 ml) then Pd/C, 1 g (10% palladium content) was added under argon atmosphere then the reaction mixture was vacuumed and flushed with hydrogen and stirred at RT under H_2 atmosphere for 3 h. TLC indicated completion of the reaction, filtered through pad of celite and washed with methanol, evaporated to dryness to yield a foamy white solid.



[001805] Yield 98%, ^{1}H NMR (CD_3OD): δ = 8.35 (t, 1H), 8.01 (t, 1H), 7.82 (d, 6H), 7.27 (d, 1H), 6.99 (d, 6H), 3.85 (s, 9H), 3.68 (m, 12H), 3.41 (m, 6H), 3.29 (m, 6H), 2.42 (m, 6H), 2.31 (q, 2H), 2.21 (td, 2H), 1.80 (m, 8H) ppm.



[001806] Yield 94%, ^{1}H NMR (CD_3OD): δ = 8.36 (t, 2H), 8.02 (t, 2H), 7.82 (d, 6H), 7.23 (d, 1H), 6.98 (d, 6H), 3.85 (s, 9H), 3.70 (s, 6H), 3.67 (t, 6H), 3.41 (q, 4H), 3.28 (m, 8H), 2.42 (t, 6H), 2.27 (t, 2H), 2.13 (t, 2H), 1.79 (p, 6H), 1.54 (dp, 4H), 1.25 (m, 12H) ppm.

Example 19. Timelines for 'Pre-differentiation' of patient myoblasts for gymnotic dosing

[001807] Various technologies, e.g., those described in US 9394333, US 9744183, US 9605019, US 9598458, US 2015/0211006, US 2017/0037399, WO 2017/015555, WO 2017/192664, WO 2017/015575, WO 2017/062862, WO 2017/160741, WO 2017/192679, and WO 2017/210647, etc., can be utilized in accordance with the present disclosure to assess properties and/or activities of technologies of the present disclosure. In some embodiments, technologies of the present disclosure, e.g., oligonucleotides and compositions and methods of use thereof, demonstrate unexpectedly superior results compared to a suitable reference technology (e.g., a technology based on a stereorandom composition of oligonucleotides having the same base sequence but no neutral and/or cationic internucleotidic linkages at physiological pH). Described below are example technologies that can be useful for assessing properties and/or activities of oligonucleotides described in the present disclosure. Those skilled in the art understand that conditions illustrated below may be varied/modified, and additionally and/or alternatively, other suitable reagents, temperatures, conditions, time periods, amounnts, etc., may be utilized in accordance with the present disclosure.

[001808] *Maintenance of Patient Derived Myoblast Cell Lines:*

[001809] DMD Δ52 and DMD Δ45-52 myoblast cells were maintained in complete Skeletal Muscle Growth Medium (Promocell, Heidelberg, Germany) supplemented with 5% FBS, 1X Penicillin-Streptomycin and 1X L-Glutamine. Flasks or plates were coated with Matrigel:DMEM solution (1:100) for a suitable period of time, e.g., 30 mins, after which Matrigel:DMEM solution was removed via aspiration before seeding of cells in complete Skeletal Muscle Growth Medium.

[001810] *Standard Dosing Procedure (0 days pre-differentiation)*

[001811] On Day 1: Coat suitable cell growth containers, e.g., 6-well plates or 24-well plates, with Matrigel: DMEM Solution. Incubate at a condition, e.g., 37 °C, 5% CO_2 for a suitable period of time, e.g., 30 mins. Aspirate, and seed a suitable number of cells to cell growth containers, e.g., 150K cells/well in a total of 1500 µl of complete growth medium in 6-well plate, and 30K cells/well in 500 ul of growth medium in a 24-well plate. Incubate at a suitable condition for a suitable period of time, .e.g., 37 °C, 5% CO_2 overnight.

[001812] On Day 2: Prepare a suitable Differentiation medium, e.g., DMEM + 5% Horse Serum + 10µg/ml Insulin. Prepare suitable oligonucleotide dilutions in Differentiation Medium, e.g., serial dilutions of 30 uM, 10 uM, 3.33 uM, 1.11 uM, 0.37 uM. Aspirate growth medium off of adherent cells, and add oligonucleotide:Differentiation Medium solution to cells. Oligonucleotides remain on cells (no media change) until cell harvesting.

[001813] On Day 6: Obtain RNA. In a typical procedure, a suitable number of cells, e.g., cells from

wells of a 24-well plate, were washed, e.g., with cold PBS, followed by addition of a suitable amount of a reagent for RNA extraction and storage of sample/RNA extraction, e.g., 500 ul/well TRIZOL in 24-well plate and freezing plate at -80°C or continuing with RNA extraction to obtain RNA.

[001814] On Day 8: Obtain protein. In a typical procedure, a suitable number of cells, e.g., cells in wells of 6-well plate, were washe, e.g., with cold PBS. A suitable amount of a suitable lysis buffer was then added - e.g., in a typical procedure, 200 ul/well of RIPA supplemented with protease inhibitors for a 6-well plate. After lysis the sample can be stored, e.g., freezing at -80 °C, or continue with protein extraction.

[001815] Other suitable procedures may be employed, for example, those described below. As appreciated by those skilled in the art, many parameters, such as reagents, temperatures, conditions, time periods, amounnts, etc., may be modified.

[001816] *4 days Pre-Differentiation Dosing Procedure*

[001817] On Day 1: Coat 6-well plates or 24-well plates with Matrigel: DMEM Solution. Incubate at 37 °C, 5% CO_2 for 30 mins. Aspirate, seed 150K cells/well in a total of 1500 µl of complete growth medium in 6-well plate, and 30K cells/well in 500 ul of growth medium in a 24-well plate. Incubate at 37 °C, 5% CO_2 overnight.

[001818] On Day 2: Prepare Differentiation medium as follows: DMEM + 5% Horse Serum + 10µg/ml Insulin. Aspirate Growth Media and replace with Differentiation Media.

[001819] On Day 6: Cells have differentiated for 4 days. Prepare oligonucleotide dilutions in Differentiation Medium, for example serial dilutions of 30 uM, 10 uM, 3.33 uM, 1.11 uM, 0.37 uM. Aspirate Differentiation medium off of adherent cells, and add oligonucleotide:Differentiation Medium solution to cells. Oligonucleotides remain on cells (no media change) until cell harvesting.

[001820] On Day 10: Wash cells in 24-well plate with cold PBS, add 500 ul/well TRIZOL in 24-well plate and freeze plate at -80 °C or continue with RNA extraction.

[001821] On Day 12: Wash cells in 6-well plate with cold PBS. Add 200 ul/well of RIPA supplemented with protease inhibitors. Freeze plate at -80 °C or continue with protein extraction.

[001822] *7 days Pre-Differentiation Dosing Procedure*

[001823] On Day 1: Coat 6-well plates or 24-well plates with Matrigel: DMEM Solution. Incubate at 37 °C, 5% CO_2 for 30 mins. Aspirate, seed 150K cells/well in a total of 1500 µl of complete growth medium in 6-well plate, and 30K cells/well in 500 ul of growth medium in a 24-well plate. Incubate at 37 °C, 5% CO_2 overnight.

[001824] On Day 2: Prepare Differentiation medium as follows: DMEM + 5% Horse Serum + 10µg/ml Insulin. Aspirate Growth Media and replace with Differentiation Media.

[001825] On Day 9: Cells have differentiated for 7 days. Prepare oligonucleotide dilutions in Differentiation Medium, for example serial dilutions of 30 uM, 10 uM, 3.33 uM, 1.11 uM, 0.37 uM. Aspirate Differentiation medium off of adherent cells, and add oligonucleotide:Differentiation Medium solution to cells. Oligonucleotides remain on cells (no media change) until cell harvesting.

[001826] On Day 13: Wash cells in 24-well plate with cold PBS, add 500 ul/well TRIZOL in 24-well plate and freeze plate at -80 °C or continue with RNA extraction.

[001827] On Day 15: Wash cells in 6-well plate with cold PBS. Add 200 ul/well of RIPA supplemented with protease inhibitors. Freeze plate at -80 °C or continue with protein extraction.

[001828] *10 days Pre-Differentiation Dosing Procedure*

[001829] On Day 1: Coat 6-well plates or 24-well plates with Matrigel: DMEM Solution. Incubate at 37 °C, 5% CO_2 for 30 mins. Aspirate, seed 150K cells/well in a total of 1500 µl of complete growth medium in 6-well plate, and 30K cells/well in 500 ul of growth medium in a 24-well plate. Incubate at 37 °C, 5% CO_2 overnight.

[001830] On Day 2: Prepare Differentiation medium as follows: DMEM + 5% Horse Serum + 10µg/ml Insulin. Aspirate Growth Media and replace with Differentiation Media.

[001831] On Day 12: Cells have differentiated for 10 days. Prepare oligonucleotide dilutions in Differentiation Medium, for example serial dilutions of 30 uM, 10 uM, 3.33 uM, 1.11 uM, 0.37 uM. Aspirate Differentiation medium off of adherent cells, and add oligonucleotide:Differentiation Medium solution to cells. Oligonucleotides remain on cells (no media change) until cell harvesting.

[001832] On Day 16: Wash cells in 24-well plate with cold PBS, add 500 ul/well TRIZOL in 24-well plate and freeze plate at -80 °C or continue with RNA extraction.

[001833] On Day 18: Wash cells in 6-well plate with cold PBS. Add 200 ul/well of RIPA supplemented with protease inhibitors. Freeze plate at -80 °C or continue with protein extraction.

Example 20. Multi-exon skipping assay

[001834] The assay described herein can be adapted to detect any gene's splice-variants with frequency of each variant (quantification). DMD Exon43-Exon64 is used as an example.

[001835] Among other things, a unique feature of this assay is that an unique-molecular-identifier (UMI) is introduced in the reverse transcription primers with an unique PCR handler sequence (this can be any sequence without homology to genomic or transcriptome sequences). Therefore, each cDNA has its unique UMI (bar-code) that can be used in later sequencing analysis to eliminate PCR and sequencing bias toward smaller amplicons.

[001836] In a typical procedure, the steps include: Reverse RT primer containing a PCR handle at

5'-end, then 8-16 sequences of randomly incorporated nucleotides that create UMI/bar code and reverse complement sequence in exon 64 (Reverse RT primer in table), was used to prime the reverse transcription by a RT kit (e.g., SuperScript IV, ThermoFisher, Cambridge, MA). Then primary and nested PCR were run to amplify gene-specific fragments used for PacBio long range sequencing or Oxford Nanopore MinION platform.

[001837] The NGS sequences (BAM files) were mapped to reference sequence (DMD for example) to identify splice variants (exon junctions). The UMI were counted in each splice variant, and frequency of variant was calculated by UMI counts in each variant divided by total UMI counts in all variants.

[001838] An illustration of this process is shown in Figure 2.

Example Reverse RT primer:

5'-CAGTGGTATCAACGCAGAGTACG-NNNNNNNN-ctgagaatctgacattattcagg-3'

5'-capital letter = N1 binding sequence (nested secondary)

N.....N = UMI

underline = gene specific sequence in exon64

Forward primer (exon 43):

Fnest = 5'-gaagctctctcccagcttgat-3'

Among other things, the present disclosure provides the following Example Embodiments:

1. An oligonucleotide composition, comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

wherein:

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 chirally controlled internucleotidic linkages; and

the oligonucleotide composition being characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

2. The composition of any one of the preceding embodiment, wherein the transcript is a Dystrophin

transcript.

3. The composition of any one of the preceding embodiments, wherein splicing of the transcript is altered such that the level of skipping of exon 45, 51, or 53, or multiple exons is increased.

4. The composition of any one of the preceding embodiments, wherein each chiral internucleotidic linkage of the oligonucleotides of the plurality is independently a chirally controlled internucleotidic linkage.

5. The composition of any one of the preceding embodiments, wherein each chiral modified internucleotidic linkage independently has a stereopurity of at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% at its chiral linkage phosphorus.

6. The composition of any one of the preceding embodiments, wherein the base sequence is or comprises or comprises 15 contiguous bases of the base sequence of any oligonucleotide in Table A1.

7. The composition of any one of the preceding embodiments, wherein the pattern of backbone linkages comprises at least one non-negatively charged internucleotidic linkage.

8. The composition of any one of the preceding embodiments, wherein the pattern of backbone linkages comprises at least one non-negatively charged internucleotidic linkage which is a neutral internucleotidic linkage.

9. The composition of any one of the preceding embodiments, wherein the pattern of backbone linkages comprises at least one neutral internucleotidic linkage which is or comprises a triazole, neutral triazole, alkyne, or a cyclic guanidine.

10. The composition of any one of the preceding embodiments, wherein the oligonucleotide type comprises any of: cholesterol; L-carnitine (amide and carbamate bond); Folic acid; Gambogic acid; Cleavable lipid (1,2-dilaurin and ester bond); Insulin receptor ligand; CPP; Glucose (tri- and hex-antennary); or Mannose (tri- and hex-antennary, alpha and beta).

11. The composition of any one of the preceding embodiments, wherein the oligonucleotide type is any oligonucleotide listed in Table A1.

12. A composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

which composition is chirally controlled and it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same base sequence, pattern of backbone linkages and pattern of backbone phosphorus modifications, for oligonucleotides of the particular oligonucleotide type,

wherein:

the oligonucleotide composition is characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered in that level of skipping of an exon is increased relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

13. The composition of any one of the preceding embodiments, wherein the transcript is a Dystrophin transcript.

14. The composition of any one of the preceding embodiments, wherein the exon is DMD exon 45, 51 or 53 or multiple DMD exons, and wherein the splicing of the transcript is altered such that the level of skipping of exon 45, 51, or 53, or multiple exons is increased.

15. The composition of any one of the preceding embodiments, wherein the pattern of backbone chiral centers comprises at least one *S*p.

16. The composition of any one of the preceding embodiments, wherein the pattern of backbone chiral centers comprises at least one *R*p.

17. The composition of any one of the preceding embodiments, wherein the composition is a chirally pure composition.

18. The composition of any one of the preceding embodiments, wherein each chiral modified internucleotidic linkage independently has a stereopurity of at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% at its chiral linkage phosphorus.

19. The composition of any one of the preceding embodiments, wherein the base sequence is or comprises or comprises 15 contiguous bases of the base sequence of any oligonucleotide in Table A1.

20. The composition of any one of the preceding embodiments, wherein the pattern of backbone linkages comprises at least one non-negatively charged internucleotidic linkage.

21. The composition of any one of the preceding embodiments, wherein the pattern of backbone linkages comprises at least one non-negatively charged internucleotidic linkage which is a neutral internucleotidic linkage.

22. The composition of any one of the preceding embodiments, wherein the pattern of backbone linkages comprises at least one neutral internucleotidic linkage which is or comprises a triazole, neutral triazole, alkyne, or a cyclic guanidine.

23. The composition of any one of the preceding embodiments, wherein the oligonucleotide type comprises any of: cholesterol; L-carnitine (amide and carbamate bond); Folic acid; Gambogic acid; Cleavable lipid (1,2-dilaurin and ester bond); Insulin receptor ligand; CPP; Glucose (tri- and hex-antennary); or Mannose (tri- and hex-antennary, alpha and beta).

24. The composition of any one of the preceding embodiments, wherein the oligonucleotide type is

any oligonucleotide listed in Table A1.

25. A composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages; and

3) pattern of backbone phosphorus modifications,

wherein:

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 non-negatively charged internucleotidic linkages;

the oligonucleotide composition is characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered in that level of skipping of an exon is increased relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

26. The composition of any one of the preceding embodiments, wherein the transcript is a Dystrophin transcript.

27. The composition of any one of the preceding embodiments, wherein the exon is DMD exon 45, 51, or 53 or multiple DMD exons, and the splicing of the transcript is altered such that the level of skipping of exon 45, 51, or 53, or multiple exons is increased.

28. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage is independently an internucleotidic linkage at least 50% of which exists in its non-negatively charged form at pH 7.4.

29. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage is independently a neutral internucleotidic linkage, wherein at least 50% of the internucleotidic linkage exists in its neutral form at pH 7.4.

30. The composition of any one of the preceding embodiments, wherein the neutral form of each non-negatively charged internucleotidic linkage independently has a pKa no less than 8, 9, 10, 11, 12, 13, or 14.

31. The composition of any one of the preceding embodiments, wherein the neutral form of each non-negatively charged internucleotidic linkage, when the units which it connects are replaced with $-CH_3$, independently has a pKa no less than 8, 9, 10, 11, 12, 13, or 14.

32. The composition of any one of the preceding embodiments, wherein the reference condition is absence of the composition.

33. The composition of any one of the preceding embodiments, wherein the reference condition is presence of a reference composition.

34. The composition of any one of the preceding embodiments, wherein the reference composition is an otherwise identical composition wherein the oligonucleotides of the plurality comprise no chirally controlled internucleotidic linkages.

