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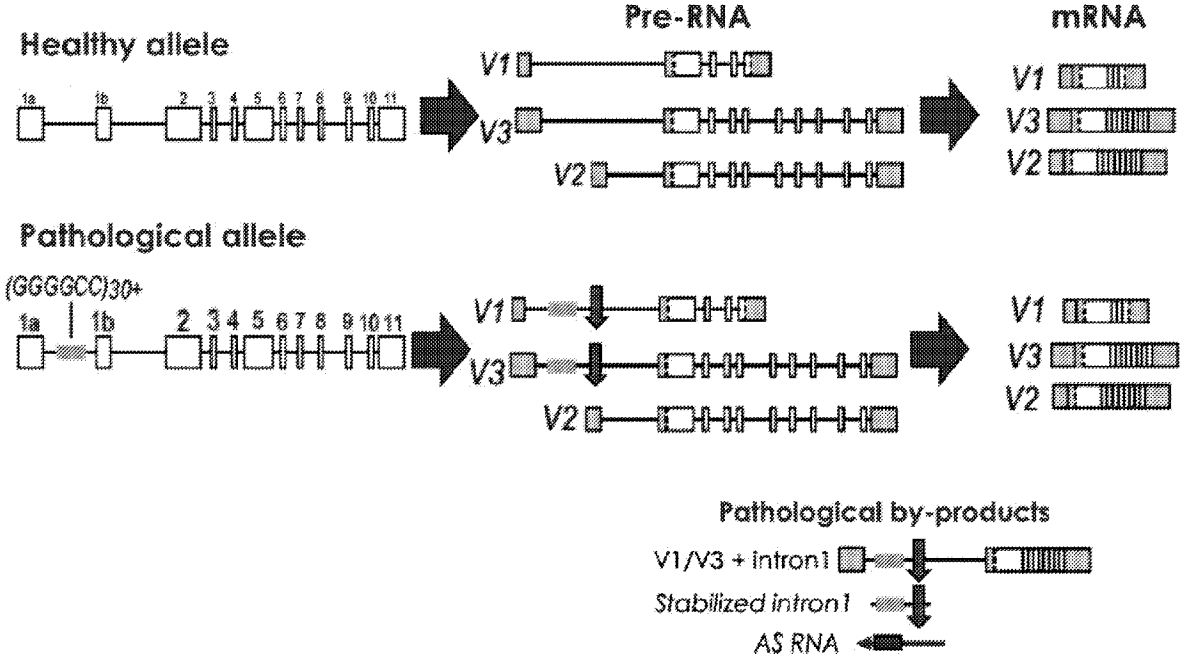
(54) Title: OLIGONUCLEOTIDE COMPOSITIONS AND METHODS THEREOF

FIG. 4



(57) Abrégé/Abstract:
Among other things, the present disclosure provides oligonucleotides, compositions, and methods thereof. Among other things, the present disclosure encompasses the recognition that structural elements of oligonucleotides, such as base sequence,

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(57) Abrégé(suite)/Abstract(continued):
chemical modifications (e.g., modifications of sugar, base, and/or internucleotidic linkages) or patterns thereof, conjugation with additional chemical moieties, and/or stereochemistry [e.g., stereochemistry of backbone chiral centers (chiral internucleotidic linkages)], and/or patterns thereof, can have significant impact on oligonucleotide properties and activities, e.g., knockdown ability, stability, delivery, etc. In some embodiments, the oligonucleotides decrease the expression, activity and/or level of a C9orf72 gene, including but not limited to, one comprising a repeat expansion, or a gene product thereof. In some embodiments, the present disclosure provides methods for treatment of diseases using provided oligonucleotide compositions, for example, in treatment of C9orf72-related disorders.

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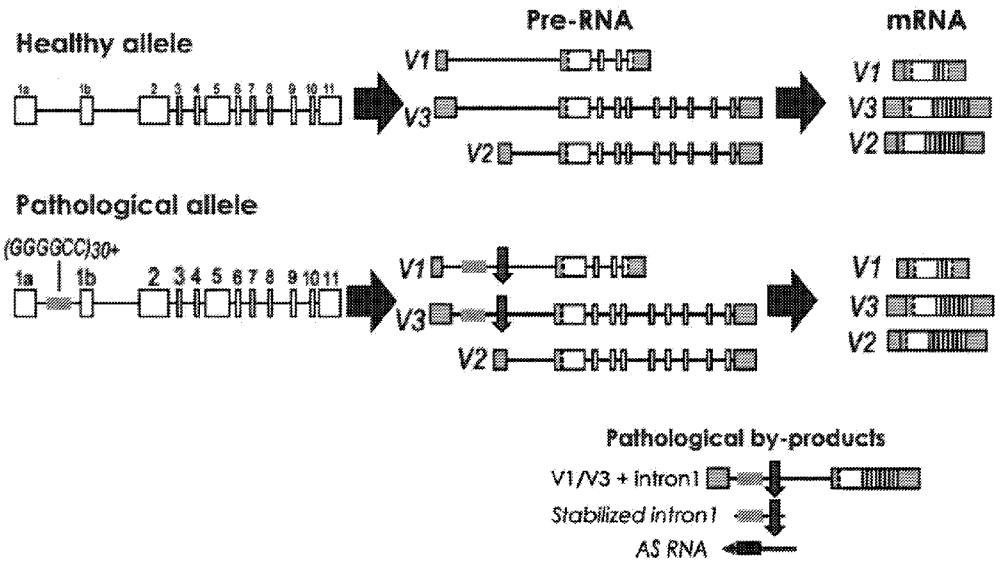
(54) **Title:** OLIGONUCLEOTIDE COMPOSITIONS AND METHODS THEREOF

FIG. 4



(57) **Abstract:** Among other things, the present disclosure provides oligonucleotides, compositions, and methods thereof. 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) or patterns thereof, conjugation with additional chemical moieties, and/or stereochemistry [e.g., stereochemistry of backbone chiral centers (chiral internucleotidic linkages)], and/or patterns thereof, can have significant impact on oligonucleotide properties and activities, e.g., knockdown ability, stability, delivery, etc. In some embodiments, the oligonucleotides decrease the expression, activity and/or level of a C9orf72 gene, including but not limited to, one comprising a repeat expansion, or a gene product thereof. In some embodiments, the present disclosure provides methods for treatment of diseases using provided oligonucleotide compositions, for example, in treatment of C9orf72-related disorders.

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[Continued on next page]

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NOTE POUR LE TOME / VOLUME NOTE:

OLIGONUCLEOTIDE COMPOSITIONS AND METHODS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to United States Provisional Application No. 62/542,778, filed August 8, 2017, the entirety of which is incorporated herein by reference.

BACKGROUND

[0002] Oligonucleotides are useful in various applications, e.g., therapeutic, diagnostic, and/or research applications, including but not limited to treatment of various conditions, disorders, and/or diseases.

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 a significant impact on activities and properties, *e.g.*, stability, toxicity, delivery, *etc.*, of oligonucleotides. In some embodiments, the present disclosure demonstrates that oligonucleotides and compositions comprising oligonucleotides with controlled structural elements, *e.g.,* controlled chemical modification and/or controlled backbone stereochemistry patterns, provide unexpected activities and properties including but not limited to those described herein. In some embodiments, the present disclosure demonstrates that combinations of chemical modifications and stereochemistry can provide unexpected, greatly improved activities and properties. In some embodiments, the present disclosure provides oligonucleotides and compositions comprising oligonucleotides that have a particular sequence of bases, and/or pattern of sugar modifications (e.g., 2'-OMe, 2'-F, 2'-MOE, etc.), and/or pattern or base modifications (e.g., 5-methylcytosine), and/or pattern of backbone modifications (*e.g.*, natural phosphate linkages, modified internucleotidic linkages, *etc.*), and/or pattern of backbone chiral centers (*e.g.*, *R*p or *S*p, and/or stereorandom, and/or non-chiral, backbone linkage phosphorus atoms).

[0004] In some embodiments, the present disclosure provides novel oligonucleotides, and compositions thereof (e.g., chirally controlled oligonucleotide compositions), wherein the oligonucleotides comprise a format of wing-core-wing, wherein the first and the second wing differ from the core and from each other chemically, e.g., in sugars or sugar modifications or combinations or patterns thereof, backbone internucleotidic linkages or combinations or patterns thereof, and/or combination or pattern of stereochemistry of the backbone internucleotidic linkages. Particularly, in

some embodiments, the present disclosure provides oligonucleotides comprising a wing-core-wing structure, wherein each wing independently comprises one or more sugar modifications, wherein the pattern of sugar modifications of one wing is different from the other wing. In some embodiments, one wing comprises a sugar modification which is not in the other wing. In some embodiments, each sugar moiety of the core independently comprises no substituents at the 2'-position (two −H at the 2'-position). In some embodiments, each sugar moiety of the core is independently a natural DNA sugar moiety (a D-2-deoxyribose moiety) which is optionally substituted at the 5'-position. In some embodiments, each sugar moiety of the core is independently a natural DNA sugar moiety (a D-2-deoxyribose moiety). In some embodiments, such oligonucleotides comprise one or more chiral internucleotidic linkages (e.g., phosphorothioate linkage [−O−P(O)(SH)−O− which may exist as anion form −O−P(O)(S^-)−O− at certain pH], neutral internucleotidic linkages as described herein, etc.). In some embodiments, such oligonucleotides comprise one or more (e.g., at least 5, 6, 7, 8, 9 or 10) chiral neutral internucleotidic linkages. In some embodiments, the present disclosure provides chirally controlled oligonucleotide compositions of such oligonucleotides. In some embodiments, provided oligonucleotides comprise a pattern of backbone chiral centers (linkage phosphorus) of (*N*p)t[(*O*p/*R*p)n(*S*p)m]y, wherein each variable is independently as described in the present disclosure. Unless otherwise specified, as appreciated by those skilled in the art, a stereochemistry pattern is from the 5' to the 3' direction.