35. The composition of any one of the preceding embodiments, wherein the reference composition is an otherwise identical composition wherein the oligonucleotides of the plurality comprise no non-negatively charged internucleotidic linkages.

36. The composition of any one of the preceding embodiments, wherein the pattern of backbone linkages comprises one or more backbone linkages selected from phosphodiester, phosphorothioate and phosphodithioate linkages.

37. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality each comprise one or more sugar modifications.

38. The composition of any one of the preceding embodiments, wherein the sugar modifications comprise one or more modifications selected from: 2'-O-methyl, 2'-MOE, 2'-F, morpholino and bicyclic sugar moieties.

39. The composition of any one of the preceding embodiments, wherein one or more sugar modifications are 2'-F modifications.

40. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality each comprise a 5'-end region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleoside units comprising a 2'-F modified sugar moiety.

41. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality each comprise a 3'-end region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleoside units comprising a 2'-F modified sugar moiety.

42. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality each comprise a middle region between the 5'-end region and the 3'-region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleotidic units comprising a phosphodiester linkage.

43. The composition of any one of the preceding embodiments, wherein the base sequence is or comprises or comprises 15 contiguous bases of the base sequence of any oligonucleotide in Table A1.

44. The composition of any one of the preceding embodiments, wherein the pattern of backbone linkages comprises at least one non-negatively charged internucleotidic linkage.

45. The composition of any one of the preceding embodiments, wherein the pattern of backbone linkages comprises at least one non-negatively charged internucleotidic linkage which is a neutral internucleotidic linkage.

46. The composition of any one of the preceding embodiments, wherein the pattern of backbone linkages comprises at least one neutral internucleotidic linkage which is or comprises a triazole, neutral

triazole, alkyne, or a cyclic guanidine.

47. The composition of any one of the preceding embodiments, wherein the oligonucleotide type comprises any of: cholesterol; L-carnitine (amide and carbamate bond); Folic acid; Gambogic acid; Cleavable lipid (1,2-dilaurin and ester bond); Insulin receptor ligand; CPP; Glucose (tri- and hex-antennary); or Mannose (tri- and hex-antennary, alpha and beta).

48. The composition of any one of the preceding embodiments, wherein the oligonucleotide type is any oligonucleotide listed in Table A1.

49. A composition comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages; and

3) pattern of backbone phosphorus modifications,

wherein:

oligonucleotides of the plurality comprise:

1) a 5'-end region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleoside units comprising a 2'-F modified sugar moiety;

2) a 3'-end region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleoside units comprising a 2'-F modified sugar moiety; and

3) a middle region between the 5'-end region and the 3'-region comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleotidic units comprising a phosphodiester linkage.

50. The composition of embodiment 43 or 49, wherein the oligonucleotide composition is characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered in that level of skipping of an exon is increased relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

51. The composition of any one of the preceding embodiments, wherein the transcript is a Dystrophin transcript.

52. The composition of any one of the preceding embodiments, wherein the exon is DMD exon 45, 51, or 53 or multiple DMD exons, and the splicing of the transcript is altered such that the level of skipping of exon 45, 51, or 53, or multiple exons is increased.

53. The composition of any one of the preceding embodiments, wherein the 5'-end region comprises 1 or more nucleoside units not comprising a 2'-F modified sugar moiety.

54. The composition of any one of the preceding embodiments, wherein the 3'-end region comprises 1 or more nucleoside units not comprising a 2'-F modified sugar moiety.

55. The composition of any one of the preceding embodiments, wherein the middle region comprises 1 or more nucleotidic units comprising no phosphodiester linkage.

56. The composition of any one of the preceding embodiments, wherein the first of the 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleoside units comprising a 2'-F modified sugar moiety and a modified internucleotidic linkage of the 5'-end is the first, second, third, fourth or fifth nucleoside unit of the oligonucleotide from the 5'-end, and the last of the 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleoside units comprising a 2'-F modified sugar moiety and a modified internucleotidic linkage of the 3'-end is the last, second last, third last, fourth last, or fifth last nucleoside unit of the oligonucleotide.

57. The composition of any one of the preceding embodiments, wherein the 5'-end region comprising 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive nucleoside units comprising a 2'-F modified sugar moiety.

58. The composition of any one of the preceding embodiments, wherein the 5'-end region comprising 5, 6, 7, 8, 9, 10 or more consecutive nucleoside units comprising a 2'-F modified sugar moiety.

59. The composition of any one of the preceding embodiments, wherein the 3'-end region comprising 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive nucleoside units comprising a 2'-F modified sugar moiety.

60. The composition of any one of the preceding embodiments, wherein the 3'-end region comprising 5, 6, 7, 8, 9, 10 or more consecutive nucleoside units comprising a 2'-F modified sugar moiety.

61. The composition of any one of the preceding embodiments, wherein each internucleotidic linkage between two nucleoside units comprising a 2'-F modified sugar moiety in the 5'-end region is independently a modified internucleotidic linkage.

62. The composition of any one of the preceding embodiments, wherein each internucleotidic linkage between two nucleoside units comprising a 2'-F modified sugar moiety in the 3'-end region is independently a modified internucleotidic linkage.

63. The composition of embodiment 61 or 62, wherein each modified internucleotidic linkage is independently a chiral internucleotidic linkage.

64. The composition of embodiment 61 or 62, wherein each modified internucleotidic linkage is independently a chirally controlled internucleotidic linkage.

65. The composition of embodiment 61 or 62, wherein each modified internucleotidic linkage is a phosphorothioate internucleotidic linkage.

66. The composition of embodiment 61 or 62, wherein each modified internucleotidic linkage is a chirally controlled phosphorothioate internucleotidic linkage.

67. The composition of embodiment 61 or 62, wherein each modified internucleotidic linkage is a *Sp* chirally controlled phosphorothioate internucleotidic linkage.

68. The composition of any one of the preceding embodiments, wherein the middle region comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more natural phosphate linkages.

69. The composition of any one of the preceding embodiments, wherein the middle region comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more natural phosphate linkages each independently between a nucleoside unit comprising a 2'−OR^1 modified sugar moiety and a nucleoside unit comprising a 2'−F modified sugar moiety, or between two nucleoside units each independently comprising a 2'−OR^1 modified sugar moiety, wherein R^1 is optionally substituted C_{1-6} alkyl.

70. The composition of any one of the preceding embodiments, wherein the middle region comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more non-negatively charged internucleotidic linkages.

71. The composition of any one of the preceding embodiments, wherein the middle region comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more non-negatively charged internucleotidic linkages each independently between a nucleoside unit comprising a 2'−OR^1 modified sugar moiety and a nucleoside unit comprising a 2'−F modified sugar moiety, or between two nucleoside units each independently comprising a 2'−OR^1 modified sugar moiety, wherein R^1 is optionally substituted C_{1-6} alkyl.

72. The composition of embodiment 69 or 71, wherein 2'−OR^1 is 2'−OCH_3.

73. The composition of embodiment 69 or 71, wherein 2'−OR^1 is 2'−$OCH_2CH_2OCH_3$.

74. The composition of any one of the preceding embodiments, wherein the 5'-end region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 chiral modified internucleotidic linkages.

75. The composition of any one of the preceding embodiments, wherein the 5'-end region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive chiral modified internucleotidic linkages.

76. The composition of any one of the preceding embodiments, wherein each internucleotidic linkage in the 5'-end region is a chiral modified internucleotidic linkage.

77. The composition of any one of the preceding embodiments, wherein the 3'-end region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 chiral modified internucleotidic linkages.

78. The composition of any one of the preceding embodiments, wherein the 3'-end region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive chiral modified internucleotidic linkages.

79. The composition of any one of the preceding embodiments, wherein each internucleotidic linkage in the 3'-end region is a chiral modified internucleotidic linkage.

80. The composition of any one of the preceding embodiments, wherein the middle region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 chiral modified internucleotidic linkages.

81. The composition of any one of the preceding embodiments, wherein the middle region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive chiral modified internucleotidic linkages.

82. The composition of any one of embodiments 74-81, wherein each chiral modified internucleotidic linkage is independently a chirally controlled internucleotidic linkage.

83. The composition of any one of embodiments 74-81, wherein each chiral modified internucleotidic linkage is independently a chirally controlled internucleotidic linkage wherein its chirally controlled

linkage phosphorus has a *Sp* configuration.

84. The composition of any one of embodiments 74-83, wherein each chiral modified internucleotidic linkage is independently a chirally controlled phosphorothioate internucleotidic linkage.

85. The composition of any one of the preceding embodiments, wherein the middle region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-negatively charged internucleotidic linkages.

86. The composition of any one of the preceding embodiments, wherein the middle region comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 neutral internucleotidic linkages.

87. The composition of any one of the preceding embodiments, wherein a neutral internucleotidic linkage is a chiral internucleotidic linkage.

88. The composition of any one of the preceding embodiments, wherein a neutral internucleotidic linkage is a chirally controlled internucleotidic linkage independently of *Rp* or *Sp* at its linkage phosphorus.

89. The composition of any one of the preceding embodiments, wherein the base sequence comprises a sequence having no more than 5 mismatches from a 20 base long portion of the dystrophin gene or its complement.

90. The composition of any one of the preceding embodiments, wherein the length of the base sequence of the oligonucleotides of the plurality is no more than 50 bases.

91. The composition of any one of the preceding embodiments, wherein the pattern of backbone chiral centers comprises at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 chirally controlled centers independently of *Rp* or *Sp*.

92. The composition of any one of the preceding embodiments, wherein the pattern of backbone chiral centers comprises at least 5 chirally controlled centers independently of *Rp* or *Sp*.

93. The composition of any one of the preceding embodiments, wherein the pattern of backbone chiral centers comprises at least 6 chirally controlled centers independently of *Rp* or *Sp*.

94. The composition of any one of the preceding embodiments, wherein the pattern of backbone chiral centers comprises at least 10 chirally controlled centers independently of *Rp* or *Sp*.

95. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the particular oligonucleotide type are capable of mediating skipping of one or more exons of the dystrophin gene.

96. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality are capable of mediating the skipping of exon 45, 51 or 53 of the dystrophin gene.

97. The composition of embodiment 96, wherein the oligonucleotides of the plurality are capable of mediating the skipping of exon 45 of the dystrophin gene.

98. The composition of embodiment 96, wherein the oligonucleotides of the plurality are capable of

mediating the skipping of exon 51 of the dystrophin gene.

99. The composition of embodiment 96, wherein the oligonucleotides of the plurality are capable of mediating the skipping of exon 53 of the dystrophin gene.

100. The composition of embodiment 97, wherein the base sequence comprises a sequence having no more than 5 mismatches from the sequence of any oligonucleotide disclosed herein.

101. The composition of embodiment 97, wherein the base sequence comprises or is the sequence of any oligonucleotide disclosed herein..

102. The composition of embodiment 97, wherein the base sequence is that of any oligonucleotide disclosed herein.

103. The composition of embodiment 97, wherein the base sequence comprises a sequence having no more than 5 mismatches from the sequence of any oligonucleotide disclosed herein.

104. The composition of embodiment 97, wherein the base sequence comprises or is any oligonucleotide disclosed herein.

105. The composition of embodiment 97, wherein the base sequence is any oligonucleotide disclosed herein.

106. The composition of any of the preceding embodiments, wherein the oligonucleotides of the plurality are any oligonucleotide disclosed herein.

107. The composition of embodiment 18, wherein oligonucleotides of the particular oligonucleotide type are any oligonucleotide disclosed herein.

108. The composition of any one of the preceding embodiments, wherein the base sequence is or comprises or comprises 15 contiguous bases of the base sequence of any oligonucleotide in Table A1.

109. The composition of any one of the preceding embodiments, wherein the pattern of backbone linkages comprises at least one non-negatively charged internucleotidic linkage.

110. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more non-negatively charged internucleotidic linkages.

111. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more chirally controlled non-negatively charged internucleotidic linkages.

112. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive non-negatively charged internucleotidic linkages.

113. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive chirally controlled non-negatively charged

internucleotidic linkages.

114. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure.

115. The composition of any one of the preceding embodiments, wherein a wing comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more non-negatively charged internucleotidic linkages.

116. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure, and wherein a wing comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more chirally controlled non-negatively charged internucleotidic linkages.

117. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure, and wherein a wing comprises 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive non-negatively charged internucleotidic linkages.

118. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure, and wherein a wing comprises 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive chirally controlled non-negatively charged internucleotidic linkages.

119. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise or consist of a wing-core-wing structure, and wherein only one wing comprise one or more non-negatively charged internucleotidic linkages.

120. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure, and wherein a core comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more non-negatively charged internucleotidic linkages.

121. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure, and wherein a core comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more chirally controlled non-negatively charged internucleotidic linkages.

122. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure, and wherein a core comprises 2, 3, 4, 5, 6, 7, 8, 9, 10 or more consecutive non-negatively charged internucleotidic linkages.

123. The composition of any one of the preceding embodiments, wherein the oligonucleotides comprise a wing-core-wing, core-wing, or wing-core structure, and wherein a core comprises 2,

3, 4, 5, 6, 7, 8, 9, 10 or more consecutive chirally controlled non-negatively charged internucleotidic linkages.

124. The composition of any one of the preceding embodiments, wherein 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of internucleotidic linkages of a wing is independently a non-negatively charged internucleotidic linkage, a natural phosphate internucleotidic linkage or a *Rp* chiral internucleotidic linkage.

125. The composition of any one of the preceding embodiments, wherein 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of internucleotidic linkages of a wing is independently a non-negatively charged internucleotidic linkage or a natural phosphate internucleotidic linkage.

126. The composition of any one of the preceding embodiments, wherein 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of internucleotidic linkages of a wing is independently a non-negatively charged internucleotidic linkage.

127. The composition of any one of embodiments 124-126, wherein the percentage is 50% or more.

128. The composition of any one of embodiments 124-126, wherein the percentage is 60% or more.

129. The composition of any one of embodiments 124-126, wherein the percentage is 75% or more.

130. The composition of any one of embodiments 124-126, wherein the percentage is 80% or more.

131. The composition of any one of embodiments 124-126, wherein the percentage is 90% or more.

132. The composition of any one of the preceding embodiments, wherein the oligonucleotides each comprise a non-negatively charged internucleotidic linkage and a natural phosphate internucleotidic linkage.

133. The composition of any one of the preceding embodiments, wherein the oligonucleotides each comprise a non-negatively charged internucleotidic linkage, a natural phosphate internucleotidic linkage and a *Rp* chiral internucleotidic linkage.

134. The composition of any one of the preceding embodiments, wherein a wing comprises a non-negatively charged internucleotidic linkage and a natural phosphate internucleotidic linkage.

135. The composition of any one of the preceding embodiments, wherein a wing comprises a non-negatively charged internucleotidic linkage, a natural phosphate internucleotidic linkage and a *Rp* chiral internucleotidic linkage.

136. The composition of any one of the preceding embodiments, wherein a core comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more non-negatively charged internucleotidic linkages.

137. The composition of any one of the preceding embodiments, wherein all non-negatively charged internucleotidic linkages of the same oligonucleotide have the same constitution.

138. The composition of any one of the preceding embodiments, wherein each of the non-negatively charged internucleotidic linkages independently has the structure of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2, II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof.

139. The composition of any one of the preceding embodiments, wherein each of the non-negatively charged internucleotidic linkages independently has the structure of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2, II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof.

140. The composition of any one of the preceding embodiments, wherein each of the non-negatively charged internucleotidic linkages independently has the structure of formula **II**, **II-a-1**, **II-a-2, II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof.

141. The composition of any one of the preceding embodiments, wherein each of the non-negatively charged internucleotidic linkages independently has the structure of formula **II**, **II-a-1**, **II-a-2, II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof.

142. The composition of any one of the preceding embodiments, wherein the pattern of backbone linkages comprises at least one non-negatively charged internucleotidic linkage which is a neutral internucleotidic linkage.

143. The composition of any one of the preceding embodiments, wherein the pattern of backbone linkages comprises at least one neutral internucleotidic linkage which is or comprises a triazole, neutral triazole, alkyne, or a cyclic guanidine.

144. The composition of any one of the preceding embodiments, wherein the oligonucleotide type comprises any of: cholesterol; L-carnitine (amide and carbamate bond); Folic acid; Gambogic acid; Cleavable lipid (1,2-dilaurin and ester bond); Insulin receptor ligand; CPP; Glucose (tri- and hex-antennary); or Mannose (tri- and hex-antennary, alpha and beta).

145. The composition of any one of the preceding embodiments, wherein the oligonucleotide type is

any oligonucleotide listed in Table A1.

146. The composition of any one of the preceding embodiments, wherein each of the oligonucleotides comprises a chemical moiety conjugated to the oligonucleotide chain of the oligonucleotide optionally through a linker moiety, wherein the chemical moiety comprises a carbohydrate moiety, a peptide moiety, a receptor ligand moiety, or a moiety having the structure of $-N(R^1)_2$, $-N(R^1)_3$, or $-N=C(N(R^1)_2)_2$.