[0005] In some embodiments, the present disclosure demonstrates that oligonucleotides comprising certain stereochemistry patterns, such as (*N*p)t[(*O*p/*R*p)n(*S*p)m]y, and chirally controlled oligonucleotide compositions thereof can provide highly improved activities (e.g., when used for cleavage of target nucleic acids), specificity (e.g., when used for cleavage of target nucleic acids wherein nucleic acids of similar sequences exist [e.g., transcripts of wild-type and mutant alleles, transcripts from alleles comprising single nucleotide polymorphisms (SNPs), etc.) and/or other properties (e.g., stability, delivery, etc.) compared to suitable control oligonucleotides and/or compositions thereof (e.g., unmodified oligonucleotides of the same base sequence; stereorandom oligonucleotides optionally of the same constitution; chirally controlled oligonucleotides optionally of the same constitution; or stereorandom and/or chirally controlled compositions thereof). In some embodiments, provided oligonucleotides comprises a stereochemistry pattern of (*N*p)t[(*O*p/*R*p)n(*S*p)m]y, wherein each variable is independently as described in the present disclosure. In some embodiments, each *N*p is *S*p. In some embodiments, a pattern comprises at least one *O*p. In some embodiments, n is 1. In some embodiments, m is at least 2, 3, 4, or 5. In some embodiments, y is 1. In some embodiments, y is 2, 3, 4, or 5. In some embodiments, (*N*p)t[(*O*p/*R*p)n(*S*p)m]y is (*S*p)t[(*O*p/*R*p)(*S*p)m]y. In some embodiments, (*N*p)t[(*O*p/*R*p)n(*S*p)m]y is (*S*p)t[*O*p(*S*p)m]y. In some embodiments, each *N*p, *R*p, and/or *S*p linkage phosphorus is independent a linkage phosphorus of phosphorothioate linkage. In some embodiments,

each *O*p is independently a linkage phosphorus of a natural internucleotidic linkage (−O−P(O)(OH)−O− which may exist as anion form −O−P(O)(O^-)−O− at certain pH. In some embodiments, each sugar moiety that connects to a linkage phosphorus of a stereochemistry pattern, e.g., (*N*p)t[(*O*p/*R*p)n(*S*p)m]y, contains no 2'-modifications. In some embodiments, each sugar moiety that connects at its 3'-position to a linkage phosphorus of a stereochemistry pattern, e.g., (*N*p)t[(*O*p/*R*p)n(*S*p)m]y, contains no 2'-modifications. In some embodiments, each sugar moiety that connects at its 5'-position to a linkage phosphorus of a stereochemistry pattern, e.g., (*N*p)t[(*O*p/*R*p)n(*S*p)m]y, contains no 2'-modifications. In some embodiments, each sugar moiety that connects to a linkage phosphorus of a stereochemistry pattern, e.g., (*N*p)t[(*O*p/*R*p)n(*S*p)m]y, is independently a natural DNA sugar moiety (a D-2-deoxyribose moiety), wherein the 5'-position is optionally substituted. In some embodiments, the 5'-position is not substituted. In some embodiments, a 5'-position is substituted, e.g., wherein the 5'-position is connected to a linkage phosphorus of *O*p.

[0006] In some embodiments, as demonstrated in the present disclosure, oligonucleotides that comprise a stereochemistry pattern comprising *N*p*N*p*O*p(*S*p)m can cleave target sequences at an internucleotidic linkage position wise corresponding to the second internucleotidic linkage of the oligonucleotides upstream of the internucleotidic linkage comprising *O*p (at an internucleotidic linkage of the target that corresponds to the internucleotidic linkage comprising the underlined *N*p of <u>*N*p</u>*N*p*O*p(*S*p)m).

[0007] In some embodiments, the present disclosure provides methods for controlled cleavage of a target nucleic acid, comprising providing an oligonucleotide or a chirally controlled oligonucleotide composition thereof, wherein the stereochemistry pattern of the oligonucleotide comprises (*N*p)t[(*O*p/*R*p)n(*S*p)m]y as described in the present disclosure.

[0008] In some embodiments, the present disclosure provides methods for controlled cleavage of a nucleic acid target, comprising contacting the target with a provided an oligonucleotide or composition thereof. In some embodiments, the present disclosure provides methods for selective cleavage of a nucleic acid target, comprising contacting the target with a provided an oligonucleotide or composition thereof. In some embodiments, the present disclosure provides methods for allele-specific cleavage of a transcript of a specific allele, comprising contacting the target with a provided an oligonucleotide or composition thereof. In some embodiments, such a provided oligonucleotide has a pattern of backbone chiral centers comprising *O*p(*S*p)m. In some embodiments, a composition is a chirally controlled oligonucleotide composition of a plurality of oligonucleotides, whose pattern of backbone chiral centers comprises *O*p(*S*p)m. In some embodiments, m is 2. In some embodiments, such a provided oligonucleotide has a pattern of backbone chiral centers comprising (*N*p)t[(*O*p/*R*p)n(*S*p)m]y, wherein each variable is as described in the present disclosure, n is 1, m is 2 or greater, and t is 2 or greater. In

some embodiments, a composition is a chirally controlled oligonucleotide composition of a plurality of oligonucleotides, whose pattern of backbone chiral centers comprises (*N*p)t[(*O*p/*R*p)n(*S*p)m]y, wherein each variable is as described in the present disclosure, n is 1, m is 2 or greater, and t is 2 or greater. In some embodiments, *N*p is *S*p.

[0009] In some embodiments, oligonucleotides that comprise an asymmetrical format and/or a stereochemistry pattern described in the present disclosure are capable of decreasing the level, expression and/or activity of a gene target or a gene product thereof.

[0010] Oligonucleotides of the present disclosure may function through various mechanisms. In some embodiments, provided oligonucleotides are capable of decreasing the level, expression and/or activity of a gene target or a gene product thereof via a mechanism involving RNase H, which recognizes a DNA/RNA duplex. In some embodiments, the core of an oligonucleotide comprises multiple deoxyribose (e.g., 2'-deoxyribose or 2'-DNA sugars as found in naturally-occurring DNA) moieties and is capable of annealing to a RNA (e.g., a target mRNA) to form a substrate for RNase H, allowing RNase H to cleave the RNA.

[0011] In some embodiments, provided oligonucleotides are capable of decreasing the level, expression and/or activity of a gene target or a gene product thereof via a mechanism involving steric hindrance. In some embodiments, provided oligonucleotides block or decrease translation of a target mRNA.

[0012] The present disclosure pertains to any oligonucleotide which has an asymmetrical format and operates through any mechanism, and which comprises any structure or format (or portion thereof) described herein, wherein the oligonucleotide comprises at least one non-naturally-occurring modification of a base, sugar and/or internucleotidic linkage.

[0013] In some embodiments, a provided oligonucleotide comprises at least one stereorandom internucleotidic linkage (non-chirally controlled internucleotidic linkage) (e.g., a stereorandom phosphorothioate linkage, a stereorandom neutral internucleotidic linkage, etc.). In some embodiments, a provided oligonucleotide comprises at least one stereocontrolled internucleotidic linkage (chirally controlled internucleotidic linkage) (e.g., a Rp or Sp phosphorothioate linkage, a Rp or Sp neutral internucleotidic linkage, etc.).

[0014] In some embodiments, the present disclosure encompasses the recognition that various optional additional chemical moieties, such as carbohydrate moieties, sugar moieties, targeting moieties, etc., when incorporated into oligonucleotides, can improve one or more properties. In some embodiments, an additional chemical moiety is selected from: glucose, GluNAc (N-acetyl amine glucosamine) and anisamide moieties. In some embodiments, an oligonucleotide can comprise two or more additional chemical moieties, wherein the additional chemical moieties are identical or non-

identical, or are of the same or different categories (e.g., carbohydrate moiety, sugar moiety, targeting moiety, etc.). In some embodiments, certain additional chemical moieties facilitate delivery of oligonucleotides to desired cells, tissues and/or organs, facilitate internalization of oligonucleotides, and/or increase oligonucleotide stability.

[0015] In some embodiments, the present disclosure demonstrates that surprisingly high target specificity can be achieved with oligonucleotides which have an asymmetrical format. In some embodiments, an oligonucleotide which has an asymmetrical format is allele-specific, e.g., the oligonucleotide can preferential knockdown disease-associated transcript(s) of a gene target relative to wild-type (e.g., non-disease-associated) transcript(s). In some embodiments, a disease-associated transcript can comprise a disease-associated mutation or repeat expansion.

[0016] In some embodiments, the present disclosure provides an oligonucleotide which has an asymmetrical format and comprises any structure or format (or portion thereof) described herein, an optional additional chemical moiety (including but not limited to a carbohydrate moiety, and a targeting moiety), stereochemistry or patterns of stereochemistry, internucleotidic linkage or pattern of internucleotidic linkages; modification of sugar(s) or pattern of modifications of sugars; modification of base(s) or patterns of modifications of bases.

[0017] In some embodiments, the present disclosure provides methods for reducing levels of a nucleic acid or a product encoded thereby, comprising contacting the nucleic acid with a provided oligonucleotide or a composition thereof, wherein the base sequence of the oligonucleotide is complementary to the base sequence of the nucleic acid or a portion thereof. In some embodiments, the present disclosure provides a method for treating and/or preventing and/or treating various related conditions, disorders and/or diseases in a subject, wherein the method comprises the step of administering to the subject a provided oligonucleotide or a composition thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] Figure 1. Figure 1 presents certain provided formats of oligonucleotides having an asymmetric format as non-limiting examples. Figure 1A and Figure 1B present non-limiting examples of sugar modifications and/or patterns thereof in the first and second wing of an oligonucleotide having an asymmetric format. Figure 1C presents non-limiting examples of internucleotidic linkages in the first and second wing of an oligonucleotide having an asymmetric format. Figure 1D provides a legend to Figure 1A, Figure 1B and Figure 1C.