147. The composition of any one of the preceding embodiments, wherein each of the oligonucleotides comprises a chemical moiety conjugated to the oligonucleotide chain of the oligonucleotide optionally through a linker moiety, wherein the chemical moiety comprises a guanidine moiety.

148. The composition of any one of the preceding embodiments, wherein each of the oligonucleotides comprises a chemical moiety conjugated to the oligonucleotide chain of the oligonucleotide optionally through a linker moiety, wherein the chemical moiety comprises $-N=C(N(CH_3)_2)_2$.

149. The composition of any one of the preceding embodiments, wherein at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the oligonucleotides in the composition that have the base sequence of the particular oligonucleotide type are oligonucleotides of the particular oligonucleotide type.

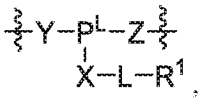
150. The composition of any one of the preceding embodiments, wherein at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the oligonucleotides in the composition that have the base sequence, pattern of backbone linkages, and pattern of backbone phosphorus modifications of the particular oligonucleotide type are oligonucleotides of the particular oligonucleotide type.

151. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the particular type are structurally identical.

152. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage is a phosphoramidate linkage.

153. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage comprises a guanidine moiety.

154. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula I:



I

or a salt form thereof, wherein:

P^L is P(=W), P, or P→B(R')$_3$;

W is O, N(–L–R^5), S or Se;

each of R^1 and R^5 is independently –H, –L–R', halogen, –CN, $-NO_2$, –L–Si(R')$_3$, –OR', –SR', or $-N(R')_2$;

each of X, Y and Z is independently –O–, –S–, –N(–L–R^5)–, or L;

each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, –C≡C–, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, –$C(R')_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –$S(O)_2$–, –$S(O)_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[$B(R')_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[$B(R')_3$]O–, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L;

each –Cy– is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Cy^L is independently an optionally substituted trivalent or tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each R' is independently –R, –C(O)R, –C(O)OR, or –$S(O)_2$R;

each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

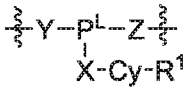
two R groups are optionally and independently taken together to form a covalent bond, or

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms, or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

155. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **I** or a salt form thereof.

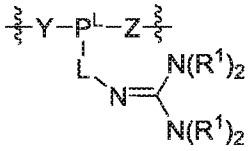
156. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **I-n-1** or a salt form thereof:



I-n-1

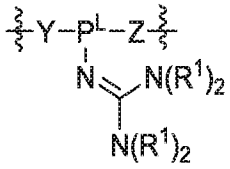
157. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **I-n-1** or a salt form thereof.

158. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **I-n-2** or a salt form thereof:



I-n-2

159. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **I-n-3** or a salt form thereof:



I-n-3

160. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **I-n-3** or a salt form thereof.

161. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **I-n-3** or a salt form thereof, wherein one R' from one $-N(R')_2$ and one R' from the other $-N(R')_2$ are taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

162. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **I-n-3** or a salt form thereof, wherein one R' from one $-N(R')_2$ and one R' from the other $-N(R')_2$ are taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

163. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **I-n-3** or a salt form thereof, wherein one R' from one $-N(R')_2$ and one R' from the other $-N(R')_2$ are taken together with their intervening atoms to form an

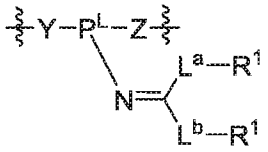
optionally substituted 5- membered monocyclic ring having no more than two nitrogen atoms.

164. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **I-n-3** or a salt form thereof, wherein one R' from one $-N(R')_2$ and one R' from the other $-N(R')_2$ are taken together with their intervening atoms to form an optionally substituted 5- membered monocyclic ring having no more than two nitrogen atoms.

165. The composition of any one of embodiments 159-162, wherein the ring formed is a saturated ring.

166. The composition of any one of embodiments 159-162, wherein the ring formed is a partially unsaturated ring.

167. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **I-n-4** or a salt form thereof:



I-n-4

168. The composition of embodiment 167, wherein L^a is a covalent bond.

169. The composition of embodiment 167, wherein L^a is $-N(R^1)-$.

170. The composition of embodiment 167, wherein L^a is $-N(R')-$.

171. The composition of embodiment 167, wherein L^a is $-N(R)-$.

172. The composition of embodiment 167, wherein L^a is $-S(O)-$.

173. The composition of embodiment 167, wherein L^a is $-S(O)_2-$.

174. The composition of embodiment 167, wherein L^a is $-S(O)_2N(R')-$.

175. The composition of any one of embodiments 167-174, wherein L^b is a covalent bond.

176. The composition of any one of embodiments 167-174, wherein L^b is $-N(R^1)-$.

177. The composition of any one of embodiments 167-174, wherein L^b is $-N(R')-$.

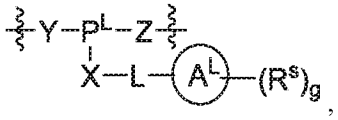
178. The composition of any one of embodiments 167-174, wherein L^b is $-N(R)-$.

179. The composition of any one of embodiments 167-174, wherein L^b is $-S(O)-$.

180. The composition of any one of embodiments 167-174, wherein L^b is $-S(O)_2-$.

181. The composition of any one of embodiments 167-174, wherein L^b is $-S(O)_2N(R')-$.

182. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II**:



II

or a salt form thereof, wherein:

P^L is P(=W), P, or P→B(R')$_3$;

W is O, N(–L–R^5), S or Se;

each of X, Y and Z is independently –O–, –S–, –N(–L–R^5)–, or L;

R^5 is –H, –L–R', halogen, –CN, –NO_2, –L–Si(R')$_3$, –OR', –SR', or –N(R')$_2$;

Ring A^L is an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms;

each R^s is independently –H, halogen, –CN, –N_3, –NO, –NO_2, –L–R', –L–Si(R)$_3$, –L–OR', –L–SR', –L–N(R')$_2$, –O–L–R', –O–L–Si(R)$_3$, –O–L–OR', –O–L–SR', or –O–L–N(R')$_2$;

g is 0-20;

each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L;

each –Cy– is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Cy^L is independently an optionally substituted trivalent or tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each R' is independently –R, –C(O)R, –C(O)OR, or –S(O)$_2$R;

each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl

having 1-10 heteroatoms, or

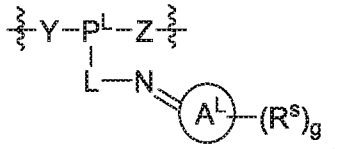
two R groups are optionally and independently taken together to form a covalent bond, or

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms, or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

183. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **II**, or a salt form thereof.

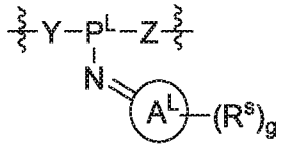
184. The composition any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II-a-1**:



II-a-1

or a salt form thereof.

185. The composition any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II-a-2**:

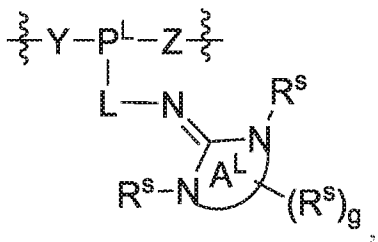


II-a-2

or a salt form thereof.

186. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **II-a-1** or **II-a-2**, or a salt form thereof.

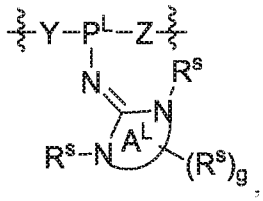
187. The composition of any one of embodiments 182-186, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II-b-1**:



II-b-1

or a salt form thereof, wherein g is 0-18.

188. The composition of any one of embodiments 182-187, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II-b-2**:



II-b-2

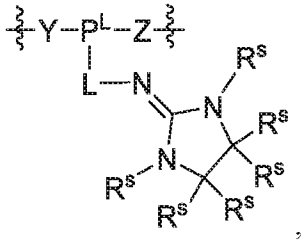
or a salt form thereof, wherein g is 0-18.

189. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **II-b-1** or **II-b-2**, or a salt form thereof.

190. The composition of any one of embodiments 182-188, wherein Ring A^L is an optionally substituted 3-20 membered monocyclic ring having 0-10 heteroatoms (in addition to the two nitrogen atoms for formula **II-b-1** or **II-b-2**).

191. The composition of any one of embodiments 182-188, wherein Ring A^L is an optionally substituted 5- membered monocyclic saturated ring.

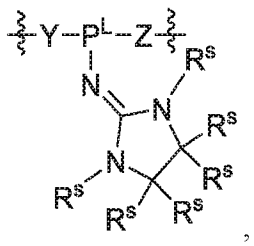
192. The composition of any one of embodiments 182-191, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II-c-1**:



II-c-1

or a salt form thereof, wherein g is 0-4.

193. The composition of any one of embodiments 182-193, wherein a non-negatively charged internucleotidic linkage has the structure of formula **II-c-2**:



II-c-2

or a salt form thereof, wherein g is 0-4.

194. The composition of any one of the preceding embodiments, wherein each non-negatively charged internucleotidic linkage independently has the structure of formula **II-c-1** or **II-c-2**, or a salt form thereof.

195. The composition of any one of embodiments 182-193, wherein each non-negatively charged internucleotidic linkage has the same structure.

196. The composition of any one of the preceding embodiments, wherein, if applicable, each internucleotidic linkage in the oligonucleotides of the plurality that is not a non-negatively charged internucleotidic linkage independently has the structure of formula **I**.

197. The composition of any one of the preceding embodiments, wherein each internucleotidic linkage in the oligonucleotides of the plurality independently has the structure of formula **I**.

198. The composition of any one of the preceding embodiments, wherein one or more P^L is P(=W).

199. The composition of any one of the preceding embodiments, wherein each P^L is independently P(=W).

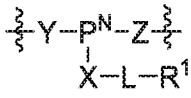
200. The composition of any one of the preceding embodiments, wherein one or more W is O.

201. The composition of any one of the preceding embodiments, wherein each W is O.

202. The composition of any one of the preceding embodiments, wherein one or more W is S.

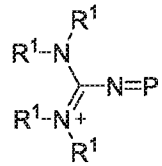
203. The composition of any one of the preceding embodiments, wherein one or more W is independently N(–L–R^5).

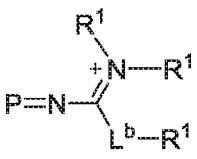
204. The composition of any one of the preceding embodiments, wherein one or more internucleotidic linkage independently has the structure of formula **III** or salt form thereof:



III

205. The composition of embodiment 204, wherein P^N is P(=N–L–R^5).

206. The composition of embodiment 204, wherein P^N is  Q^-.

207. The composition of embodiment 204, wherein P^N is  Q^-.

208. The composition of embodiment 207, wherein L^a is a covalent bond.

209. The composition of embodiment 207, wherein L^a is $-N(R^1)-$.

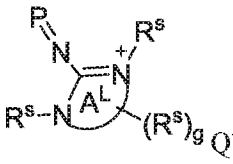
210. The composition of embodiment 207, wherein L^a is $-N(R')-$.

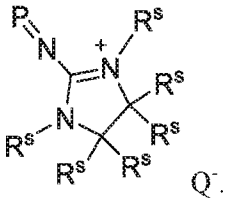
211. The composition of embodiment 207, wherein L^a is $-N(R)-$.

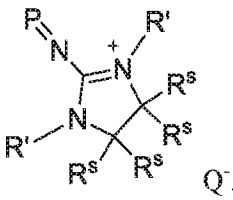
212. The composition of embodiment 207, wherein L^a is $-S(O)-$.

213. The composition of embodiment 207, wherein L^a is $-S(O)_2-$.

214. The composition of embodiment 207, wherein L^a is $-S(O)_2N(R')-$.

215. The composition of embodiment 204, wherein P^N is  Q^-.

216. The composition of embodiment 204, wherein P^N is  Q^-.

217. The composition of embodiment 204, wherein P^N is  Q^-.

218. The composition of any one of the preceding embodiments, wherein one or more Y is O.

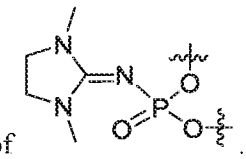
219. The composition of any one of the preceding embodiments, wherein each Y is O.

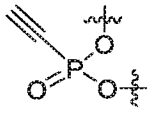
220. The composition of any one of the preceding embodiments, wherein one or more Z is O.

221. The composition of any one of the preceding embodiments, wherein each Z is O.

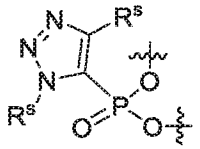
222. The composition of any one of the preceding embodiments, wherein one or more X is O.

223. The composition of any one of the preceding embodiments, wherein one or more X is S.

224. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of  .

225. The composition of any one of the preceding embodiments, wherein a non-negatively charged internucleotidic linkage has the structure of  .

226. The composition of any one of the preceding embodiments, wherein a non-negatively charged

internucleotidic linkage has the structure of  .

227. The composition of any one of the preceding embodiments, wherein for each internucleotidic linkage of formula I or a salt fore thereof that is not a non-negatively charged internucleotidic linkage, X is independently O or S, and $-L-R^1$ is $-H$ (natural phosphate linkage or phosphorothioate linkage, respectively).

228. The composition of any one of the preceding embodiments, wherein each phosphorothioate linkage, if any, in the oligonucleotides of the plurality is independently a chirally controlled internucleotidic linkage.

229. The composition of any one of the preceding embodiments, wherein at least one non-negatively charged internucleotidic linkage is a chirally controlled internucleotidic linkage.

230. The composition of any one of the preceding embodiments, wherein at least one non-negatively charged internucleotidic linkage is a chirally controlled internucleotidic linkage.

231. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality comprise a targeting moiety wherein the targeting moiety is independently connected to an oligonucleotide backbone through a linker.

232. The composition of embodiment 231, wherein the targeting moiety is a carbohydrate moiety.

233. The composition of embodiment 231 or 232, wherein the targeting moiety comprises or is a GalNac moiety.

234. The composition of any one of the preceding embodiments, wherein the oligonucleotides of the plurality comprise a lipid moiety wherein the lipid moiety is independently connected to an oligonucleotide backbone through a linker.

235. The composition of any one of the preceding embodiments, wherein oligonucleotides of the plurality exist as salts, wherein one or more non-neutral internucleotidic linkages at the condition of the composition independently exist as a salt form.

236. The composition of any one of the preceding embodiments, wherein oligonucleotides of the plurality exist as salts, wherein one or more negatively-charged internucleotidic linkages at the condition of the composition independently exist as a salt form.

237. The composition of any one of the preceding embodiments, wherein oligonucleotides of the plurality exist as salts, wherein one or more negatively-charged internucleotidic linkages at the condition of the composition independently exist as a metal salt.

238. The composition of any one of the preceding embodiments, wherein oligonucleotides of the

plurality exist as salts, wherein each negatively-charged internucleotidic linkage at the condition of the composition independently exists as a metal salt.

239. The composition of any one of the preceding embodiments, wherein oligonucleotides of the plurality exist as salts, wherein each negatively-charged internucleotidic linkage at the condition of the composition independently exists as sodium salt.

240. The composition of any one of the preceding embodiments, wherein oligonucleotides of the plurality exist as salts, wherein each negatively-charged internucleotidic linkage is independently a natural phosphate linkage (the neutral form of which is −O−P(O)(OH)−O) or phosphorothioate internucleotidic linkage (the neutral form of which is −O−P(O)(SH)−O).

241. An oligonucleotide composition, comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

wherein:

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 chirally controlled internucleotidic linkages; and

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 non-negatively charged internucleotidic linkages.

242. The composition of any one of the preceding embodiments, wherein at least one non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage.

243. The composition of any one of the preceding embodiments, wherein a neutral internucleotidic linkage is or comprises a triazole, neutral triazole, alkyne, or a cyclic guanidine.

244. The oligonucleotide composition of any one of the preceding embodiments, wherein the oligonucleotide composition is characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

245. The oligonucleotide composition of any one of the preceding embodiments, wherein the transcript is a Dystrophin transcript.

246. The oligonucleotide composition of any one of the preceding embodiments, wherein the splicing of the transcript is altered such that the level of skipping of exon 45, 51, or 53, or multiple exons is increased.

247. The oligonucleotide composition of any one of the preceding embodiments, wherein the oligonucleotide composition is capable of mediating knockdown of a target gene.

248. An oligonucleotide composition, comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

wherein:

the oligonucleotides of the plurality comprise cholesterol; L-carnitine (amide and carbamate bond); Folic acid; Cleavable lipid (1,2-dilaurin and ester bond); Insulin receptor ligand; Gambogic acid; CPP; Glucose (tri- and hex-antennary); or Mannose (tri- and hex-antennary, alpha and beta).

249. The composition of embodiment 248, wherein the oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 chirally controlled internucleotidic linkages.