[0019] Figure 2. Example cleavage data of oligonucleotides comprising certain stereochemistry patterns. Arrows indicate observed cleavage sites. As demonstrated, oligonucleotides comprising certain stereochemistry patterns can direct cleavage to selected sites. In some embodiments, as shown herein,

cleavage occurs predominately at one site when chirally controlled oligonucleotide compositions of oligonucleotides comprising certain stereochemistry patterns were utilized.

[0020] Figure 3. Example cleavage data by provided oligonucleotides.

[0021] Figure 4. Example C9orf72 transcripts. V3, V2 and V1 transcripts produced from a healthy and a pathological C9orf72 allele are illustrated, wherein the pathological allele contains a hexanucleotide repeat expansion [horizontal bar, indicated by $(GGGGCC)_{30+}$]. The downward-pointing arrow indicates the position of some example C9orf72 oligonucleotides.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

Definitions

[0022] 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.

[0023] *Aliphatic*: As used herein, "aliphatic" 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 substituted or unsubstituted monocyclic, bicyclic, or polycyclic hydrocarbon ring that is completely saturated or that contains one or more units of unsaturation (but not aromatic), or combinations thereof. In some embodiments, aliphatic groups contain 1-50 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. 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.

[0024] *Alkenyl*: As used herein, the term "alkenyl" refers to an alkyl group, as defined herein, having one or more double bonds.

[0025] *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).

[0026] *Alkynyl*: As used herein, the term "alkynyl" refers to an alkyl group, as defined herein, having one or more triple bonds.

[0027] *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.

[0028] *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 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 a group in which an aromatic ring is fused to one or more non–aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0029] *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.

[0030] *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 tetrahydronaphthyl. 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, that has a single point of attachment to the rest of the molecule, 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, that has a single point of attachment to the rest of the molecule.

[0031] *Heteroaliphatic*: The term "heteroaliphatic", as used herein, is given its ordinary meaning in the art and refers to aliphatic groups as described herein in which one or more carbon atoms are independently replaced with one or more heteroatoms (*e.g.*, oxygen, nitrogen, sulfur, silicon, phosphorus, and the like). In some embodiments, one or more units selected from C, CH, CH_2, and CH_3 are independently replaced by one or more heteroatoms (including oxidized and/or substituted form thereof). In some embodiments, a heteroaliphatic group is heteroalkyl. In some embodiments, a heteroaliphatic group is heteroalkenyl.

[0032] *Heteroalkyl*: The term "heteroalkyl", as used herein, is given its ordinary meaning in the art and refers to alkyl groups as described herein in which one or more carbon atoms are independently replaced with one or more heteroatoms (*e.g.*, oxygen, nitrogen, sulfur, silicon, phosphorus, and the like). Examples of heteroalkyl groups include, but are not limited to, alkoxy, poly(ethylene glycol)-, alkyl-substituted amino, tetrahydrofuranyl, piperidinyl, morpholinyl, etc.

[0033] *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 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, 4*H*–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.

[0034] *Heteroatom*: The term "heteroatom", as used herein, means an atom that is not carbon or hydrogen. In some embodiments, a heteroatom is boron, oxygen, sulfur, nitrogen, phosphorus, 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.).

[0035] *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–2*H*–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 groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*–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.

[0036] *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).

[0037] *In vivo:* As used herein, the term "*in vivo*" refers to events that occur within an organism (*e.g.*, animal, plant and/or microbe).

[0038] *Optionally Substituted*: As described herein, compounds, *e.g.*, oligonucleotides, of the disclosure may contain optionally substituted and/or 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. In some embodiments, an optionally substituted group is unsubstituted. 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.

[0039] Suitable monovalent substituents on a substitutable atom, *e.g.*, a suitable carbon atom, are independently halogen; $-(CH_2)_{0-4}R°$; $-(CH_2)_{0-4}OR°$; $-O(CH_2)_{0-4}R^o$, $-O-(CH_2)_{0-4}C(O)OR°$; $-(CH_2)_{0-4}CH(OR°)_2$; $-(CH_2)_{0-4}Ph$, 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; $-N_3$; $-(CH_2)_{0-4}N(R°)_2$; $-(CH_2)_{0-4}N(R°)C(O)R°$; $-N(R°)C(S)R°$; $-(CH_2)_{0-4}N(R°)C(O)NR°_2$; $-N(R°)C(S)NR°_2$; $-(CH_2)_{0-4}N(R°)C(O)OR°$; $-N(R°)N(R°)C(O)R°$; $-N(R°)N(R°)C(O)NR°_2$; $-N(R°)N(R°)C(O)OR°$; $-(CH_2)_{0-4}C(O)R°$; $-C(S)R°$; $-(CH_2)_{0-4}C(O)OR°$; –

$(CH_2)_{0-4}C(O)SR°$; $-(CH_2)_{0-4}C(O)OSiR°_3$; $-(CH_2)_{0-4}OC(O)R°$; $-OC(O)(CH_2)_{0-4}SR°$, $-SC(S)SR°$; $-(CH_2)_{0-4}SC(O)R°$; $-(CH_2)_{0-4}C(O)NR°_2$; $-C(S)NR°_2$; $-C(S)SR°$; $-SC(S)SR°$, $-(CH_2)_{0-4}OC(O)NR°_2$; $-C(O)N(OR°)R°$; $-C(O)C(O)R°$; $-C(O)CH_2C(O)R°$; $-C(NOR°)R°$; $-(CH_2)_{0-4}SSR°$; $-(CH_2)_{0-4}S(O)_2R°$; $-(CH_2)_{0-4}S(O)_2OR°$; $-(CH_2)_{0-4}OS(O)_2R°$; $-S(O)_2NR°_2$; $-(CH_2)_{0-4}S(O)R°$; $-N(R°)S(O)_2NR°_2$; $-N(R°)S(O)_2R°$; $-N(OR°)R°$; $-C(NH)NR°_2$; $-Si(R°)_3$; $-OSi(R°)_3$; $-B(R°)_2$; $-OB(R°)_2$; $-OB(OR°)_2$; $-P(R°)_2$; $-P(OR°)_2$; $-OP(R°)_2$; $-OP(OR°)_2$; $-P(O)(R°)_2$; $-P(O)(OR°)_2$; $-OP(O)(R°)_2$; $-OP(O)(OR°)_2$; $-OP(O)(OR°)(SR°)$; $-SP(O)(R°)_2$; $-SP(O)(OR°)_2$; $-N(R°)P(O)(R°)_2$; $-N(R°)P(O)(OR°)_2$; $-P(R°)_2[B(R°)_3]$; $-P(OR°)_2[B(R°)_3]$; $-OP(R°)_2[B(R°)_3]$; $-OP(OR°)_2[B(R°)_3]$; $-(C_{1-4}$ straight or branched alkylene)$O-N(R°)_2$; or $-(C_{1-4}$ straight or branched alkylene)$C(O)O-N(R°)_2$, 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, $-CH_2-(C_{6-14}$ aryl), $-O(CH_2)_{0-1}(C_{6-14}$ aryl), $-CH_2$-(5-14 membered heteroaryl ring), 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 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, which may be substituted as defined below.

[0040] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^•$, -(haloR•), $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^•$, $-(CH_2)_{0-2}CH(OR^•)_2$; $-O$(haloR•), $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^•$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^•$, $-(CH_2)_{0-2}SR^•$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^•$, $-(CH_2)_{0-2}NR^•_2$, $-NO_2$, $-SiR^•_3$, $-OSiR^•_3$, -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.

[0041] Suitable divalent substituents, *e.g.*, on a suitable carbon atom, are independently the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, and an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from

nitrogen, oxygen, and sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, and an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0042] Suitable substituents on the aliphatic group of R^* 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, and sulfur.

[0043] *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.

[0044] *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.

[0045] *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.

[0046] *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, an active agent is present in unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a predetermined 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.

[0047] *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.

[0048] *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.

[0049] *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 salt 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. 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 defined and described in the present disclosure) salt. Representative alkali or alkaline earth metal salts include 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), all ionizable hydrogen in the acidic groups are replaced with cations. In some embodiments, a pharmaceutically acceptable salt is a sodium salt of a provided oligonucleotide. In some embodiments, a pharmaceutically acceptable salt is a sodium salt of a provided oligonucleotide, wherein each acidic phosphate group exists as a salt form (all sodium salt). In some embodiments, a pharmaceutically acceptable salt is a calcium salt of a provided oligonucleotide.

[0050] *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 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*–nitophenylacetamide, *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.

[0051] 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.

[0052] 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.

[0053] 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.

[0054] In some embodiments, a phosphorous linkage protecting group is a group attached to the phosphorous linkage (e.g., an internucleotidic linkage) throughout oligonucleotide synthesis. In some embodiments, a protecting group is attached to a sulfur atom of an phosphorothioate group. In some embodiments, a protecting group is attached to an oxygen atom of an internucleotide phosphorothioate linkage. In some embodiments, a protecting group is attached to an oxygen atom of the internucleotide phosphate linkage. In some embodiments a 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-l-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, or 4-[*N*-methyl-*N*-(2,2,2-trifluoroacetyl)amino]butyl.

[0055] *Sample*: A "sample" as used herein is a specific organism or material obtained therefrom. In some embodiments, a sample is a biological sample obtained or derived from a source of interest, as described herein. In some embodiments, a source of interest comprises an organism, such as an animal or human. In some embodiments, a biological sample comprises biological tissue or fluid. In some embodiments, a biological sample is or comprises bone marrow; blood; blood cells; ascites; tissue or fine needle biopsy samples; cell-containing body fluids; free floating nucleic acids; sputum; saliva; urine; cerebrospinal fluid, peritoneal fluid; pleural fluid; feces; lymph; gynecological fluids; skin swabs; vaginal swabs; oral swabs; nasal swabs; washings or lavages such as a ductal lavages or broncheoalveolar lavages; aspirates; scrapings; bone marrow specimens; tissue biopsy specimens; surgical specimens; feces, other body fluids, secretions and/or excretions; and/or cells therefrom, etc. In some embodiments, a biological sample is or comprises cells obtained from an individual. In some embodiments, a sample is a "primary sample" obtained directly from a source of interest by any appropriate means. For example, in some embodiments, a primary biological sample is obtained by methods selected from the group

consisting of biopsy (*e.g.*, fine needle aspiration or tissue biopsy), surgery, collection of body fluid (*e.g.*, blood, lymph, feces etc.), etc. In some embodiments, as will be clear from context, the term "sample" refers to a preparation that is obtained by processing (*e.g.*, by removing one or more components of and/or by adding one or more agents to) a primary sample. For example, filtering using a semi-permeable membrane. Such a "processed sample" may comprise, for example nucleic acids or proteins extracted from a sample or obtained by subjecting a primary sample to techniques such as amplification or reverse transcription of mRNA, isolation and/or purification of certain components, etc. In some embodiments, a sample is an organism. In some embodiments, a sample is a plant. In some embodiments, a sample is an animal. In some embodiments, a sample is a human. In some embodiments, a sample is an organism other than a human.

[0056] *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.

[0057] *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. A base sequence which is substantially complementary to a second sequence is not identical to the second sequence, but is mostly or nearly identical to the second sequence. In addition, 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.

[0058] *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.

[0059] *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 is predisposed to have that disease, disorder and/or condition. 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.

[0060] *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.

[0061] *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.

[0062] *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.

[0063] *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.

[0064] *Unsaturated:* The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[0065] *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.

[0066] *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).

[0067] *Nucleic acid*: The term "nucleic acid", as used herein, includes any nucleotides and polymers thereof. The term "polynucleotide", as used herein, refers to a polymeric form of nucleotides of any length, either ribonucleotides (RNA) or deoxyribonucleotides (DNA). These terms refer to the primary structure of the molecules and, thus, 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 modified nucleotides and/or 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 internucleotide linkages. The term encompasses nucleic acids containing any combinations of nucleobases, modified nucleobases, sugars, modified sugars, phosphate bridges or modified 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.

[0068] *Nucleotide:* The term "nucleotide" as used herein refers to a monomeric unit of a polynucleotide that consists of a nucleobase, a sugar, and one or more internucleotidic linkages. The 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. The naturally occurring sugar is the pentose (five-carbon sugar) deoxyribose (which forms DNA) or ribose (which forms RNA), though it should be understood that naturally and non-naturally occurring sugar analogs are also included. 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, phosphate, phosphorothioates, boranophosphates 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, such as those described herein. In some embodiments, a natural nucleotide comprises a naturally occurring base, sugar and internucleotidic linkage. As used herein, the term "nucleotide" also encompasses structural analogs used in lieu of natural or naturally-occurring nucleotides, such as modified nucleotides and nucleotide analogs.

[0069] *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.

[0070] *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; etc.

[0071] *Nucleoside*: The term "nucleoside" refers to a moiety wherein a nucleobase or a modified nucleobase is covalently bound to a sugar or a modified sugar.

[0072] *Modified nucleoside:* The term "modified nucleoside" refers to a moiety 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.

[0073] *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.

[0074] *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.

[0075] *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.

[0076] *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, 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.

[0077] *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.

[0078] *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.

[0079] *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.

[0080] *Solid support*: The term "solid support" refers to any support which enables synthesis of nucleic acids. 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).

[0081] *Homology*: "Homology" or "identity" or "similarity" refers to sequence similarity

between two nucleic acid molecules. Homology and identity can each be determined by comparing a position in each sequence which can be aligned for purposes of comparison. When an equivalent position in the compared sequences is occupied by the same base, then the molecules are identical at that position; when the equivalent site occupied by the same or a similar nucleic acid residue (*e.g.*, similar in steric and/or electronic nature), then the molecules can be referred to as homologous (similar) at that position. Expression as a percentage of homology/similarity or identity refers to a function of the number of identical or similar nucleic acids at positions shared by the compared sequences. A sequence which is "unrelated" or "non-homologous" shares less than 40% identity, less than 35% identity, less than 30% identity, or less than 25% identity with a sequence described herein. In comparing two sequences, the absence of residues (amino acids or nucleic acids) or presence of extra residues also decreases the identity and homology/similarity.

[0082] In some embodiments, the term "homology" describes a mathematically based comparison of sequence similarities which is used to identify genes with similar functions or motifs. The nucleic acid sequences described herein can be used as a "query sequence" to perform a search against public databases, for example, to identify other family members, related sequences or homologs. In some embodiments, such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) J. Mol. Biol. 215:403-10. In some embodiments, BLAST nucleotide searches can be performed with the NBLAST program, score=100, wordlength=12 to obtain nucleotide sequences homologous to nucleic acid molecules of the disclosure. In some embodiments, to obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) Nucleic Acids Res. 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and BLAST) can be used (See www.ncbi.nlm.nih.gov).

[0083] *Identity*: As used herein, "identity" means the percentage of identical nucleotide residues at corresponding positions in two or more sequences when the sequences are aligned to maximize sequence matching, *i.e.*, taking into account gaps and insertions. Identity can be readily calculated by known methods, including but not limited to those described in (Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; and Carillo, H., and Lipman, D., SIAM J. Applied Math., 48: 1073 (1988). Methods to determine identity are designed to give the largest match between the sequences tested. Moreover, methods to determine identity are codified in publicly available

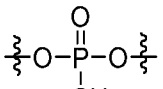
computer programs. Computer program methods to determine identity between two sequences include, but are not limited to, the GCG program package (Devereux, J., *et al.*, Nucleic Acids Research 12(1): 387 (1984)), BLASTP, BLASTN, and FASTA (Altschul, S. F. *et al.*, J. Molec. Biol. 215: 403-410 (1990) and Altschul *et al.* Nuc. Acids Res. 25: 3389-3402 (1997)). The BLAST X program is publicly available from NCBI and other sources (BLAST Manual, Altschul, S., *et al.*, NCBI NLM NIH Bethesda, Md. 20894; Altschul, S., *et al.*, J. Mol. Biol. 215: 403-410 (1990). The well-known Smith Waterman algorithm can also be used to determine identity.

[0084] *Oligonucleotide:* The term "oligonucleotide" refers to a polymer or oligomer of nucleotides, and may contain any combination of natural and non-natural nucleobases, sugars, and internucleotidic linkages.

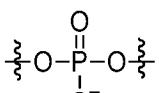
[0085] Oligonucleotides can be single-stranded or double-stranded. A single-stranded oligonucleotide can have double-stranded regions (formed by two portions of the single-stranded oligonucleotide) and a double-stranded oligonucleotide, which comprises two oligonucleotide chains, can have single-stranded regions for example, at regions where the two oligonucleotide chains are not complementary to each other. 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 RNAi agents and other RNA interference reagents (RNAi agents or iRNA agents), shRNA, antisense oligonucleotides, ribozymes, microRNAs, microRNA mimics, supermirs, aptamers, antimirs, antagomirs, Ul adaptors, triplex-forming oligonucleotides, G-quadruplex oligonucleotides, RNA activators, immuno-stimulatory oligonucleotides, and decoy oligonucleotides.

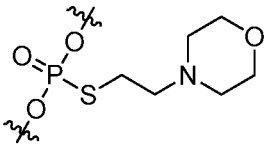
[0086] Oligonucleotides of the present disclosure can be of any of various lengths. In particular embodiments, oligonucleotides can range from about 2 to about 200 nucleotides in length. In various related embodiments, oligonucleotides, single-stranded, double-stranded, and triple-stranded, can range in length from about 4 to about 10 nucleotides, from about 10 to about 50 nucleotides, from about 20 to about 50 nucleotides, from about 15 to about 30 nucleotides, or from about 20 to about 30 nucleotides in length. In some embodiments, an oligonucleotide is from about 10 to about 40 nucleotides in length. In some embodiments, an oligonucleotide is from about 9 to about 39 nucleotides in length. In some embodiments, the oligonucleotide is at least 4 nucleotides in length. In some embodiments, the oligonucleotide is at least 5 nucleotides in length. In some embodiments, the oligonucleotide is at least 6 nucleotides in length. In some embodiments, the oligonucleotide is at least 7 nucleotides in length. In some embodiments, the oligonucleotide is at least 8 nucleotides in length. In some embodiments, the oligonucleotide is at least 9 nucleotides in length. In some embodiments, the oligonucleotide is at least 10 nucleotides in length. In some embodiments, the oligonucleotide is at least 11 nucleotides in length. In some embodiments, the oligonucleotide is at least 12 nucleotides in length. In some embodiments, the

oligonucleotide is at least 15 nucleotides in length. In some embodiments, the oligonucleotide is at least 20 nucleotides in length. In some embodiments, the oligonucleotide is at least 25 nucleotides in length. In some embodiments, the oligonucleotide is at least 30 nucleotides in length. In some embodiments, the oligonucleotide is a duplex of complementary strands of at least 18 nucleotides in length. In some embodiments, the oligonucleotide is a duplex of complementary strands of at least 21 nucleotides in length. In some embodiments, each nucleotide counted in a length independently comprises an optionally substituted nucleobase selected from adenine, cytosine, guanosine, thymine, and uracil.