250. The composition of any one of the preceding embodiments, wherein the oligonucleotide composition is characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

251. The composition of any one of the preceding embodiments, wherein the transcript is a Dystrophin transcript.

252. The composition of any one of the preceding embodiments, wherein the splicing of the transcript is altered such that the level of skipping of exon 45, 51, or 53, or multiple exons is increased.

253. The composition of any one of the preceding embodiments, wherein the oligonucleotide composition is capable of mediating knockdown of a target gene.

254. The composition of any one of the preceding embodiments, wherein each heteroatom is independently boron, nitrogen, oxygen, silicon, sulfur, or phosphorus.

255. A pharmaceutical composition comprising an oligonucleotide composition of any one of the preceding embodiments and a pharmaceutically acceptable carrier.

256. A method for altering splicing of a target transcript, comprising administering an oligonucleotide composition of any one of the preceding embodiments.

257. The method of embodiment 256, wherein the splicing of the target transcript is altered relative to absence of the composition.

258. The method of any one of the preceding embodiments, wherein the alteration is that one or more exon is skipped at an increased level relative to absence of the composition.

259. The method of any one of the preceding embodiments, wherein the target transcript is pre-mRNA of dystrophin.

260. The method of any one of the preceding embodiments, wherein exon 45 of dystrophin is skipped at an increased level relative to absence of the composition.

261. The method of any one of the preceding embodiments, wherein exon 51 of dystrophin is skipped at an increased level relative to absence of the composition.

262. The method of any one of embodiments 256-259, wherein exon 53 of dystrophin is skipped at an increased level relative to absence of the composition.

263. The method of any one of the preceding embodiments, wherein a protein encoded by the mRNA with the exon skipped provides one or more functions better than a protein encoded by the corresponding mRNA without the exon skipping.

264. A method for treating muscular dystrophy, Duchenne (Duchenne's) muscular dystrophy (DMD), or Becker (Becker's) muscular dystrophy (BMD), comprising administering to a subject susceptible thereto or suffering therefrom a composition of any one of the preceding embodiments.

265. A method for treating muscular dystrophy, Duchenne (Duchenne's) muscular dystrophy (DMD), or Becker (Becker's) muscular dystrophy (BMD), comprising administering to a subject susceptible thereto or suffering therefrom a composition comprising any oligonucleotide disclosed herein.

266. A method for treating muscular dystrophy, Duchenne (Duchenne's) muscular dystrophy (DMD), or Becker (Becker's) muscular dystrophy (BMD), comprising (a) administering to a subject susceptible thereto or suffering therefrom a composition comprising any oligonucleotide disclosed herein, and (b) administering to the subject additional treatment which is capable of preventing, treating, ameliorating or slowing the progress of muscular dystrophy, Duchenne (Duchenne's) muscular dystrophy (DMD), or Becker (Becker's) muscular dystrophy (BMD).

267. The method of embodiment 266, wherein the additional treatment is a second oligonucleotide.

268. The composition of any of the preceding embodiments, wherein the transcript splicing system comprises a myoblast or myotubule.

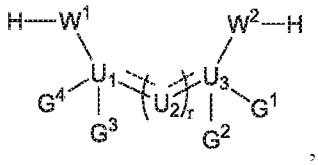
269. The composition of any of the preceding embodiments, wherein the transcript splicing system comprises a myoblast cell.

270. The composition of any of the preceding embodiments, wherein the transcript splicing system comprises a myoblast cell, which is contacted with the composition after 0, 4 or 7 days of pre-differentiation.

271. A composition comprising a combination comprising: (a) a first composition of any of the

preceding embodiments; (b) a second composition of any of the preceding embodiments; and, optionally (c) a third composition of any of the preceding embodiments, wherein the first, second and third compositions are different.

272. A method for preparing an oligonucleotide or an oligonucleotide composition thereof, comprising providing a compound having the structure of:

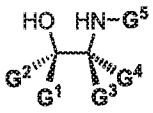
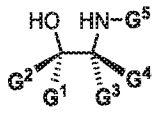
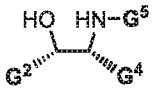
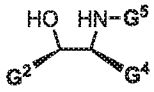
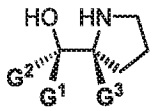
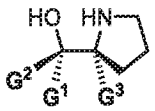
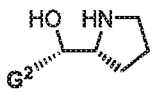
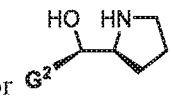


Formula 3-I

or a salt thereof.

273. A method for preparing an oligonucleotide or an oligonucleotide composition thereof, comprising providing a compound having the structure of:

or a salt thereof.

274. A method for preparing an oligonucleotide or an oligonucleotide composition thereof, comprising providing a compound having the structure of  ,  ,  ,  ,  ,  ,  , or  , or a salt thereof.

275. The method of any one of embodiments 272-274, wherein the compound is stereochemically pure.

276. The method of any one of embodiments 272-275, wherein the compound is a compound of Tables CA-1, CA-2, CA-3, CA-4, CA-5, CA-6, CA-7, CA-8, CA-9, CA-10, CA-11, or CA-12, or a related diastereomer or enantiomer thereof.

277. The method of any one of embodiments 272-275, wherein the compound is a compound of Table CA-2 or a related diastereomer or enantiomer thereof.

278. The method of any one of embodiments 272-275, wherein the compound is a compound of Table CA-3 or a related diastereomer or enantiomer thereof.

279. The method of any one of embodiments 272-275, wherein the compound is a compound of Table

CA-4 or a related diastereomer or enantiomer thereof.

280. The method of any one of embodiments 272-275, wherein the compound is a compound of Table CA-5 or a related diastereomer or enantiomer thereof.

281. The method of any one of embodiments 272-275, wherein the compound is a compound of Table CA-6 or a related diastereomer or enantiomer thereof.

282. The method of any one of embodiments 272-275, wherein the compound is a compound of Table CA-7 or a related diastereomer or enantiomer thereof.

283. The method of any one of embodiments 272-275, wherein the compound is a compound of Table CA-8 or a related diastereomer or enantiomer thereof.

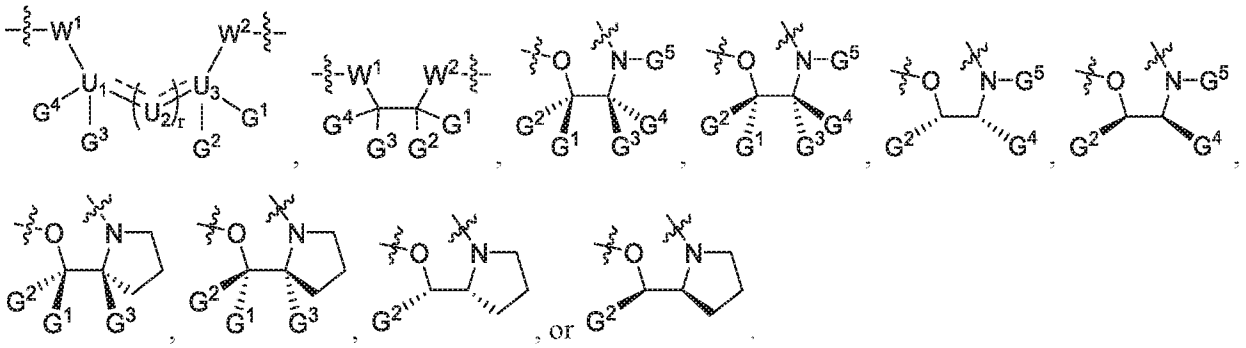
284. The method of any one of embodiments 272-275, wherein the compound is a compound of Table CA-9 or a related diastereomer or enantiomer thereof.

285. The method of any one of embodiments 272-275, wherein the compound is a compound of Table CA-10 or a related diastereomer or enantiomer thereof.

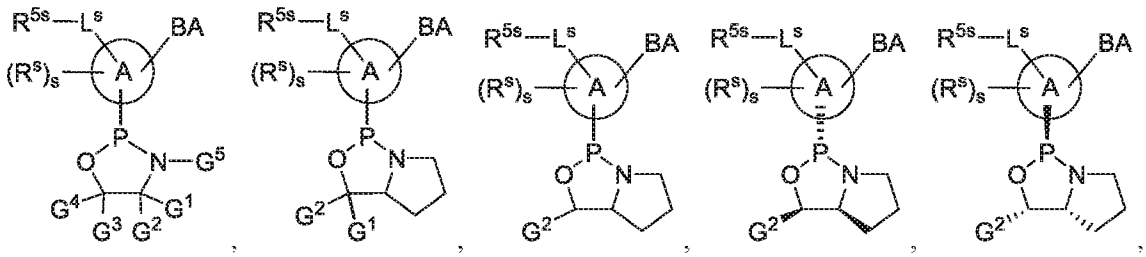
286. The method of any one of embodiments 272-275, wherein the compound is a compound of Table CA-11 or a related diastereomer or enantiomer thereof.

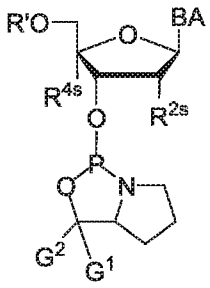
287. The method of any one of embodiments 272-275, wherein the compound is a compound of Table CA-12 or a related diastereomer or enantiomer thereof.

288. A method for preparing an oligonucleotide or an oligonucleotide composition thereof, comprising providing a phosphoramidite compound comprising a chiral auxiliary moiety having the structure of



289. A method for preparing an oligonucleotide or an oligonucleotide composition thereof, comprising providing a phosphoramidite compound having the structure of:





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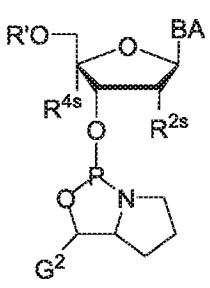

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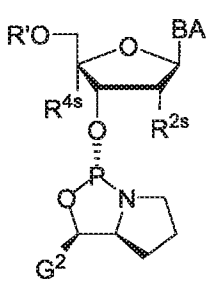

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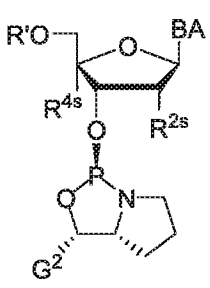

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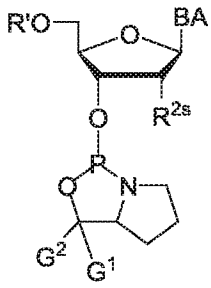

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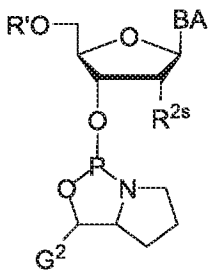

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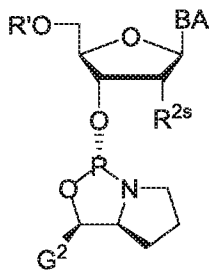

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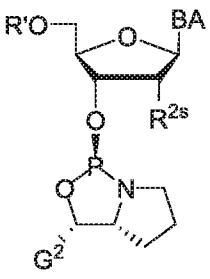


, or a salt thereof.

290. The method of any one of embodiments 272-289, wherein W^1 is $-NG^5-$.

291. The method of any one of embodiments 272-290, wherein G^5 and one of G^3 and G^4 are taken together to form an optionally substituted 3-8 membered saturated ring having 0-3 heteroatoms in addition to the nitrogen of $-NG^5-$.

292. The method of any one of embodiments 272-290, wherein G^5 and one of G^3 and G^4 are taken together to form an optionally substituted 5-membered saturated ring having no heteroatoms in addition to the nitrogen of $-NG^5-$.

293. The method of any one of embodiments 272-292, wherein W^2 is $-O-$.

294. The method of any one of embodiments 272-293, wherein G^2 comprises an electron-withdrawing group.

295. The method of any one of embodiments 272-293, wherein G^2 is methyl substituted with one or more electron-withdrawing groups.

296. The method of any one of embodiments 294-295, wherein an electron-withdrawing group is $-CN$, $-NO_2$, halogen, $-C(O)R^1$, $-C(O)OR'$, $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$, or aryl or heteroaryl substituted with one or more of $-CN$, $-NO_2$, halogen, $-C(O)R^1$, $-C(O)OR'$, $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$.

297. The method of any one of embodiments 294-295, wherein an electron-withdrawing group is $-CN$, $-NO_2$, halogen, $-C(O)R^1$, $-C(O)OR'$, $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$, or phenyl substituted with one or more of $-CN$, $-NO_2$, halogen, $-C(O)R^1$, $-C(O)OR'$, $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$.

298. The method of any one of embodiments 294-295, wherein an electron-withdrawing group is

–CN, –NO_2, halogen, –$C(O)R^1$, –C(O)OR', –$C(O)N(R')_2$, –$S(O)R^1$, –$S(O)_2R^1$, –$P(W)(R^1)_2$, –$P(O)(R^1)_2$, –$P(O)(OR')_2$, or –$P(S)(R^1)_2$.

299. The method of any one of embodiments 272-294, wherein G^2 is –L'–L"–R', wherein L' is –$C(R)_2$– or optionally substituted –CH_2– , and L" is a covalent bond, –P(O)(R')–, –P(O)(R')O–, –P(O)(OR')–, –P(O)(OR')O–, –P(O)[N(R')]–, –P(O)[N(R')]O–, –P(O)[N(R')][N(R')]–, –P(S)(R')–, –$S(O)_2$–, –$S(O)_2$–, –$S(O)_2O$–, –S(O)–, –C(O)–, or –C(O)N(R')–.

300. The method of any one of embodiments 272-294, wherein G^2 is –L'–L"–R', wherein L' is –$C(R)_2$– or optionally substituted –CH_2– , and L" is –P(O)(R')–, –P(O)(R')O–, –P(O)(OR')–, –P(O)(OR')O–, –P(O)[N(R')]–, –P(O)[N(R')]O–, –P(O)[N(R')][N(R')]–, –P(S)(R')–, –$S(O)_2$–, –$S(O)_2$–, –$S(O)_2O$–, –S(O)–, –C(O)–, or –C(O)N(R')–.

301. The method of any one of embodiments 272-300, wherein G^2 is –L'–$S(O)_2$R'.

302. The method of embodiment 301, wherein R' is optionally substituted C_{1-6} aliphatic.

303. The method of embodiment 301, wherein R' is optionally substituted C_{1-6} alkyl.

304. The method of embodiment 301, wherein R' is methyl, isopropyl or t-butyl.

305. The method of embodiment 301, wherein R' is optionally substituted phenyl.

306. The method of embodiment 301, wherein R' is phenyl.

307. The method of embodiment 301, wherein R' is substituted phenyl.

308. The method of any one of embodiments 272-300, wherein G^2 is –L'–$P(O)(R')_2$.

309. The method of embodiment 308, wherein one R' is optionally substituted C_{1-6} aliphatic.

310. The method of embodiment 308, wherein one R' is optionally substituted C_{1-6} alkyl.

311. The method of embodiment 308, wherein one R' is optionally substituted phenyl.

312. The method of embodiment 308, wherein one R' is phenyl.

313. The method of embodiment 308, wherein one R' is substituted phenyl.

314. The method of any one of embodiments 309-313, wherein the other R' is optionally substituted C_{1-6} aliphatic.

315. The method of any one of embodiments 309-313, wherein the other R' is optionally substituted C_{1-6} alkyl.

316. The method of any one of embodiments 309-313, wherein the other R' is optionally substituted phenyl.

317. The method of any one of embodiments 309-313, wherein the other R' is phenyl.

318. The method of any one of embodiments 309-313, wherein the other R' is substituted phenyl.

319. The method of any one of embodiments 299-318, wherein L' is –$C(R')_2$–.

320. The method of any one of embodiments 299-318, wherein L' is optionally substituted –CH_2–.

321. The method of any one of embodiments 299-318, wherein L' is –CH_2–.

322. The method of any one of embodiments 272-321, comprising providing one or more additional compounds, wherein each compound is independently a compound of any one of embodiments 272-321.

323. The method of embodiment 322, wherein an additional compound has a different structure than the compound.

324. The method of embodiment 322, wherein in an additional compound, G^2 is $-L'-Si(R)_3$, wherein each R is independently not –H.

325. The method of embodiment 322, wherein in an additional compound, G^2 is $-CH_2SiCH_3Ph_2$.

326. The method of any one of embodiments 272-325, comprising one or more cycles, each of which independently comprises or consisting of:

1) deblocking;

2) coupling;

3) optionally a first capping;

4) modifying; and

5) optionally a second capping.

327. A method for preparing an oligonucleotide or a composition thereof, comprising one or more cycles, each of which independently comprises or consisting of:

1) deblocking;

2) coupling;

3) optionally a first capping;

4) modifying; and

5) optionally a second capping.

328. The method of any one of embodiments 326-327, wherein at least one cycle comprises or consists of 1) to 5).

329. The method of any one of embodiments 326-328, wherein the steps are performed sequentially from 1) to 5).

330. The method of any one of embodiments 326-329, wherein the cycles are performed until a desired length of an oligonucleotide is achieved.

331. The method of any one of embodiments 326-330, wherein deblocking removes a protection group on 5'--OH and provides a free 5'–OH.