[0087] *Internucleotidic linkage:* As used herein, the phrase "internucleotidic linkage" refers generally to a linkage linking nucleoside units of an oligonucleotide or a nucleic acid. In some embodiments, an internucleotidic linkage is a phosphodiester linkage, as found in naturally occurring DNA and RNA molecules (natural phosphate linkage). In some embodiments, an internucleotidic linkage includes a modified internucleotidic linkage. In some embodiments, an internucleotidic linkage is a "modified internucleotidic linkage" wherein each oxygen atom of the phosphodiester linkage is optionally and independently replaced by an organic or inorganic moiety. 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 in the present disclosure. In some embodiments, an internucleotidic linkage is a phosphotriester linkage, phosphorothioate diester linkage (), or modified phosphorothioate triester linkage. In some embodiments, an internucleotidic linkage is one of, *e.g.*, PNA (peptide nucleic acid) or PMO (phosphorodiamidate Morpholino oligomer) linkage. 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.

[0088] Non-limiting examples of modified internucleotidic linkages are modified internucleotidic linkages designated s, s1, s2, s3, s4, s5, s6, s7, s8, s9, s10, s11, s12, s13, s14, s15, s16, s17 and s18 as described in WO 2017/210647.

[0089] For instance, (*R*p, *S*p)–ATsCs1GA has 1) a phosphorothioate internucleotidic linkage () between T and C; and 2) a phosphorothioate triester internucleotidic linkage having the

structure of  between C and G. Unless otherwise specified, the *R*p/*S*p designations preceding an oligonucleotide sequence describe the configurations of chiral linkage phosphorus atoms in the internucleotidic linkages sequentially from 5' to 3' of the oligonucleotide sequence. For instance, in (*R*p, *S*p)–ATsCs1GA, the phosphorus in the "s" linkage between T and C has *R*p configuration and the phosphorus in "s1" linkage between C and G has *S*p configuration. In some embodiments, "All-(*R*p)" or "All-(*S*p)" is used to indicate that all chiral linkage phosphorus atoms in oligonucleotide have the same *R*p or *S*p configuration, respectively.

[0090] *Oligonucleotide type:* As used herein, the phrase "oligonucleotide type" is used to define an oligonucleotide that has a particular base sequence, pattern of backbone linkages (*i.e.*, pattern of internucleotidic linkage types, for example, phosphate, phosphorothioate, *etc.*), pattern of backbone chiral centers (*i.e.* pattern of linkage phosphorus stereochemistry (*R*p/*S*p)), and pattern of backbone phosphorus modifications (*e.g.*, pattern of "–XLR^1" groups in formula **I**). In some embodiments, oligonucleotides of a common designated "type" are structurally identical to one another.

[0091] 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. In some embodiments, 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 (*i.e.*, are structurally identical to one another). In many embodiments, however, provided compositions comprise a plurality of oligonucleotides of different types, typically in pre-determined relative amounts.

[0092] *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.

[0093] *Chirally controlled oligonucleotide composition:* The terms "chirally controlled oligonucleotide composition", "chirally controlled nucleic acid composition", and the like, as used herein, refers to a composition that comprises a plurality of oligonucleotides (or nucleic acids) which share 1) a common base sequence, 2) a common pattern of backbone linkages, and 3) a common pattern of backbone phosphorus modifications, 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 *R*p or *S*p in the composition, not a random *R*p and *S*p mixture as non-chirally controlled internucleotidic linkage). Level of the plurality of oligonucleotides (or nucleic acids) in a chirally controlled oligonucleotide composition is pre-determined/controlled (*e.g.*, through chirally controlled oligonucleotide preparation to stereoselectively form one or more chiral internucleotidic linkages). In some embodiments, about 1%-100%, (*e.g.*, about 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 1%-100%, (*e.g.*, about 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, a predetermined level is be about 1%-100%, (*e.g.*, about 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 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 are oligonucleotides of the plurality, 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. 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 1%-100% (*e.g.*, about 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 non-random or controlled levels of individual oligonucleotide or nucleic acids types. For instance, in some embodiments a chirally controlled oligonucleotide composition comprises one oligonucleotide type. In some embodiments, a chirally controlled oligonucleotide composition comprises more than one oligonucleotide type. In some embodiments, a chirally controlled oligonucleotide composition comprises multiple oligonucleotide types. In some embodiments, a chirally controlled oligonucleotide composition is a composition of oligonucleotides of an oligonucleotide type, which composition comprises a non-random or controlled level of a plurality of oligonucleotides of the oligonucleotide type.

[0094] *Chirally pure:* as used herein, the phrase "chirally pure" is used to describe an oligonucleotide or compositions thereof, in which all are nearly all (the rest are impurities) of the oligonucleotide molecules exist in a single diastereomeric form with respect to the linkage phosphorus atoms.

[0095] *Predetermined:* By predetermined (or pre-determined) is meant deliberately selected or non-random or controlled, for example as opposed to randomly occurring, random, or achieved without

control. Those of ordinary skill in the art, reading the present specification, will appreciate that the present disclosure provides technologies that permit selection of particular chemistry and/or stereochemistry features to be incorporated into oligonucleotide compositions, and further permits controlled preparation of oligonucleotide compositions having such chemistry and/or stereochemistry features. Such provided compositions are "predetermined" as described herein. Compositions that may contain certain oligonucleotides because they happen to have been generated through a process that are not controlled to intentionally generate the particular chemistry and/or stereochemistry features are not "predetermined" compositions. In some embodiments, a predetermined composition is one that can be intentionally reproduced (*e.g.*, through repetition of a controlled process). In some embodiments, a predetermined level of a plurality of oligonucleotides in a composition means that the absolute amount, and/or the relative amount (ratio, percentage, *etc.*) of the plurality of oligonucleotides in the composition is controlled. In some embodiments, a predetermined level of a plurality of oligonucleotides in a composition is achieved through chirally controlled oligonucleotide preparation.

[0096] *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 the internucleotidic linkage, which phosphorus atom corresponds to the phosphorus atom of a phosphodiester internucleotidic linkage as occurs in naturally occurring DNA and RNA. In some embodiments, a linkage phosphorus atom is in a modified internucleotidic linkage, wherein each oxygen atom of a phosphodiester linkage is optionally and independently replaced by an organic or inorganic moiety. In some embodiments, a linkage phosphorus atom is the P of Formula **I**. In some embodiments, a linkage phosphorus atom is chiral. In some embodiments, a linkage phosphorus atom is achiral.

[0097] *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 $-X-L-R^1$ wherein each of X, L and R^1 is independently as defined and described in the present disclosure.

[0098] *Blockmer:* the term "blockmer," as used herein, refers to an oligonucleotide strand 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 internucleotidic phosphorus linkage. By common structural feature is meant common stereochemistry at the linkage phosphorus or a common modification at the linkage phosphorus. In some embodiments, the at least two consecutive nucleotide units sharing a common structure feature at the internucleotidic phosphorus linkage are referred to as a "block". In some embodiments, a provided oligonucleotide is a blockmer.

[0099] 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."

[00100] 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.

[00101] 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.

[00102] In some embodiments, a blockmer comprises one or more blocks independently selected from 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.

[00103] *Altmer:* the term "altmer," as used herein, refers to an oligonucleotide strand 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 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. In some embodiments, a provided oligonucleotide is a altmer.

[00104] In some embodiments, an altmer is a "stereoaltmer," *e.g.*, no two consecutive nucleotide units have the same stereochemistry at the linkage phosphorus.

[00105] In some embodiments, an altmer is a "P-modification altmer" *e.g.*, no two consecutive nucleotide units have the same modification at the linkage phosphorus. For instance, All-(*S*p)-CAs1GsT, in which each linkage phosphorus has a different P-modification than the others.

[00106] In some embodiments, an altmer is a "linkage altmer," *e.g.*, no two consecutive nucleotide units have identical stereochemistry or identical modifications at the linkage phosphorus.

[00107] *Unimer:* the term "unimer," as used herein, refers to an oligonucleotide strand whose pattern of structural features characterizing each individual nucleotide unit is such that all nucleotide units

within the strand share at least one common structural feature at the internucleotidic phosphorus linkage. By common structural feature is meant common stereochemistry at the linkage phosphorus or a common modification at the linkage phosphorus. In some embodiments, a provided oligonucleotide is a unimer.

[00108] In some embodiments, a unimer is a "stereounimer," *e.g.*, all nucleotide units have the same stereochemistry at the linkage phosphorus.

[00109] In some embodiments, a unimer is a "P-modification unimer", *e.g.*, all nucleotide units have the same modification at the linkage phosphorus.

[00110] In some embodiments, a unimer is a "linkage unimer," *e.g.*, all nucleotide units have the same stereochemistry and the same modifications at the linkage phosphorus.

[00111] *Gapmer*: as used herein, the term "gapmer" refers to an oligonucleotide strand characterized in that at least one internucleotidic phosphorus linkage of the oligonucleotide strand is a phosphate diester linkage, for example such as those found in naturally occurring DNA or RNA. In some embodiments, more than one internucleotidic phosphorus linkage of the oligonucleotide strand is a phosphate diester linkage such as those found in naturally occurring DNA or RNA. In some embodiments, a provided oligonucleotide is a gapmer.

[00112] *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, 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. In some embodiments, a provided oligonucleotide is a skipmer.

[00113] 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.

[00114] The methods and structures described herein relating to compounds and compositions of the disclosure also apply to the pharmaceutically acceptable acid or base addition salts and all stereoisomeric forms of these compounds and compositions.