332. The method of embodiment 331, wherein the protection group is R'-C(O)–.

333. The method of embodiment 331, wherein the protection group is DMTr.

334. The method of any one of embodiments 331-333, comprising contacting the oligonucleotides to be de-blocked with an acid.

335. The method of any one of embodiments 272-334, comprising a coupling that comprises: 1)

providing a phosphoramidite; and 2) reacting the phosphoramidite with an oligonucleotide, wherein a P–O bond is formed between the phosphorus of the phosphoramidite and the 5'–OH of the oligonucleotide.

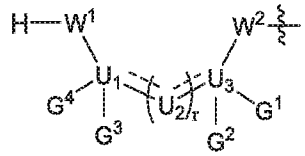
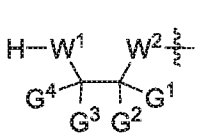
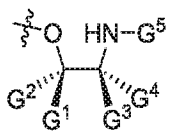
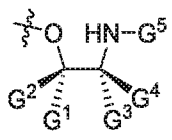
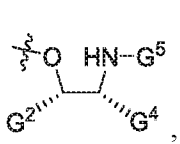
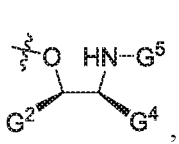
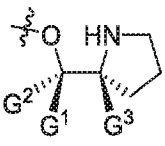
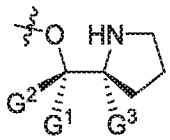
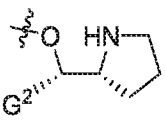
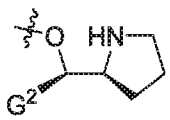
336. The method of any one of embodiments 272-335, comprising a coupling that comprises: 1) providing a phosphoramidite; and 2) reacting the phosphoramidite with an oligonucleotide, wherein a P–O bond is formed between the phosphorus of the phosphoramidite and the 5'–OH of the oligonucleotide, wherein the phosphoramidite is a compound of any one of embodiments 288-321.

337. The method of any one of embodiments 272-336, comprising a coupling that comprises: 1) providing a phosphoramidite; and 2) reacting the phosphoramidite with an oligonucleotide, wherein a P–O bond is formed between the phosphorus of the phosphoramidite and the 5'–OH of the oligonucleotide, wherein the phosphoramidite is a compound of any one of embodiments 288-293, wherein G^2 is $-L'-Si(R)_3$, wherein each R is independently not –H.

338. The method of embodiment 337, wherein G^2 is $-CH_2SiCH_3Ph_2$.

339. The method of any one of embodiments 336-338, wherein the coupling forms an internucleotidic linkage with a stereoselectivity of 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more.

340. The method of embodiment 339, wherein the internucleotidic linkage formed is an internucleotidic linkage of formula I or a salt form thereof.

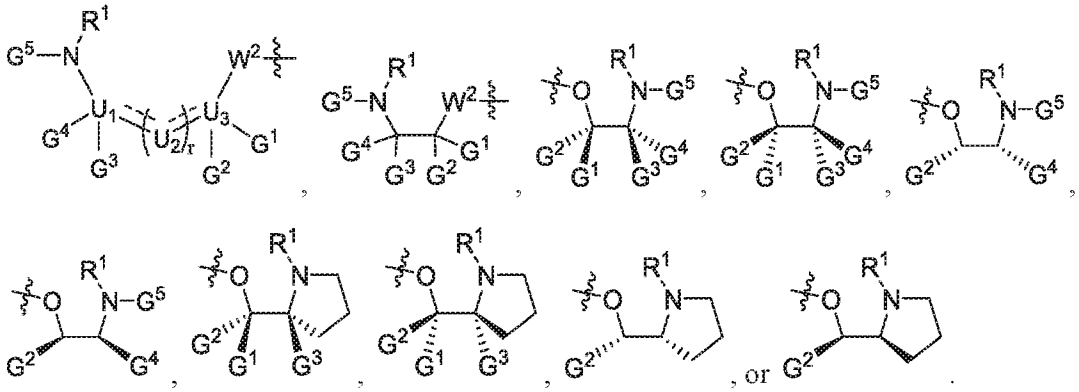
341. The method of embodiment 340, wherein $-X-L-R^1$ is  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

342. The method of embodiment 340 or 341, wherein P^L is P.

343. The method of any one of embodiments 272-342, comprising a coupling that comprises: 1) providing a phosphoramidite; and 2) reacting the phosphoramidite with an oligonucleotide, wherein a P–O bond is formed between the phosphorus of the phosphoramidite and the 5'–OH of the oligonucleotide, wherein the phosphoramidite is a standard phosphoramidite for oligonucleotide synthesis wherein the phosphorus atom is bonded to a protected nucleoside, $-N(i\text{-}Pr)_2$, and 2-cyanoethyl.

344. The method of any one of embodiments 272-343, comprising a first capping comprises: 1) providing an acylating reagent, and 2) contacting an oligonucleotide with the acylating reagent, wherein the first capping caps an amino group of an internucleotidic linkage.

345. The method of any one of embodiments 272-344, comprising a first capping which forms an internucleotidic linkage of formula I or a salt form thereof, wherein −X−L−R^1 is



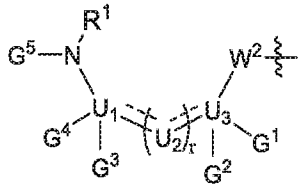
346. The method of embodiment 345, wherein P^L is P and R^1 is −C(O)R.

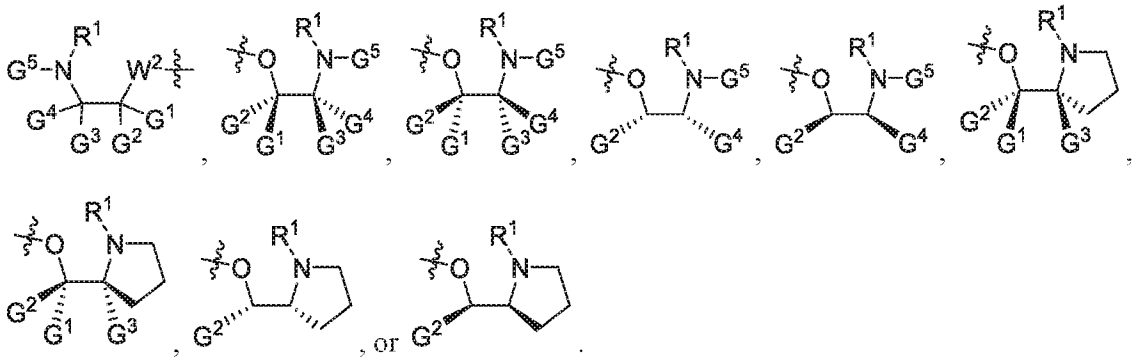
347. The method of any one of embodiments 272-346, wherein a first capping is performed after each coupling of embodiment 339.

348. The method of any one of embodiments 272-347, comprising a modifying step which is or comprises sulfurization.

349. The method of embodiment 348, wherein the sulfurization installs =S on a linkage phosphorus.

350. The method of embodiment 348 or 349, wherein the sulfurization forms an internucleotidic linkage of formula I or a salt form thereof, wherein P^L is P(=S).

351. The method of embodiment 350, wherein −X−L−R^1 is  ,

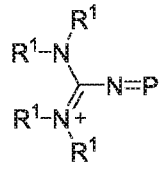
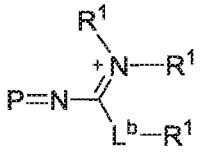
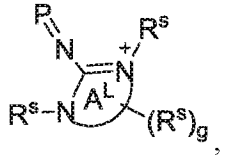
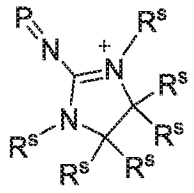
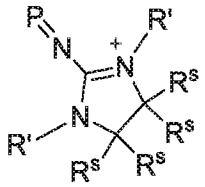


352. The method of embodiment 351, wherein R^1 is −C(O)R.

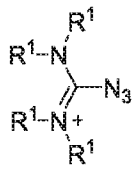
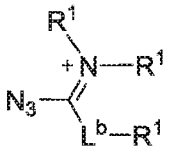
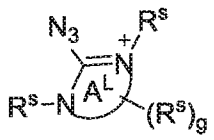
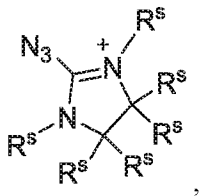
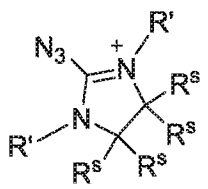
353. The method of any one of embodiments 272-352, comprising a modifying step which is or comprises oxidation.

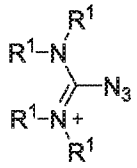
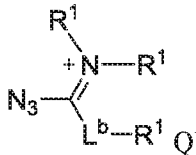
354. The method of embodiment 348, wherein the sulfurization installs =O on a linkage phosphorus.

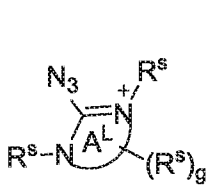
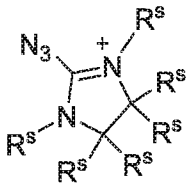
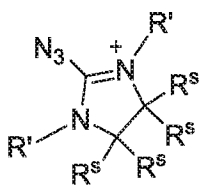
355. The method of any one of embodiments 272-354, comprising a modifying step which installs =N–L–R^5 on a linkage phosphorus.

356. The method of any one of embodiments 272-354, comprising a modifying step which converts a linkage phosphorus into  ,  ,  ,  , or  .

357. The method of any one of embodiments 272-356, comprising a modifying step which comprises contact the oligonucleotide with an azido imidazolinium salt.

358. The method of any one of embodiments 272-356, comprising a modifying step which comprises contact the oligonucleotide with a compound comprising  ,  ,  ,  , or  .

359. The method of any one of embodiments 272-356, comprising a modifying step which comprises contact the oligonucleotide with a compound having the structure of  Q^-,  Q^-,

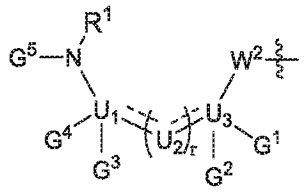
Q^-, Q^-, or Q^-, wherein Q^- is an anion.

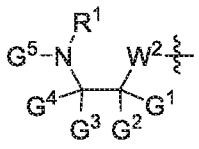
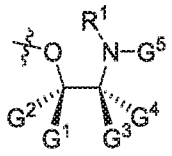
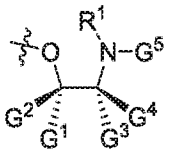
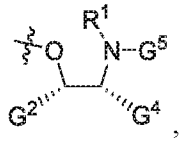
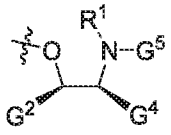
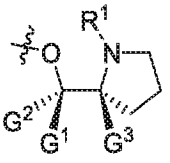
360. The method of embodiment 359, wherein Q^- is F^-, Cl^-, Br^-, BF_4^-, PF_6^-, TfO^-, Tf_2N^-, AsF_6^-, ClO_4^-, or SbF_6^-.

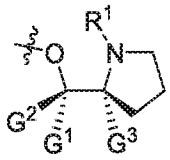
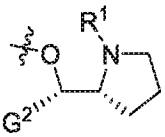
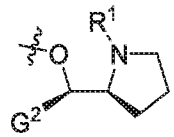
361. The method of embodiment 360, wherein Q^- is PF_6^-.

362. The method of any one of embodiments 272-362, wherein a modifying step forms an internucleotidic linkage of formula I or a salt form thereof, wherein P^L is $P(=N\text{–}L\text{–}R^5)$.

363. The method of any one of embodiments 272-362, wherein a modifying step forms an internucleotidic linkage of formula III or a salt form thereof.

364. The method of embodiment 362 or 363, wherein $-X\text{–}L\text{–}R^1$ is  ,






 ,


 , or  .

365. The method of embodiment 364, wherein R^1 is $-C(O)R$.

366. The method of any one of embodiments 272-365, comprising a second capping which caps free 5'–OH.

367. The method of any one of embodiments 272-366, comprising a second capping which caps free 5'–OH, wherein a second capping is performed in each cycle.

368. The method of any one of embodiments 272-366, comprising a second capping which caps free 5'–OH, wherein a second capping is performed in each cycle that is followed by another cycle.

369. The method of any one of embodiments 366-368, wherein a 5'–OH is capped as –OAc.

370. The method of any one of embodiments 272-369, wherein the oligonucleotide is attached to a solid support.

371. The method of embodiment 370, wherein the solid support is CPG.

372. The method of any one of embodiments 370-371, comprising a contact in which the oligonucleotide is contacted with a base.

373. The method of embodiment 372, wherein the contact is performed substantially absent of water.

374. The method of embodiment 372 or 373, wherein the contact is after the oligonucleotide length is achieved before deprotection and cleavage of oligonucleotide.

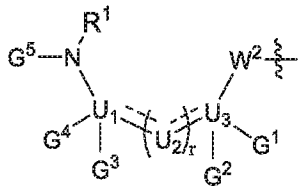
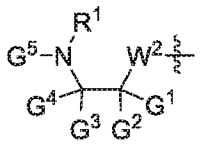
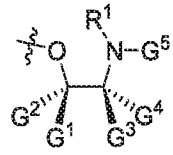
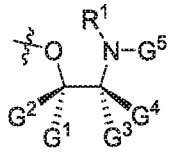
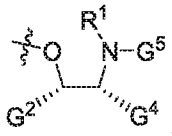
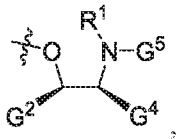
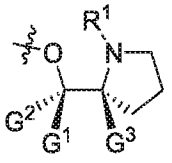
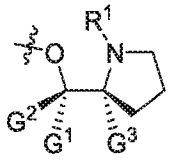
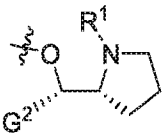
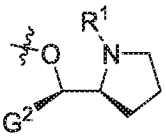
375. The method of any one of embodiments 372-374, wherein the base is an amine base having the structure of NR_3.

376. The method of embodiment 375, wherein the base is triethylamine.

377. The method of embodiment 375, wherein the base is *N*, *N*-diethylamine.

378. The method of any one of embodiments 372-377, wherein the contact removes a chiral auxiliary.

379. The method of any one of embodiments 372-378, wherein the contact removes a $-X-L-R^1$ group.

380. The method of embodiment 379, wherein $-X-L-R^1$ is  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

381. The method of any one of embodiments 372-380, wherein the contact forms an internucleotidic linkage of formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, or **II-d-2**, wherein P^L is P(O).

382. The method of any one of embodiments 364-381, wherein G^2 comprises an electron-withdrawing group.

383. The method of any one of embodiments 364-382, wherein G^2 is methyl substituted with one or more electron-withdrawing groups.

384. The method of any one of embodiments 382-383, wherein an electron-withdrawing group is $-CN$, $-NO_2$, halogen, $-C(O)R^1$, $-C(O)OR'$, $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$, or aryl or heteroaryl substituted with one or more of $-CN$, $-NO_2$, halogen,

$-C(O)R^1$, $-C(O)OR'$, $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$.

385. The method of any one of embodiments 382-383, wherein an electron-withdrawing group is $-CN$, $-NO_2$, halogen, $-C(O)R^1$, $-C(O)OR'$, $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$, or phenyl substituted with one or more of $-CN$, $-NO_2$, halogen, $-C(O)R^1$, $-C(O)OR'$, $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$.

386. The method of any one of embodiments 382-383, wherein an electron-withdrawing group is $-CN$, $-NO_2$, halogen, $-C(O)R^1$, $-C(O)OR'$, $-C(O)N(R')_2$, $-S(O)R^1$, $-S(O)_2R^1$, $-P(W)(R^1)_2$, $-P(O)(R^1)_2$, $-P(O)(OR')_2$, or $-P(S)(R^1)_2$.

387. The method of any one of embodiments 364-386, wherein G^2 is $-L'-L''-R'$, wherein L' is $-C(R)_2-$ or optionally substituted $-CH_2-$, and L'' is a covalent bond, $-P(O)(R')-$, $-P(O)(R')O-$, $-P(O)(OR')-$, $-P(O)(OR')O-$, $-P(O)[N(R')]-$, $-P(O)[N(R')]O-$, $-P(O)[N(R')][N(R')]-$, $-P(S)(R')-$, $-S(O)_2-$, $-S(O)_2-$, $-S(O)_2O-$, $-S(O)-$, $-C(O)-$, or $-C(O)N(R')-$.

388. The method of any one of embodiments 364-386, wherein G^2 is $-L'-L''-R'$, wherein L' is $-C(R)_2-$ or optionally substituted $-CH_2-$, and L'' is $-P(O)(R')-$, $-P(O)(R')O-$, $-P(O)(OR')-$, $-P(O)(OR')O-$, $-P(O)[N(R')]-$, $-P(O)[N(R')]O-$, $-P(O)[N(R')][N(R')]-$, $-P(S)(R')-$, $-S(O)_2-$, $-S(O)_2-$, $-S(O)_2O-$, $-S(O)-$, $-C(O)-$, or $-C(O)N(R')-$.

389. The method of any one of embodiments 364-388, wherein G^2 is $-L'-S(O)_2R'$.

390. The method of embodiment 389, wherein R' is optionally substituted C_{1-6} aliphatic.

391. The method of embodiment 389, wherein R' is optionally substituted C_{1-6} alkyl.

392. The method of embodiment 389, wherein R' is methyl, isopropyl or t-butyl.

393. The method of embodiment 389, wherein R' is optionally substituted phenyl.

394. The method of embodiment 389, wherein R' is phenyl.

395. The method of embodiment 389, wherein R' is substituted phenyl.

396. The method of any one of embodiments 364-388, wherein G^2 is $-L'-P(O)(R')_2$.

397. The method of embodiment 396, wherein one R' is optionally substituted C_{1-6} aliphatic.

398. The method of embodiment 396, wherein one R' is optionally substituted C_{1-6} alkyl.

399. The method of embodiment 396, wherein one R' is optionally substituted phenyl.

400. The method of embodiment 396, wherein one R' is phenyl.

401. The method of embodiment 396, wherein one R' is substituted phenyl.

402. The method of any one of embodiments 397-401, wherein the other R' is optionally substituted C_{1-6} aliphatic.

403. The method of any one of embodiments 397-401, wherein the other R' is optionally substituted C_{1-6} alkyl.

404. The method of any one of embodiments 309-313, wherein the other R' is optionally substituted phenyl.

405. The method of any one of embodiments 309-313, wherein the other R' is phenyl.

406. The method of any one of embodiments 309-313, wherein the other R' is substituted phenyl.

407. The method of any one of embodiments 387-406, wherein L' is $-C(R')_2-$.

408. The method of any one of embodiments 387-406, wherein L' is optionally substituted $-CH_2-$.

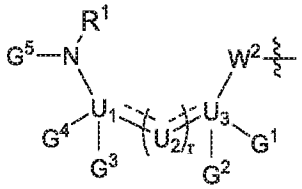
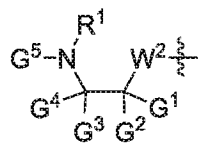
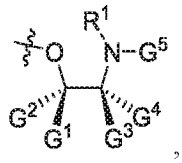
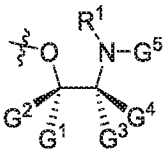
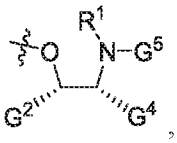
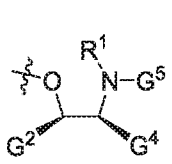
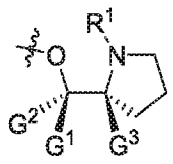
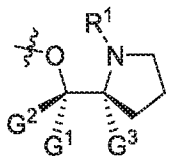
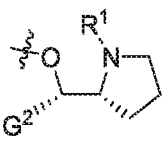
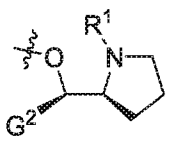
409. The method of any one of embodiments 387-406, wherein L' is $-CH_2-$.

410. The method of any one of embodiments 372-409, wherein the contact removes 2'-cyanoethyl.

411. The method of any one of embodiments 372-410, wherein the contact forms a natural phosphate linkage or a salt form thereof.

412. The method of any one of embodiments 272-410, comprising removing of another chiral auxiliary or group that having a different structure than that of any one of embodiments 378-410.

413. The method of any one of embodiments 272-410, comprising removing of











, wherein G^2 is $-L'-Si(R)_3$, wherein each R is independently not $-H$.

414. The method of embodiment 413, wherein G^2 is $-CH_2SiCH_3Ph_2$.

415. The method of any one of embodiments 412-414, comprising contacting an oligonucleotide with a fluoride.

416. The method of any one of embodiments 412-414, comprising contacting an oligonucleotide with a solution comprising TEA-HF and a base.

417. The method of any one of embodiments 272-416, comprising cleaving oligonucleotide from a solid support.

418. The method of any one of embodiments 272-417, wherein the oligonucleotide or a composition thereof is an oligonucleotide or composition of any one of embodiments 1-254.

419. The compound of any one of embodiments 272-321, or a related diastereomer or enantiomer.

420. An oligonucleotide, wherein the oligonucleotide is, WV-20104, WV-20103, WV-20102, WV-20101, WV-20100, WV-20099, WV-20098, WV-20097, WV-20096, WV-20095, WV-20094, WV-20106, WV-20119, WV-20118, WV-13739, WV-13740, WV-9079, WV-9082, WV-9100, WV-9096, WV-9097, WV-9106, WV-9133, WV-9148, WV-9154, WV-9898, WV-9899, WV-9900, WV-9906, WV-9907, WV-9908, WV-9909, WV-9756, WV-9757, WV-9517, WV-9714, WV-9715, WV-9519, WV-9521, WV-9747, WV-9748, WV-9749, WV-9897, WV-9898, WV-9900, WV-9899, WV-9906, WV-9912, WV-9524, WV-9912, WV-9906, WV-9900, WV-9899, WV-9899, WV-9898, WV-9898, WV-9898, WV-9898, WV-9898, WV-9897, WV-9897, WV-9897, WV-9897, WV-9897, WV-9747, WV-9714, WV-9699, WV-9517, WV-9517, WV-13409, WV-13408, WV-12887, WV-12882, WV-12881, WV-12880, WV-12880, WV-WV12880, WV-12878, WV-12877, WV-12877, WV-12876, WV-12873, WV-12872, WV-12559, WV-12559, WV-12558, WV-12558, WV-12557, WV-12556, WV-12556, WV-12555, WV-12555, WV-12554, WV-12553, WV-12129, WV-12127, WV-12125, WV-12123, WV-11342, WV-11342, WV-11341, WV-11341, WV-11340, WV-10672, WV-10671, WV-10670, WV-10461, WV-10455, WV-9897, WV-9898, WV-13826, WV-13827, WV-13835, WV-12880, WV-14344, WV-13864, WV-13835, WV-14791, WV-14344, WV-13754, WV-13766,, WV-11086, WV-11089, WV-17859, WV-17860, WV-20070, WV-20073, WV-20076, WV-20052, WV-20099, WV-20049, WV-20085, WV-20087, WV-20034, WV-20046, WV-20052, WV-20061, WV-20064, WV-20067, WV-20092, WV-20091, WV-20093, WV-20084, WV-9738, WV-9739, WV-9740, WV-9741, WV-15860, WV-15862, WV-11084, WV-11086, WV-11088, WV-11089, WV-14522, WV-14523, WV-17861, WV-17862, WV-13815, WV-13816, WV-13817, WV-13780, WV-17862, WV-17863, WV-17864, WV-17865, WV-17866, WV-20082, WV-20081, WV-20080, WV-20079, WV-20076, WV-20075, WV-20074, WV-20073, WV-20072, WV-20071, WV-20064, WV-20059, WV-20058, WV-20057, WV-20056, WV-20053, WV-20052, WV-20051, WV-20050, WV-20049, WV-20094, WV-20095, or a salt form thereof.

EQUIVALENTS

[001839] Having described some illustrative embodiments of the disclosure, it should be apparent to those skilled in the art that the foregoing is merely illustrative and not limiting, having been presented by way of example only. Numerous modifications and other illustrative embodiments are within the scope of one of ordinary skill in the art and are contemplated as falling within the scope of the disclosure. In particular, although many of the examples presented herein involve specific combinations of method acts or system elements, it should be understood that those acts and those elements may be combined in other ways to accomplish the same objectives. Acts, elements, and features discussed only in connection with one embodiment are not intended to be excluded from a similar role in other embodiments. Further, for the one or more means-plus-function limitations, if any, recited in the following claims, the means are not intended to be limited to the means disclosed herein for performing the recited function, but are intended to cover in scope any means, known now or later developed, for performing the recited function.

[001840] Use of ordinal terms such as "first", "second", "third", *etc*., in the claims to modify a claim element does not by itself connote any priority, precedence, or order of one claim element over another or the temporal order in which acts of a method are performed, but are used merely as labels to distinguish one claim element having a certain name from another element having a same name (but for use of the ordinal term) to distinguish the claim elements. Similarly, use of a), b), *etc*., or i), ii), *etc*. does not by itself connote any priority, precedence, or order of steps in the claims. Similarly, the use of these terms in the specification does not by itself connote any required priority, precedence, or order.

[001841] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present disclosure is not to be limited in scope by examples provided. Examples are intended as illustration of one or more aspect of an invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. Advantages and objects of the invention are not necessarily encompassed by each embodiment of the invention..

CLAIMS

1. An oligonucleotide composition, comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

wherein:

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 chirally controlled internucleotidic linkages; and

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 non-negatively charged internucleotidic linkages.

2. An oligonucleotide composition, comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

wherein:

oligonucleotides of the plurality comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 chirally controlled internucleotidic linkages; and

the oligonucleotide composition being characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

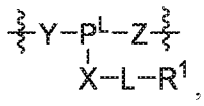
3. The oligonucleotide of claim 2, wherein the pattern of backbone linkages comprises at least one non-negatively charged internucleotidic linkage.

4. The oligonucleotide composition of claim 1, wherein when the oligonucleotide composition is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

5. The oligonucleotide of any one of claims 1-4, wherein one or more non-negatively charged internucleotidic linkage are independently chirally controlled.

6. The composition of claim 5, wherein a non-negatively charged internucleotidic linkage has the

structure of formula I:



I

or a salt form thereof, wherein:

P^L is P(=W), P, or P→B(R')$_3$;

W is O, N(–L–R^5), S or Se;

each of R^1 and R^5 is independently –H, –L–R', halogen, –CN, –NO_2, –L–Si(R')$_3$, –OR', –SR', or –N(R')$_2$;

X is –N(–L–R^5)–;

each of Y and Z is independently –O–, –S–, –N(–L–R^5)–, or L;

each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L;

each –Cy– is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Cy^L is independently an optionally substituted trivalent or tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each R' is independently –R, –C(O)R, –C(O)OR, or –S(O)$_2$R;

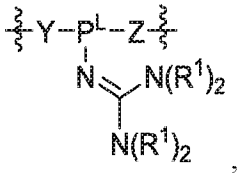
each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

two R groups are optionally and independently taken together to form a covalent bond, or

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms, or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

7. The composition of claim 5, wherein a non-negatively charged internucleotidic linkage has the structure of formula **I-n-3**:



I-n-3

or a salt form thereof, wherein:

P^L is P(=W), P, or P→$B(R')_3$;

W is O, N(–L–R^5), S or Se;

each of R^1 and R^5 is independently –H, –L–R', halogen, –CN, $–NO_2$, –L–$Si(R')_3$, –OR', –SR', or $–N(R')_2$;

each of Y and Z is independently –O–, –S–, –N(–L–R^5)–, or L;

each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, $–C(R')_2–$, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, $–S(O)_2–$, $–S(O)_2N(R')–$, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[$B(R')_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[$B(R')_3$]O–, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L;

each –Cy– is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Cy^L is independently an optionally substituted trivalent or tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and

a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

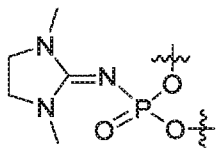
each R' is independently –R, –C(O)R, –C(O)OR, or –$S(O)_2$R;

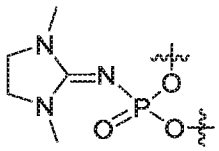
each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

two R groups are optionally and independently taken together to form a covalent bond, or

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms, or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

8. The composition of claim 5, wherein a non-negatively charged internucleotidic linkage has the structure of  .

9. The composition of claim 8, wherein the non-negatively charged internucleotidic linkage  is chirally controlled and is *Rp*.

10. The composition of claim 8, wherein the transcript is a Dystrophin transcript.

11. The composition of claim 10, wherein splicing of the transcript is altered such that the level of skipping of exon 45, 51, or 53, or multiple exons is increased.

12. The composition of claim 8, wherein each chiral internucleotidic linkage of the oligonucleotides of the plurality is independently a chirally controlled internucleotidic linkage.

13. The composition of claim 8, wherein the base sequence is or comprises or comprises 15 contiguous bases of the base sequence of any oligonucleotide in Table A1.

14. The composition of claim 11, wherein the oligonucleotide type comprises any of: cholesterol; L-carnitine (amide and carbamate bond); Folic acid; Gambogic acid; Cleavable lipid (1,2-dilaurin and ester bond); Insulin receptor ligand; CPP; Glucose (tri- and hex-antennary); or Mannose (tri- and hex-antennary, alpha and beta).

15. The composition of claim 11, wherein each non-negatively charged internucleotidic linkage is

independently an internucleotidic linkage at least 50% of which exists in its non-negatively charged form at pH 7.4.

16. The composition of claim 11, wherein the oligonucleotides of the plurality each comprise one or more sugar modifications.

17. The composition of claim 16, wherein one or more sugar modifications are 2'-F modifications.

18. The composition of any one of the preceding claims, wherein each heteroatom is independently boron, nitrogen, oxygen, silicon, sulfur, or phosphorus.

19. A pharmaceutical composition comprising an oligonucleotide composition of any one of the preceding claims and a pharmaceutically acceptable carrier.

20. A method for altering splicing of a target transcript, comprising administering an oligonucleotide composition of any one of the preceding claims.

21. The method of claim 20, wherein the target transcript is pre-mRNA of dystrophin.

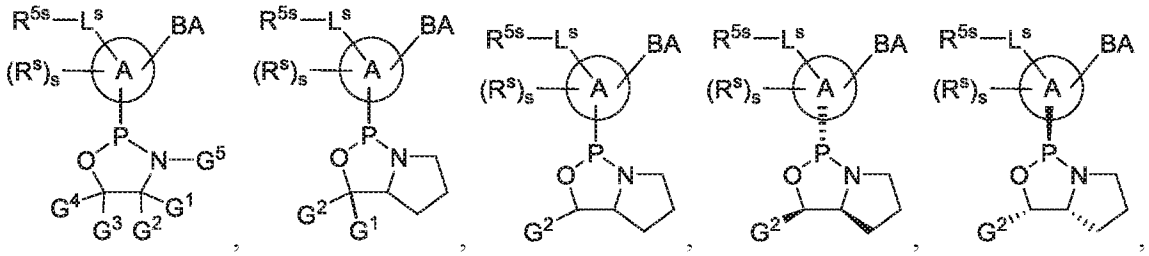
22. The method of claim 21, wherein exon 45 of dystrophin is skipped at an increased level relative to absence of the composition.

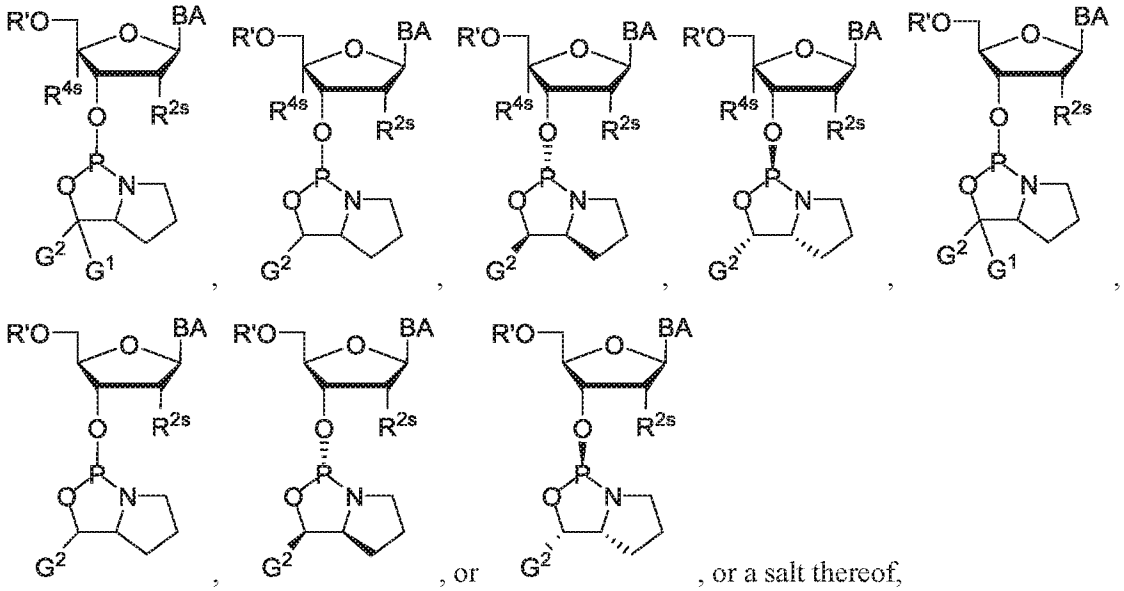
23. The method of claim 21, wherein exon 51 of dystrophin is skipped at an increased level relative to absence of the composition.

24. The method of claim 21, wherein exon 53 of dystrophin is skipped at an increased level relative to absence of the composition.