Description of Certain Embodiments

[00115] Among other things, the present disclosure provides oligonucleotides of particular structural designs comprising base, sugar and/or internucleotidic linkage modifications and/or patterns thereof as described in the present disclosure. In some embodiments, the present disclosure provides compositions, e.g., chirally controlled oligonucleotide compositions, of such oligonucleotides. As demonstrated here, provided oligonucleotides and compositions thereof provide many advantages, e.g., greatly improved stability, activity, selectivity, etc. In some embodiments, the present disclosure provides

technologies for assessing and/or using provided oligonucleotides and compositions thereof. For example, in some embodiments, the present disclosure provides methods for reducing levels of a nucleic acid (e.g., a transcript) and/or a product encoded thereby (e.g., a protein) using provided oligonucleotides and/or compositions thereof. In some embodiments, as demonstrated in the present disclosure, provided technologies (e.g., oligonucleotides, compositions, methods, etc.) provides high efficacy and/or specificity.

Certain Oligonucleotides and Compositions

[00116] In some embodiments, the present disclosure provides an oligonucleotide comprising a region of consecutive nucleotidic units:

$$(Nu^M)t[(Nu^O)n(Nu^M)m]y$$

wherein:

each Nu^M is independently a nucleotidic unit comprising a modified internucleotidic linkage;

each Nu^O is independently a nucleotidic unit comprising a natural phosphate linkage;

each of t, n, and m is independently 1-20; and

y is 1-10.

[00117] In some embodiments, as demonstrated in the present disclosure, such oligonucleotides provide improved properties, *e.g.*, improved stability, and/or activities.

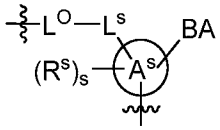
[00118] In some embodiments, y is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, y is 1. In some embodiments, y is 2. In some embodiments, y is 3. In some embodiments, y is 4. In some embodiments, y is 5. In some embodiments, y is 6. In some embodiments, y is 7. In some embodiments, y is 8. In some embodiments, y is 9. In some embodiments, y is 10.

[00119] As defined herein, each Nu^M independently comprises a modified internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is of formula I or a salt form thereof. In some embodiments, a modified internucleotidic linkage is chiral and is of formula I or a salt form thereof. In some embodiments, a modified internucleotidic linkage is a phosphorothioate diester linkage. In some embodiments, a modified internucleotidic linkage is chiral and is chirally controlled. In some embodiments, each modified internucleotidic linkage is chirally controlled. In some embodiments, internucleotidic linkage of Nu^M is a chirally controlled phosphorothioate diester linkage. In some embodiments, Nu^M of a provided oligonucleotides comprises different types of modified internucleotidic linkages. In some embodiments, Nu^M of a provided oligonucleotides comprises chiral internucleotidic linkages having linkage phosphorus atoms of different configuration. In some embodiments, Nu^M of a provided oligonucleotides comprises different types of modified internucleotidic linkages. In some embodiments, Nu^M of a provided oligonucleotides comprises chiral internucleotidic linkages having

linkage phosphorus atoms of different configuration. In some embodiments, at least one chiral internucleotidic linkage of Nu^M is *S*p at its linkage phosphorus. In some embodiments, at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 Nu^M each independently comprise a chiral internucleotidic linkage of *S*p at its linkage phosphorus. In some embodiments, each chiral internucleotidic linkage of Nu^M is *S*p at its linkage phosphorus. In some embodiments, at least one chiral internucleotidic linkage of Nu^M is *R*p at its linkage phosphorus. In some embodiments, at least one chiral internucleotidic linkage of Nu^M is *R*p at its linkage phosphorus, and at least one chiral internucleotidic linkage of Nu^M is *S*p at its linkage phosphorus. Additional nucleotidic unit comprising modified internucleotidic linkages suitable for Nu^M are known in the art and/or described in the present disclosure and can be utilized in accordance with the present disclosure.

[00120] As defined herein, each Nu^O is independently a nucleotidic unit comprising a natural phosphate linkage. In some embodiments, at least one Nu^O is a nucleotidic unit comprising a natural phosphate linkage, wherein the natural phosphate linkage is bonded to a 5'-nucleotidic unit and a carbon atom of the sugar unit of the nucleotidic unit, wherein the carbon atom is bonded to less than two hydrogen atoms. In some embodiments, each Nu^O is independently a nucleotidic unit comprising a natural phosphate linkage, wherein the natural phosphate linkage is bonded to a 5'-nucleotidic unit and a carbon atom of the sugar unit of the nucleotidic unit, wherein the carbon atom is bonded to less than two hydrogen atoms. In some embodiments, at least one Nu^O comprises a structure of $-C(R^{5s})_2-$, which structure is directly boned to the natural phosphate linkage of Nu^O and a ring moiety of the sugar unit of Nu^O. In some embodiments, each Nu^O independently comprises a structure of $-C(R^{5s})_2-$, which structure is directly boned to the natural phosphate linkage of Nu^O and a ring moiety of the sugar unit of Nu^O.

[00121] In some embodiments, each Nu^O independently has the structure of formula N-I:



N-I

or a salt form thereof, wherein:

BA is an optionally substituted group selected from C_{1-30} 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;

L^O is a natural phosphate linkage;

L^s is $-C(R^{5s})_2-$, or L;

each R^{5s} and R^s is independently −F, −Cl, −Br, −I, −CN, $-N_3$, −NO, $-NO_2$, −L−R', −L−OR', −L−SR', $-L-N(R')_2$, −O−L−OR', −O−L−SR', or $-O-L-N(R')_2$;

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, 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;

Ring A^s is an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms;

s is 0-20;

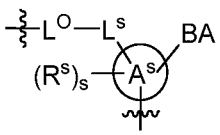
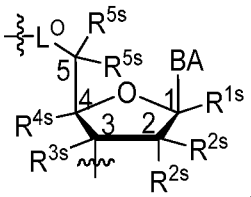
each R' is independently −R, −C(O)R, −C(O)OR, or $-S(O)_2R$; and

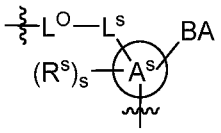
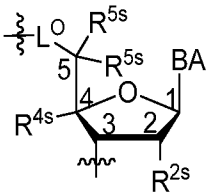
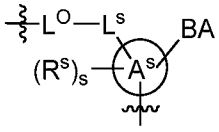
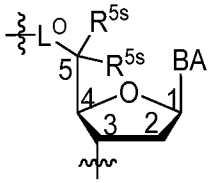
each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered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

[00122] In some embodiments,  has the structure of  , wherein each of R^{1s}, R^{2s}, R^{3s}, and R^{4s} is independently R^s and as described in the present disclosure. In

some embodiments,  has the structure of  , wherein each of R^{1s}, R^{2s}, R^{3s}, and R^{4s} is independently as described in the present disclosure. In some embodiments,  has the structure of  , wherein each of R^{1s}, R^{2s}, R^{3s}, and R^{4s} is independently as described in the present disclosure.

[00123] In some embodiments, L^s is $-C(R^{5s})_2-$. In some embodiments, one R^{5s} is $-H$ and L^s is $-CHR^{5s}-$. In some embodiments, each R^{5s} is independently R. In some embodiments, In some embodiments, $-C(R^{5s})_2-$ is $-C(R)_2-$. In some embodiments, one R^{5s} is $-H$ and $-C(R^{5s})_2-$ is $-CHR-$. In some embodiments, R 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 substituted. In some embodiments, R is unsubstituted. In some embodiments, R is methyl. Additional example R groups are widely described in the present disclosure. In some embodiments, the C of $-C(R^{5s})_2-$ is chiral and is *R*. In some embodiments, the C of $-C(R^{5s})_2-$ is chiral and is *S*. In some embodiments, $-C(R^{5s})_2-$ is $-(R)$-CHMe$-$. In some embodiments, $-C(R^{5s})_2-$ is $-(S)$-CHMe$-$.

Certain Oligonucleotide Formats

[00124] In some embodiments, the present disclosure provides oligonucleotides that have an asymmetric format.

[00125] In some embodiments, an oligonucleotide having an asymmetric format is capable of mediating a decrease in the level, expression and/or activity of a target gene or a gene product thereof. In some embodiments, an oligonucleotide having an asymmetric format is capable of mediating a decrease in the level, expression and/or activity of a target gene or a gene product thereof in a cell *in vitro*.

[00126] In some embodiments, an oligonucleotide having an asymmetric format is capable of operating via any mechanism, including but not limited to: steric hindrance or an RNaseH-based mechanism. In some embodiments, in steric hindrance, an oligonucleotide having an asymmetric format blocks or decreases translation of a target mRNA. In some embodiments, in an RNaseH-based mechanism, an oligonucleotide having an asymmetric format comprises a core which comprises multiple deoxyribose sugars and is capable of annealing to a target RNA (including but not limited to a target gene

mRNA), thus creating a DNA-RNA duplex, which acts as a substrate for RNaseH, which is capable of cleaving the target RNA. In some embodiments, an oligonucleotide having an asymmetric format comprises a core which is flanked on either side by a wing, each which also anneal to the target RNA. In some embodiments, one or both wings of an oligonucleotide having an asymmetric format are capable of improving the target specificity, target binding, stability, deliverability, efficacy, and/or other useful characteristic of an oligonucleotide having an asymmetric format.

[00127] In some embodiments, provided oligonucleotides comprise or are of a wing-core-wing, core-wing, or wing-core structure. In some embodiments, one wing differs chemically from the core and from the other wing. In some embodiments, a wing or a core is a block, and a wing-core-wing structure is a blockmer comprising three blocks. In some embodiments, a core is also designated a gap. In some embodiments, a wing-core-wing format is also designated a wing-gap-wing format. In some embodiments, a core is a gap wherein each sugar moiety of the core comprises no sugar modification of the wing(s). In some embodiments, an oligonucleotide having a wing-core-wing structure is also designated an oligonucleotide having a wing-gap-wing structure. In some embodiments, an oligonucleotide having a wing-core-wing structure is also designated a gapmer.

[00128] In some embodiments, a first wing, a second wing and a core can differ in sugar modifications or patterns thereof, and/or internucleotidic linkages or patterns thereof, and/or stereochemistry of internucleotidic linkages or patterns thereof.