25. A method for treating muscular dystrophy, Duchenne (Duchenne's) muscular dystrophy (DMD), or Becker (Becker's) muscular dystrophy (BMD), comprising administering to a subject susceptible thereto or suffering therefrom a composition of any one of the preceding claims.

26. A method for preparing an oligonucleotide or an oligonucleotide composition thereof, wherein the oligonucleotide comprises one or more non-negatively charged internucleotidic linkages, comprising providing a phosphoramidite compound having the structure of:





, or a salt thereof,

wherein:

R^{5s} is independently R' or –OR';

each BA is independently an optionally substituted group selected from C_{3-30} cycloaliphatic, C_{6-30} aryl, C_{5-30} heteroaryl having 1-10 heteroatoms, C_{3-30} heterocyclyl having 1-10 heteroatoms, a natural nucleobase moiety, and a modified nucleobase moiety;

each R^s is independently –H, halogen, –CN, $-N_3$, –NO, $-NO_2$, –L–R', –L–Si(R)$_3$, –L–OR', –L–SR', –L–N(R')$_2$, –O–L–R', –O–L–Si(R)$_3$, –O–L–OR', –O–L–SR', or –O–L–N(R')$_2$;

each s is independently 0-20;

each L^s is independently –C(R^{5s})$_2$–, or L;

each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–, and one or more CH or carbon atoms are optionally and independently replaced with Cy^L;

each –Cy– is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Cy^L is independently an optionally substituted trivalent or tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Ring A is independently an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon;

each of G^1, G^2, G^3, G^4, G^5, and G^8 is independently R^1;

each R^1 is independently –H, –L–R', halogen, –CN, $–NO_2$, –L–$Si(R')_3$, –OR', –SR', or $–N(R')_2$;

each R' is independently –R, –C(O)R, –C(O)OR, or $–S(O)_2R$;

each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

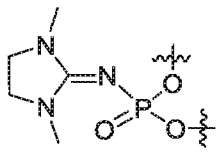
two R groups are optionally and independently taken together to form a covalent bond, or

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms, or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms; and

wherein G^2 comprises an electron-withdrawing group.

27. The method of claim 26, wherein G^5 and one of G^3 and G^4 are taken together to form an optionally substituted 3-8 membered saturated ring having 0-3 heteroatoms in addition to the nitrogen of $–NG^5–$.

28. The method of claim 26, wherein the oligonucleotide comprises an internucleotidic linkage having the structure of  .

29. The method of any one of claims 26-28, wherein G^2 comprises an electron-withdrawing group.

30. The method of claim 29, wherein G^2 is –L'–$S(O)_2R'$, wherein L' is optionally substituted $–CH_2–$.

31. The method of claim 30, wherein R' is optionally substituted C_{1-6} aliphatic.

32. The method of claim 30, wherein R' is t-butyl.

33. The method of claim 30, wherein R' is optionally substituted phenyl.

34. The method of claim 30, wherein R' is phenyl.

35. The method of claim 29, comprising one or more cycles, each of which independently comprises or consisting of:

1) deblocking;

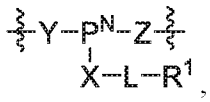
2) coupling;

3) optionally a first capping;

4) modifying; and

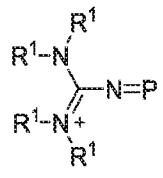
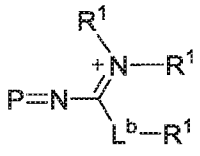
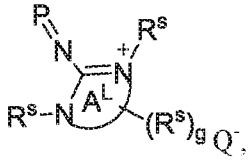
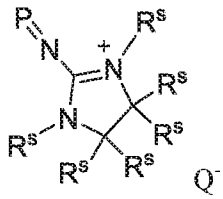
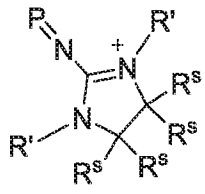
5) optionally a second capping.

36. An oligonucleotide, comprising an internucleotidic linkage having the structure of formula **III**:



III

wherein:

P^N is $P(=N-L-R^5)$,  Q^-,  Q^-,  Q^-,  Q^-,  Q^-;

Q^- is an anion;

e each of R^1 and R^5 is independently –H, –L–R', halogen, –CN, $-NO_2$, –L–$Si(R')_3$, –OR', –SR', or $-N(R')_2$;

each of Y and Z is independently –O–, –S–, $-N(-L-R^5)-$, or L;

each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, $-C(R')_2-$, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, $-S(O)_2-$, $-S(O)_2N(R')-$, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[$B(R')_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[$B(R')_3$]O–, and

one or more CH or carbon atoms are optionally and independently replaced with Cy^L;

each –Cy– is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Cy^L is independently an optionally substituted trivalent or tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

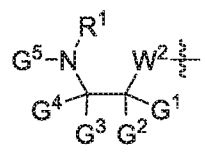
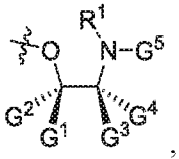
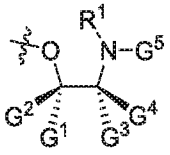
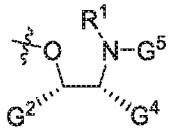
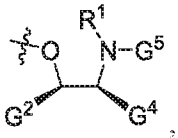
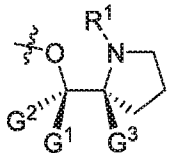
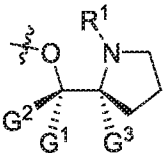
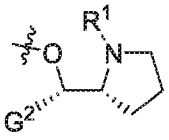
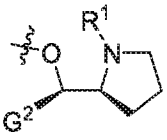
each R' is independently –R, –C(O)R, –C(O)OR, or $-S(O)_2R$;

each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

two R groups are optionally and independently taken together to form a covalent bond, or

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms, or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms; and

$-X-L-R^1$ is  ,  ,  ,  ,  ,  ,  ,  , or  , wherein G^2 comprises an electron-withdrawing group.

37. The oligonucleotide of claim 36, wherein G^2 is $-L'-S(O)_2R'$, wherein L' is optionally substituted $-CH_2-$.

38. The oligonucleotide of claim 37, wherein R' is optionally substituted C_{1-6} aliphatic.

39. The oligonucleotide of claim 38, wherein R' is t-butyl.

40. The oligonucleotide of claim 37, wherein R' is optionally substituted phenyl.

41. The oligonucleotide of claim 40, wherein R' is phenyl.

42. The oligonucleotide of any one of claims 36-41, wherein R^1 is –C(O)R'.

43. The oligonucleotide of claim 42, wherein R' is $-CH_3$.

44. The oligonucleotide of any one of claims 36-41, wherein Q^- is F^-, Cl^-, Br^-, BF_4^-, PF_6^-, TfO^-, Tf_2N^-, AsF_6^-, ClO_4^-, or SbF_6^-.

45. The oligonucleotide of any one of claims 36-44, wherein the oligonucleotide is attached to a solid support.

46. The oligonucleotide of claim 45, wherein the solid support is CPG.

47. A method for preparing an oligonucleotide, comprising contacting an oligonucleotide of any one of claims 36-46 with a base.

48. The method of claim 47, wherein the contact is performed substantially absent of water.

49. The method of claim 47 or 48, wherein the contact is after the oligonucleotide length is achieved before deprotection and cleavage of oligonucleotide.

50. The method of any one of claims 47-49, wherein the base is an amine base having the structure of NR_3.

51. The method of claim 50, wherein the base is *N*, *N*-diethylamine.

52. The oligonucleotide, compound or method of any one of Example Embodiments 1-420.

53. An oligonucleotide, wherein the oligonucleotide is, WV-20104, WV-20103, WV-20102, WV-20101, WV-20100, WV-20099, WV-20098, WV-20097, WV-20096, WV-20095, WV-20094, WV-20106, WV-20119, WV-20118, WV-13739, WV-13740, WV-9079, WV-9082, WV-9100, WV-9096, WV-9097, WV-9106, WV-9133, WV-9148, WV-9154, WV-9898, WV-9899, WV-9900, WV-9906, WV-9907, WV-9908, WV-9909, WV-9756, WV-9757, WV-9517, WV-9714, WV-9715, WV-9519, WV-9521, WV-9747, WV-9748, WV-9749, WV-9897, WV-9898, WV-9900, WV-9899, WV-9906, WV-9912, WV-9524, WV-9912, WV-9906, WV-9900, WV-9899, WV-9899, WV-9898, WV-9898, WV-9898, WV-9898, WV-9897, WV-9897, WV-9897, WV-9897, WV-9897, WV-9747, WV-9714, WV-9699, WV-9517, WV-9517, WV-13409, WV-13408, WV-12887, WV-12882, WV-12881, WV-12880, WV-12880, WV-WV12880, WV-12878, WV-12877, WV-12877, WV-12876, WV-12873, WV-12872, WV-12559, WV-12559, WV-12558, WV-12558, WV-12557, WV-12556, WV-12556, WV-12555, WV-12555, WV-12554, WV-12553, WV-12129, WV-12127, WV-12125, WV-12123, WV-11342, WV-11342, WV-11341, WV-11341, WV-11340, WV-10672, WV-10671, WV-10670, WV-10461, WV-10455, WV-9897, WV-9898, WV-13826, WV-13827, WV-13835, WV-12880, WV-14344, WV-13864, WV-13835, WV-14791, WV-14344, WV-13754, WV-13766,, WV-11086, WV-11089, WV-17859, WV-17860, WV-20070, WV-20073, WV-20076, WV-20052, WV-20099, WV-20049, WV-20085, WV-20087, WV-20034, WV-20046, WV-20052, WV-20061, WV-20064, WV-20067, WV-20092, WV-20091, WV-20093, WV-20084, WV-9738, WV-9739, WV-9740, WV-9741, WV-15860, WV-15862, WV-11084, WV-11086, WV-11088, WV-11089, WV-14522, WV-14523, WV-17861, WV-

17862, WV-13815, WV-13816, WV-13817, WV-13780, WV-17862, WV-17863, WV-17864, WV-17865, WV-17866, WV-20082, WV-20081, WV-20080, WV-20079, WV-20076, WV-20075, WV-20074, WV-20073, WV-20072, WV-20071, WV-20064, WV-20059, WV-20058, WV-20057, WV-20056, WV-20053, WV-20052, WV-20051, WV-20050, WV-20049, WV-20094, WV-20095, or a salt form thereof.

FIG. 1

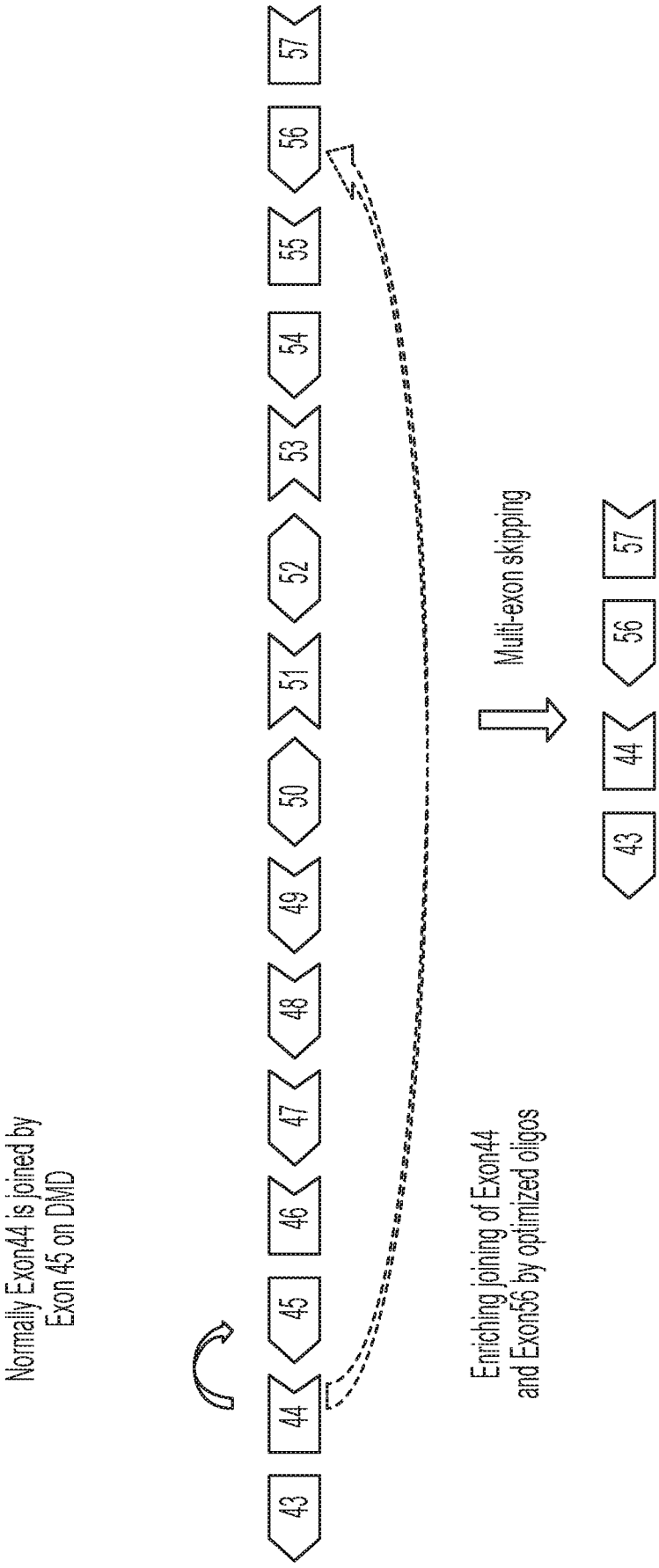

Normally Exon44 is joined by Exon 45 on DMD
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
Enriching joining of Exon44 and Exon56 by optimized oligos
Multi-exon skipping
43
44
56
57

FIG. 2

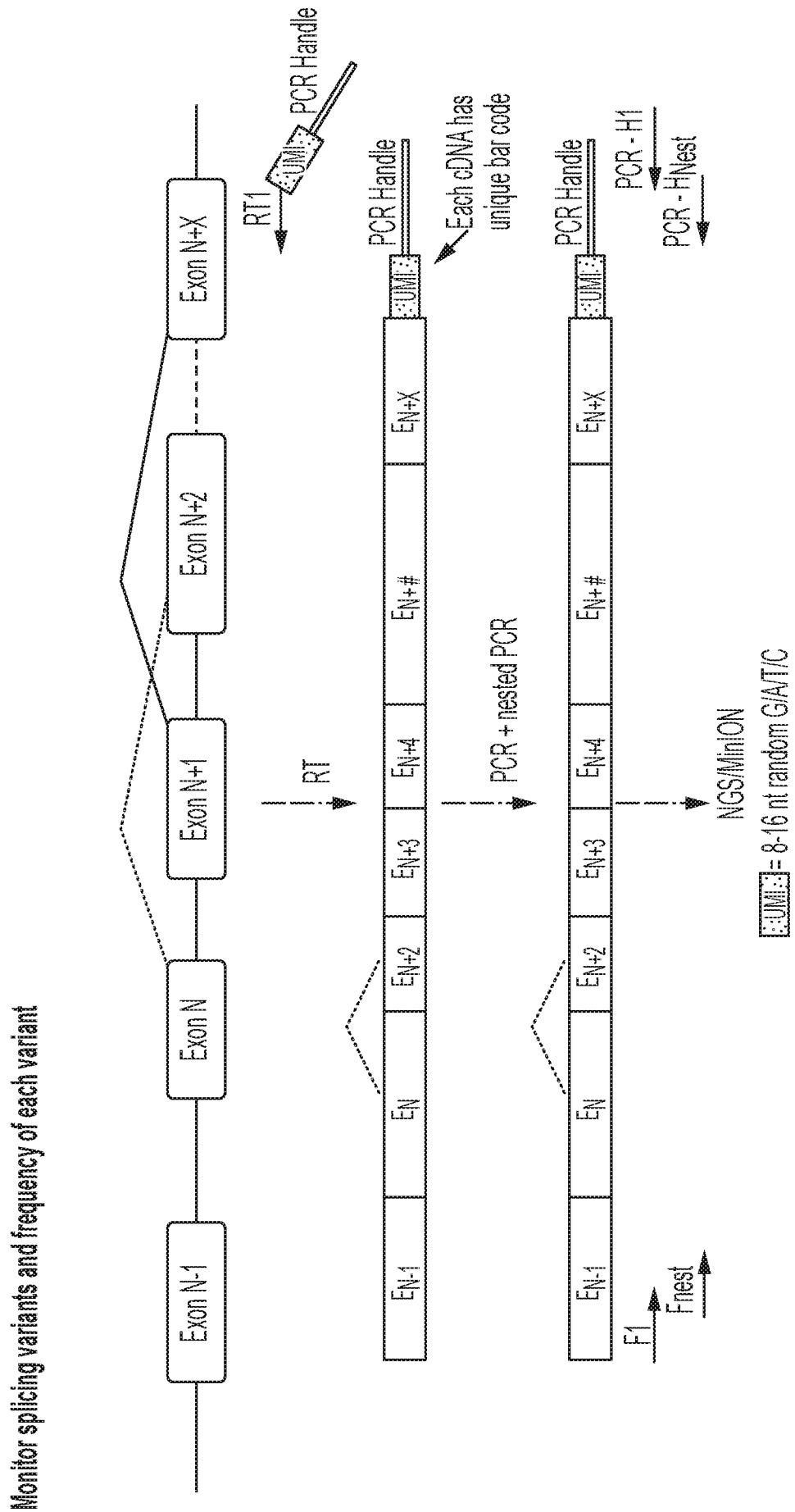

Monitor splicing variants and frequency of each variant
Exon N-1
Exon N
Exon N+1
Exon N+2
Exon N+X
RT1
UMI
PCR Handle
RT
EN-1
EN
EN+2
EN+3
EN+4
EN+#
EN+X
Each cDNA has unique bar code
PCR + nested PCR
PCR - H1
PCR - HNest
F1
Fnest
NGS/MiniION
UMI = 8-16 nt random G/A/T/C