[00129] In some embodiments, a wing-core-wing motif is described as "X-Y-Z", where "X" represents the length of the 5' wing, "Y" represents the length of the core, and "Z" represents the length of the 3' wing. In some embodiments, the core is positioned immediately adjacent to each of the 5' wing and the 3' wing. In some embodiments, X and Z are the same or different lengths and/or have the same or different modifications or patterns of modifications. In a preferred embodiment, Y is between 8 and 15 nucleotides. X, Y or Z can be any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30 or more nucleotides. In some embodiments, an oligonucleotide described herein has or comprises a wing-core-wing structure of, for example 5-10-5, 5-10-4, 4-10-4, 4-10-3, 3-10-3, 2-10-2, 5-9-5, 5-9-4, 4-9-5, 5-8-5, 5-8-4, 4-8-5, 5-7- 5, 4-7-5, 5-7-4, or 4-7-4.

[00130] In some embodiments, a core comprises at least 5 contiguous deoxyribose sugars. In some embodiments, a core comprises at least 5 contiguous deoxyribose sugars, and a first wing comprises a first type of sugar modification not in the core, and a second wing comprises a different type of sugar modification not in the core. In some embodiments, a core comprises at least 10 contiguous deoxyribose sugars, and a first wing comprises a first type of sugar modification not in the core, and a second wing comprises a different type of sugar modification not in the core. In some embodiments, a core comprises at least 10 contiguous deoxyribose sugars, and a first wing has a length of at least 5 bases and a first type

of sugar modification not in the core, and a second wing has a length of at least 5 bases and comprises a different type of sugar modification not in the core. In some embodiments, a core comprises at least 10 contiguous deoxyribose sugars, and a first wing has a length of at least 5 bases and a first type of sugar modification not in the core, and a second wing has a length of at least 5 bases and comprises a second type of sugar modification not in the core, wherein the first and second type of sugar modification are not the same. In some embodiments, a core comprises at least 10 contiguous deoxyribose sugars, and a first wing has a length of at least 5 bases and a first and a second type of sugar modification not in the core, and a second wing has a length of at least 5 bases and comprises the first but not the second type of sugar modification.

[00131] In some embodiments of an oligonucleotide having an asymmetric format, the length of the first wing and the second wing are different. In some embodiments of an oligonucleotide having an asymmetric format, the length of the first wing and the second wing are the same.

[00132] In some embodiments, an oligonucleotide has a wing-core-wing-structure, wherein the length (in bases) of the first wing is represented by X, the length of the core is represented by Y and the length of the second wing is represented by Z, wherein X-Y-Z is any of: 1-5-1, 1-6-1, 1-7-1, 1-8-1, 1-9-1, 1-10-1, 1-11-1, 1-12-1, 1-13-1, 1-14-1, 1-15-1, 1-16-1, 1-17-1, 1-18-1, 1-19-1, 1-20-1, 1-5-2, 1-6-2, 1-7-2, 1-8-2, 1-9-2, 1-10-2, 1-11-2, 1-12-2, 1-13-2, 1-14-2, 1-15-2, 1-16-2, 1-17-2, 1-18-2, 1-19-2, 1-20-2, 1-5-3, 1-6-3, 1-7-3, 1-8-3, 1-9-3, 1-10-3, 1-11-3, 1-12-3, 1-13-3, 1-14-3, 1-15-3, 1-16-3, 1-17-3, 1-18-3, 1-19-3, 1-20-3, 1-5-4, 1-6-4, 1-7-4, 1-8-4, 1-9-4, 1-10-4, 1-11-4, 1-12-4, 1-13-4, 1-14-4, 1-15-4, 1-16-4, 1-17-4, 1-18-4, 1-19-4, 1-20-4, 1-5-5, 1-6-5, 1-7-5, 1-8-5, 1-9-5, 1-10-5, 1-11-5, 1-12-5, 1-13-5, 1-14-5, 1-15-5, 1-16-5, 1-17-5, 1-18-5, 1-19-5, 1-20-5, 2-5-1, 2-6-1, 2-7-1, 2-8-1, 2-9-1, 2-10-1, 2-12-1, 2-12-1, 2-13-1, 2-14-1, 2-15-1, 2-16-1, 2-17-1, 2-18-1, 2-19-1, 2-20-1, 2-5-2, 2-6-2, 2-7-2, 2-8-2, 2-9-2, 2-10-2, 2-12-2, 2-12-2, 2-13-2, 2-14-2, 2-15-2, 2-16-2, 2-17-2, 2-18-2, 2-19-2, 2-20-2, 2-5-3, 2-6-3, 2-7-3, 2-8-3, 2-9-3, 2-10-3, 2-12-3, 2-12-3, 2-13-3, 2-14-3, 2-15-3, 2-16-3, 2-17-3, 2-18-3, 2-19-3, 2-20-3, 2-5-4, 2-6-4, 2-7-4, 2-8-4, 2-9-4, 2-10-4, 2-12-4, 2-12-4, 2-13-4, 2-14-4, 2-15-4, 2-16-4, 2-17-4, 2-18-4, 2-19-4, 2-20-4, 2-5-5, 2-6-5, 2-7-5, 2-8-5, 2-9-5, 2-10-5, 2-12-5, 2-12-5, 2-13-5, 2-14-5, 2-15-5, 2-16-5, 2-17-5, 2-18-5, 2-19-5, 2-20-5, 3-5-1, 3-6-1, 3-7-1, 3-8-1, 3-9-1, 3-10-1, 3-13-1, 3-14-1, 3-13-1, 3-14-1, 3-15-1, 3-16-1, 3-17-1, 3-18-1, 3-19-1, 3-20-1, 3-5-2, 3-6-2, 3-7-2, 3-8-2, 3-9-2, 3-10-2, 3-13-2, 3-14-2, 3-13-2, 3-14-2, 3-15-2, 3-16-2, 3-17-2, 3-18-2, 3-19-2, 3-20-2, 3-5-3, 3-6-3, 3-7-3, 3-8-3, 3-9-3, 3-10-3, 3-13-3, 3-14-3, 3-13-3, 3-14-3, 3-15-3, 3-16-3, 3-17-3, 3-18-3, 3-19-3, 3-20-3, 3-5-4, 3-6-4, 3-7-4, 3-8-4, 3-9-4, 3-10-4, 3-13-4, 3-14-4, 3-13-4, 3-14-4, 3-15-4, 3-16-4, 3-17-4, 3-18-4, 3-19-4, 3-20-4, 3-5-5, 3-6-5, 3-7-5, 3-8-5, 3-9-5, 3-10-5, 3-13-5, 3-14-5, 3-13-5, 3-14-5, 3-15-5, 3-16-5, 3-17-5, 3-18-5, 3-19-5, 3-20-5, 4-5-1, 4-6-1, 4-7-1, 4-8-1, 4-9-1, 4-10-1, 4-14-1, 4-14-1, 4-13-1, 4-14-1, 4-15-1, 4-16-1, 4-17-1, 4-18-1, 4-19-1, 4-20-1, 4-5-2, 4-6-2, 4-7-2, 4-8-2, 4-9-2, 4-10-2, 4-14-2, 4-14-2, 4-13-2, 4-14-2, 4-15-2, 4-16-2, 4-17-2, 4-