FIG. 3

- Use one ASO to block Exon45 (▨) and possibly a second ASO to block another exon
  - *Exon45 targeting being tested in cells*
  - *Selection of second ASO being explored*
- Use one ASO to block Exon45 (▨) that contains a tail sequence which binds to intron 55 (▩) causing looping of the pre-mRNA
- Use one ASO to block Exon45 (▨) and another ASO which binds to intron 55 and intron 44 (▩) causing looping of the pre-mRNA

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/27109

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C12N 15/11; C07C 317/28; C12Q 1/68; C07H 21/02, 21/04 (2019.01)

CPC - C12N 15/11; C07C 317/28; C12Q 1/68; C07H 21/02, 21/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/062862 A2 (WAVE LIFE SCIENCES LTD.) 13 April 2017; paragraphs [0009], [00633]; claim 1	1-4, 5/1-4, 6/5/1-4
A	US 2017/0037399 A1 (WAVE LIFE SCIENCES LTD.) 09 February 2017; whole document	1-4, 5/1-4, 6/5/1-4
A	US 5,750,669 A (ROSCH, H et al.) 12 May 1998; whole document	1-4, 5/1-4, 6/5/1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 September 2019 (03.09.2019)	24 SEP 2019
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/27109

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 18-25, 47-52
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-***- Please See within the Next Supplemental Page-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Group 1+ Claims 1-6, an internucleotidic linkage encompassing formula I, wherein PL is P(=O), Y and Z are O, X is -N(-CH3), L is a covalent bond, and R1 is -H (internucleotidic linkage)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/27109

-***-Continued from Box III Observations where unity of invention is lacking -***-

Groups I+, Claims 1-17, 26-46, 53, an internucleotidic linkage encompassing formula I, wherein PL is P(=O), Y and Z are O, X is -N(-CH3), L is a covalent bond, and R1 is -H (internucleotidic linkage), are directed toward an oligonucleotide composition and method for preparing an oligonucleotide.

The oligonucleotide composition and method will be searched to the extent they encompass an internucleotidic linkage encompassing formula I, wherein PL is P(=O), Y and Z are O, X is -N(-CH3), L is a covalent bond, and R1 is -H (first exemplary internucleotidic linkage). Applicant is invited to elect additional internucleotidic linkage(s), and/or corresponding compounds used to prepare oligonucleotide(s) comprising said linkage(s), with fully specified structure for each, (i.e. no optional or variable atoms, bonds, moieties, substituents or chiralities), and, where applicable, corresponding oligonucleotide compound(s) and/or oligonucleotide sequence(s), where the additionally elected species is available as an option within at least one searchable claim, to be searched. Additional internucleotidic linkage(s), and/or corresponding compounds used to prepare the oligonucleotide(s) and/or oligonucleotide compound(s) and/or oligonucleotide sequence(s) will be searched upon the payment of additional fees. It is believed that claims x1-5 and 6 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass an internucleotidic linkage encompassing formula I, wherein PL is P(=O), Y and Z are O, X is -N(-CH3), L is a covalent bond, and R1 is -H (internucleotidic linkage). Applicants must specify the claims that encompass any additionally elected internucleotidic linkage(s), and/or corresponding compounds used to prepare the oligonucleotide(s) and/or oligonucleotide compound(s) and/or oligonucleotide sequence (s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be an internucleotidic linkage encompassing formula I, wherein PL is P(=O), Y and Z are O, X is -N(-CH3-CH3), L is a covalent bond, and R1 is -H (internucleotidic linkage).

No technical features are shared between the nucleotide analogs and/or internucleotidic linkages of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: an oligonucleotide composition, comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by 1) base sequence; 2) pattern of backbone linkages; 3) pattern of backbone chiral centers: and 4) pattern of backbone phosphorus modifications, wherein: oligonucleotides of the plurality comprise at least 1-20 chirally controlled internucleotidic linkages: and oligonucleotides of the plurality comprise at least 1-20 non-negatively charged internucleotidic linkages; an oligonucleotide composition, comprising a plurality of oligonucleotides of a particular oligonucleotide type defined by: 1) base sequence: 2) pattern of backbone linkages; 3) pattern of backbone chiral centers; and 4) pattern of backbone phosphorus modifications, wherein: oligonucleotides of the plurality comprise at least 1-20 chirally controlled internucleotidic linkages: and the oligonucleotide composition being characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof; a method for preparing an oligonucleotide or an oligonucleotide composition thereof: wherein the oligonucleotide comprises one or more non-negatively charged internucleotidic linkages, comprising providing a phosphoramidite compound having the structure of: (set of structures), or a salt thereof, wherein: R5s is independently R' or -OR'; each BA is independently an optionally substituted group selected from C3-30 cycloaliphatic, C6-30 aryl, C5-30 heteroaryl having 1-10 heteroatoms, C3-30 heterocyclyl having 1-10 heteroatoms, a natural nucleobase moiety, and a modified nucleobase moiety: each R5 is independently -H, halogen, -CN, -N3, -NO, -NO2, -L-R', -L--Si(R)3, -L-OR', -L-SR', -L-N(R')2,-O-L-R', -O-L-Si(R)3, -O-L-OR', -O-L-SR', or -O-L-N(R')2; each s is independently 0-20; each Ls is independently -C(R5s)2-, or L; each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C1-30 aliphatic group and a C1-30 heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C 1-6 alkylene, C1-6 alkenylene, -C.triplebond.C-, a bivalent C1-C6 heteroaliphatic group having 1-5 heteroatoms, -C(R')2-, -Cy-, -O-, -S-, -S-S-, -N(R')-, -C(O)-, -C(S)-, -C(NR')-, -C(O)N(R')-, --N(R')C(O)N(R')-, -N(R')C(O)O-, -S(O)-, -S(O)2-, -S(O)2N(R')-, -C(O)S-, -C(O)O-, -P(O)(OR')-, -P(O)(SR')-, -P(O)(R')-, -P(O)(NR')-, -P(S)(OR')-, -P(S)(SR')-, -P(S)(R')-, -P(S)(NR')-, -P(R')-, -P(OR')-, -P(SR')-, -P(NR')-, -P(OR')[B(R')3]-, -OP(O)(OR')O-, -OP(O)(SR')O-, -OP(O)(R')O-, -OP(O)(NR')O-, -OP(OR')O-, -OP(SR')O-, -OP(NR')O-, -OP(R')O-, or -OP(OR')[B(R')3]O-, and one or more CH or carbon atoms are optionally and independently replaced with CyL, each -Cy- is independently an optionally substituted bivalent group selected from a C3-20 cycloaliphatic ring, a C6-20 aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms; each CyL is independently an optionally substituted trivalent or tetravalent group selected from a C3-20 cycloaliphatic ring, a C6-20 aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms; each Ring A is independently an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon; each of G1, G2, G3, G4, G5, and G8 is independently R1; each R1 is independently -H, -L-R', halogen, -CN, -NO2, -L-Si(R')3, -OR', -SR', or -N(R')2; each R' is independently -R, -C(O)R, -C(O)OR, or -S(O)2R; each R is independently -H, or an optionally substituted group selected from C1-30 aliphatic, C1-30 heteroaliphatic having 1-10 heteroatoms, C6-30 aryl, C6-30 arylaliphatic, C6-30 arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or two R groups are optionally and independently taken together to form a covalent bond, or two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in
addition to the atom, 0-10 heteroatoms, or two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms;

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and wherein G2 comprises an electron-withdrawing group; and an oligonucleotide, comprising an internucleotidic linkage having the structure of formula III: -Y-PN(-Z-)-X-L-R; wherein PN is P(=N-L-R5), or any one of 5 disclosed structures, each of which includes a Q anion; each of R1 and R5 is independently -H, -L-R', halogen, -CN, -NO2, -L-Si(R')3, -OR', -SR', or -N(R')2; each of Y and Z is independently -O-, -S-, -N(-L-R5)-, or L; each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C1-30 aliphatic group and a C1-30 heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C1-6 alkylene, C1-6 alkenylene, -C.triplebond.C-, a bivalent C1-C6 heteroaliphatic group having 1-5 heteroatoms, -C(R')2-, -Cy-, -O-, -S-, -S-S-, -N(R')-, -C(O)-, -C(S)-, -C(NR')-, -C(O)N(R')-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -S(O)-, -S(O)2-, -S(O)2N(R')-, -C(O)S-, -C(O)O-, -P(O)(OR')-, -P(O)(SR')-, -P(O)(R')-, -P(O)(NR')-, -P(S)(OR')-, -P(S)(SR')-, -P(S)(R')-, -P(S)(NR')-, -P(R')-, -P(OR')-, -P(SR')-, -P(NR')-, -P(OR')[B(R')3]-, OP(O)(OR')O-, -OP(O)(SR')O-, -OP(O)(R')O-, -OP(O)(NR')O-, -OP(OR')O-, -OP(SR')O-, -OP(NR')O-, -OP(R')O-, or -OP(OR')[B(R')3]O-, and one or more CH or carbon atoms are optionally and independently replaced with CyL; each -Cy- is independently an optionally substituted bivalent group selected from a C3-20 cycloaliphatic ring, a C6-20 aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms; each CyL is independently an optionally substituted trivalent or tetravalent group selected from a C3-10 cycloaliphatic ring, a C6-20 aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms; each R' is independently -R, -C(O)R, -C(O)OR, or -S(O)2R; each R is independently -H, or an optionally substituted group selected from C1-30 aliphatic, C1-30 heteroaliphatic having 1-10 heteroatoms, C6-30 aryl, C6-30 arylaliphatic, C6-30 arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or two R groups are optionally and independently taken together to form a covalent bond, or two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms, or two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms; and -X-L-R is [any one of 9 disclosed structures], wherein G2 comprises an electron-withdrawing group.

However, these shared technical features are previously disclosed by US 2017/0037399 A1 to Wave Life Sciences Ltd. (hereinafter "Wave") in view of WO 2017/062862 A2 to Wave Life Sciences, Ltd. (hereinafter 'Life').

Wave discloses an oligonucleotide composition (an oligonucleotide composition; paragraph [0005]), comprising a plurality of oligonucleotides of a particular oligonucleotide type (comprising oligonucleotides having a particular pattern of backbone chiral centers (comprising a plurality of oligonucleotides of a particular oligonucleotide type); paragraphs [0005], [0107]) defined by 1) base sequence (defined by base sequence; paragraphs [0003], [0107]); 2) pattern of backbone linkages (pattern of backbone linkages; paragraphs [0003], [0107]); 3) pattern of backbone chiral centers (pattern of backbone chiral centers; paragraphs [0003], [0107]): and 4) pattern of backbone phosphorus modifications (pattern of backbone phosphorus modifications); paragraphs [0004], [0107]), wherein: oligonucleotides of the plurality comprise at least 1-20 chirally controlled internucleotidic linkages (oligonucleotides of the plurality comprise a common pattern of backbone chiral centers, and at least 8-20 (1-20) chirally controlled internucleotidic linkages; paragraphs [0108], [0188]): and oligonucleotides of the plurality comprise at least 1-20 non-negatively charged internucleotidic linkages (and oligonucleotides of the plurality comprise at least 1-20 modified phosphate internucleotidic linkages, including any of those from Table 1 (non-negatively charged internucleotidic linkages); paragraph [0183], Table 1; wherein all of the modified phosphate linkages in Table 1 are non-negatively charged); an oligonucleotide composition, (an oligonucleotide composition; paragraph [0005]), comprising a plurality of oligonucleotides of a particular oligonucleotide type (comprising oligonucleotides having a particular pattern of backbone chiral centers (comprising a plurality of oligonucleotides of a particular oligonucleotide type); paragraphs [0005], [0107]) defined by 1) base sequence (defined by base sequence; paragraphs [0003], [0107]); 2) pattern of backbone linkages (pattern of backbone linkages; paragraphs [0003], [0107]); 3) pattern of backbone chiral centers (pattern of backbone chiral centers; paragraphs [0003], [0107]): and 4) pattern of backbone phosphorus modifications (pattern of backbone phosphorus modifications); paragraphs [0004], [0107]), wherein: oligonucleotides of the plurality comprise at least 1-20 chirally controlled internucleotidic linkages (oligonucleotides of the plurality comprise a common pattern of backbone chiral centers, and at least 8-20 (1-20) chirally controlled internucleotidic linkages; paragraphs [0108], [0188]); a method for preparing an oligonucleotide or an oligonucleotide composition thereof (a method for preparing an oligonucleotide or an oligonucleotide composition thereof; paragraph [0244]): wherein the oligonucleotide comprises one or more non-negatively charged internucleotidic linkages (oligonucleotides of the plurality comprise at least 1-20 modified phosphate internucleotidic linkages, including any of those from Table 1 (wherein the oligonucleotide comprises one or more non-negatively charged internucleotidic linkages); paragraph [0183], Table 1; wherein all of the modified phosphate linkages in Table 1 are non-negatively charged), comprising providing a phosphoramidite compound (comprising providing a phosphoramidite compound; paragraphs [0242], [0665]) having the structure of: (set of structures), or a salt thereof (having the structure of: (set of structures), or a salt thereof; paragraph [0700]), wherein: R5s is independently R' or -OR' (wherein: R5s is DMTrO (independently -OR'; paragraph [0700]); each BA is independently a natural or modified nucleobase moiety (each BA is independently a natural or modified nucleobase moiety; paragraph [0700]); each R' is independently -R, each R is an optionally substituted group selected from C1-30 aliphatic, C6-30 aryl, C6-30 arylaliphatic (wherein R' is DMTr (each R' is independently -R, each R is an optionally substituted group selected from C1-30 aliphatic, C6-30 aryl, C6-30 arylaliphatic), and wherein G2 comprises an electron-withdrawing group (wherein the sugar is modified by a 2'F (wherein G2 comprises an electron-withdrawing group); paragraph [0836]).

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Wave further discloses wherein the modified chiral oligonucleotides provide different cleavage patterns of a nucleic acid (wherein the modified chiral oligonucleotides provide different cleavage patterns of a nucleic acid; abstract); and an oligonucleotide, comprising an internucleotidic linkage having the structure of formula III: -Y-PN(-Z-)-X-L-R, wherein PN is P(=N-L-R5), or any one of 5 disclosed structures (comprising an internucleotidic linkage comprising s9 with a substitution of =NR' on the pohosphorus (comprising an internucleotidic linkage having the structure of formula III: -Y-PN(-Z-)-X-L-R, wherein PN is P(=N-L-R5), or any one of 5 disclosed structures; paragraph [0104], Table 1), R1 is -H (R1 is H; Table 1, s9), each of Y and Z is independently -O- (each of Y and Z is independently -O-; Table 1, s9); wherein G2 comprises an electron-withdrawing group (wherein the substituent comprises a heterocyclic moiety comprising a C(O)OR' attached to the second carbon after the N (wherein G2 comprises an electron-withdrawing group); Table 1, s9 [see applicants' paragraph [00982] of the instant specification for electron-withdrawing groups]).

Wave does not disclose: the oligonucleotide composition being characterized in that, when it is contacted with a transcript in a transcript splicing system, splicing of the transcript is altered relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

Life discloses oligonucleotides providing altered splicing of a transcript (oligonucleotides providing altered splicing of a transcript; abstract, paragraphs [0003], [0006]), wherein the oligonucleotides include chirally controlled modified internucleotidic backbone centers (wherein the oligonucleotides include chirally controlled modified internucleotidic backbone centers; paragraphs [0003], [0006]), wherein splicing of the transcript is altered relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof (wherein splicing of the transcript is altered relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof; paragraph [0031]).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the disclosure of Wave to have used the oligonucleotides disclosed thereby as a means of providing altered splicing of a transcript, as disclosed by Life, in order to modulate the expression of one or more forms of a polypeptide in a cell or subject.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Wave and Life references, unity of invention is lacking.