18-2, 4-19-2, 4-20-2, 4-5-3, 4-6-3, 4-7-3, 4-8-3, 4-9-3, 4-10-3, 4-14-3, 4-14-3, 4-13-3, 4-14-3, 4-15-3, 4-16-3, 4-17-3, 4-18-3, 4-19-3, 4-20-3, 4-5-4, 4-6-4, 4-7-4, 4-8-4, 4-9-4, 4-10-4, 4-14-4, 4-14-4, 4-13-4, 4-14-4, 4-15-4, 4-16-4, 4-17-4, 4-18-4, 4-19-4, 4-20-4, 4-5-5, 4-6-5, 4-7-5, 4-8-5, 4-9-5, 4-10-5, 4-14-5, 4-14-5, 4-13-5, 4-14-5, 4-15-5, 4-16-5, 4-17-5, 4-18-5, 4-19-5, 4-20-5, 5-5-1, 5-6-1, 5-7-1, 5-8-1, 5-9-1, 5-10-1, 5-15-1, 5-12-1, 5-13-1, 5-14-1, 5-15-1, 5-16-1, 5-17-1, 5-18-1, 5-19-1, 5-20-1, 5-5-2, 5-6-2, 5-7-2, 5-8-2, 5-9-2, 5-10-2, 5-15-2, 5-12-2, 5-13-2, 5-14-2, 5-15-2, 5-16-2, 5-17-2, 5-18-2, 5-19-2, 5-20-2, 5-5-3, 5-6-3, 5-7-3, 5-8-3, 5-9-3, 5-10-3, 5-15-3, 5-12-3, 5-13-3, 5-14-3, 5-15-3, 5-16-3, 5-17-3, 5-18-3, 5-19-3, 5-20-3, 5-5-4, 5-6-4, 5-7-4, 5-8-4, 5-9-4, 5-10-4, 5-15-4, 5-12-4, 5-13-4, 5-14-4, 5-15-4, 5-16-4, 5-17-4, 5-18-4, 5-19-4, 5-20-4, 5-5-5, 5-6-5, 5-7-5, 5-8-5, 5-9-5, 5-10-5, 5-15-5, 5-12-5, 5-13-5, 5-14-5, 5-15-5, 5-16-5, 5-17-5, 5-18-5, 5-19-5, 5-20-5, 1-5-6, 1-6-6, 1-7-6, 1-8-6, 1-9-6, 1-10-6, 1-11-6, 1-12-6, 1-13-6, 1-14-6, 1-15-6, 1-16-6, 1-17-6, 1-18-6, 1-19-6, 1-20-6, 2-5-6, 2-6-6, 2-7-6, 2-8-6, 2-9-6, 2-10-6, 2-11-6, 2-12-6, 2-13-6, 2-14-6, 2-15-6, 2-16-6, 2-17-6, 2-18-6, 2-19-6, 2-20-6, 3-5-6, 3-6-6, 3-7-6, 3-8-6, 3-9-6, 3-10-6, 3-11-6, 3-12-6, 3-13-6, 3-14-6, 3-15-6, 3-16-6, 3-17-6, 3-18-6, 3-19-6, 3-20-6, 4-5-6, 4-6-6, 4-7-6, 4-8-6, 4-9-6, 4-10-6, 4-11-6, 4-12-6, 4-13-6, 4-14-6, 4-15-6, 4-16-6, 4-17-6, 4-18-6, 4-19-6, 4-20-6, 5-5-6, 5-6-6, 5-7-6, 5-8-6, 5-9-6, 5-10-6, 5-11-6, 5-12-6, 5-13-6, 5-14-6, 5-15-6, 5-16-6, 5-17-6, 5-18-6, 5-19-6, 5-20-6, 6-5-6, 6-6-6, 6-7-6, 6-8-6, 6-9-6, 6-10-6, 6-11-6, 6-12-6, 6-13-6, 6-14-6, 6-15-6, 6-16-6, 6-17-6, 6-18-6, 6-19-6, 6-20-6, 7-5-6, 7-6-6, 7-7-6, 7-8-6, 7-9-6, 7-10-6, 7-11-6, 7-12-6, 7-13-6, 7-14-6, 7-15-6, 7-16-6, 7-17-6, 7-18-6, 7-19-6, 7-20-6, 1-5-7, 1-6-7, 1-7-7, 1-8-7, 1-9-7, 1-10-7, 1-11-7, 1-12-7, 1-13-7, 1-14-7, 1-15-7, 1-16-7, 1-17-7, 1-18-7, 1-19-7, 1-20-7, 2-5-7, 2-6-7, 2-7-7, 2-8-7, 2-9-7, 2-10-7, 2-11-7, 2-12-7, 2-13-7, 2-14-7, 2-15-7, 2-16-7, 2-17-7, 2-18-7, 2-19-7, 2-20-7, 3-5-7, 3-6-7, 3-7-7, 3-8-7, 3-9-7, 3-10-7, 3-11-7, 3-12-7, 3-13-7, 3-14-7, 3-15-7, 3-16-7, 3-17-7, 3-18-7, 3-19-7, 3-20-7, 4-5-7, 4-6-7, 4-7-7, 4-8-7, 4-9-7, 4-10-7, 4-11-7, 4-12-7, 4-13-7, 4-14-7, 4-15-7, 4-16-7, 4-17-7, 4-18-7, 4-19-7, 4-20-7, 5-5-7, 5-6-7, 5-7-7, 5-8-7, 5-9-7, 5-10-7, 5-11-7, 5-12-7, 5-13-7, 5-14-7, 5-15-7, 5-16-7, 5-17-7, 5-18-7, 5-19-7, 5-20-7, 6-5-7, 6-6-7, 6-7-7, 6-8-7, 6-9-7, 6-10-7, 6-11-7, 6-12-7, 6-13-7, 6-14-7, 6-15-7, 6-16-7, 6-17-7, 6-18-7, 6-19-7, 6-20-7, 7-5-7, 7-6-7, 7-7-7, 7-8-7, 7-9-7, 7-10-7, 7-11-7, 7-12-7, 7-13-7, 7-14-7, 7-15-7, 7-16-7, 7-17-7, 7-18-7, 7-19-7, or 7-20-7.

[00133] As described in the present disclosure, cores and wings can be of various lengths. In some embodiments, a core comprises no less than 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleobases. In some embodiments, a wing comprises no less than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleobases. In some embodiments, a wing comprises no more than 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleobases. In some embodiments, for a wing-core-wing structure, both wings are of the same length, for example, of 5 nucleobases. In some embodiments, the two wings are of different lengths. In some embodiments, a core is no less than 40%, 45%, 50%, 60%, 70%, 80%, or 90% of total oligonucleotide length as measured by percentage of nucleoside units within the core. In some embodiments, a core is no

less than 50% of total oligonucleotide length.

[00134] In some embodiments of an oligonucleotide having an asymmetric format, a wing has a length of 6 bases. A non-limiting example of such an oligonucleotide is WV-12485. In some embodiments of an oligonucleotide having an asymmetric format, a wing has a length of 7 bases. A non-limiting example of such an oligonucleotide is WV-12107.

[00135] In some embodiments, an oligonucleotide having an asymmetric format has a wing-core-wing structure, wherein one wing differs from the other wing. In some embodiments, a wing comprises one or more sugar modifications. In some embodiments, the two wings of a wing-core-wing structure comprise different sugar modifications. In some embodiments, sugar modifications provide improved stability compared to absence of sugar modifications.

[00136] In some embodiments, a core comprises no 2'-substitution. In some embodiments, each sugar unit of a core is a natural sugar unit found in natural unmodified DNA. In some embodiments, a core comprises one or more 2'-halogen modification. In some embodiments, a core comprises one or more 2'-F modification.

[00137] In some embodiments, certain sugar modifications, e.g., 2'-MOE increase stability against nucleases. In some embodiments, a wing comprises 2'-MOE modifications. In some embodiments, each nucleoside unit of a wing comprising a pyrimidine base (*e.g.*, C, U, T, *etc.*) comprises a 2'-MOE modification. In some embodiments, each sugar unit of a wing comprises a 2'-MOE modification. In some embodiments, each nucleoside unit of a wing comprising a purine base (*e.g.*, A, G, *etc.*) comprises no 2'-MOE modification (*e.g.*, 2'-OMe, no 2'-modification, *etc.*). In some embodiments, each nucleoside unit of a wing comprising a purine base comprises a 2'-OMe modification. In some embodiments, each internucleotidic linkage at the 3'-position of a sugar unit comprising a 2'-MOE modification is a natural phosphate linkage. In some embodiments, each internucleotidic linkage at the 3'-position of a sugar unit comprising a 2'-MOE modification is a natural phosphate linkage, except that if the wing is a 5'-wing to the core, the first internucleotidic linkage of the wing is a modified internucleotidic linkage, *e.g.*, a phosphorothioate diester linkage, and the internucleotidic linkage linking the 3'-end nucleoside unit of the wing and the 5'-end nucleoside unit of the core is a modified internucleotidic linkage, *e.g.*, a phosphorothioate diester linkage; and if the wing is a 3'-wing to the core, the last internucleotidic linkage of the wing is a modified internucleotidic linkage, *e.g.*, a phosphorothioate diester linkage, and the internucleotidic linkage linking the 3'-end nucleoside unit of the core and the 5'-end nucleoside unit of the wing is a modified internucleotidic linkage, *e.g.*, a phosphorothioate diester linkage. In some embodiments, such a wing is a 5'-wing. In some embodiments, such a wing is a 3'-wing.

[00138] In some embodiments, a wing comprises no 2'-MOE modifications. In some

embodiments, a wing comprises 2'-OMe modifications. In some embodiments, each nucleoside unit of a wing independently comprises a 2'-OMe modifications. Among other things, the present disclosure encompasses the recognition that oligonucleotides with 2'-OMe modifications are less stable than comparable oligonucleotides with 2'-MOE modifications under certain conditions. In some embodiments, modified non-natural internucleotidic linkages, such as phosphorothioate diester linkages, in some instances particularly *S*p phosphorothioate diester linkages, can be utilized to improve properties, *e.g.*, stability, of oligonucleotides. In some embodiments, a wing comprises no 2'-MOE modifications, and each internucleotidic linkage between nucleoside units of the wing is a modified internucleotidic linkage. In some embodiments, a wing comprises no 2'-MOE modifications, each nucleoside unit of the wing comprise a 2'-OMe modification, and each internucleotidic linkage between nucleoside units of the wing is a modified internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphorothioate diester linage. In some embodiments, a modified internucleotidic linkage is a chirally controlled internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a chirally controlled internucleotidic linkage wherein the linkage phosphorus is of *S*p configuration. In some embodiments, a modified internucleotidic linkage is a chirally controlled internucleotidic linkage wherein the linkage phosphorus is of *R*p configuration. In some embodiments, a modified internucleotidic linkage is a *S*p phosphorothioate diester linkage. In some embodiments, a modified internucleotidic linkage is a *R*p phosphorothioate diester linkage. In some embodiments, such a wing is a 5'-wing. In some embodiments, such a wing is a 3'-wing.

[00139] In some embodiments, 2'-modifications and/or modified internucleotidic linkages can be utilized either individually or in combination to fine-tune properties, *e.g.*, stability, and/or activities of oligonucleotides.

[00140] In some embodiments, a wing comprises one or more natural phosphate linkages. In some embodiments, a wing comprises one or more consecutive natural phosphate linkages. In some embodiments, a wing comprises one or more natural phosphate linkages and one or more modified internucleotidic linkages. In some embodiments, a modified internucleotidic linkage is a phosphorothioate diester linkage. In some embodiments, a modified internucleotidic linkage is a *S*p phosphorothioate diester linkage.

[00141] In some embodiments, a wing comprises no natural phosphate linkages, and each internucleotidic linkage of the wing is independently a modified internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is chiral and chirally controlled. In some embodiments, a modified internucleotidic linkage is a phosphorothioate diester linkage. In some embodiments, a modified internucleotidic linkage is a *S*p phosphorothioate diester linkage.

[00142] In some embodiments, for an oligonucleotide comprising or is a wing-core-wing

structure, the two wings are different in that they contain different levels and/or types of chemical modifications, backbone chiral center stereochemistry, and/or patterns thereof. In some embodiments, the two wings are different in that they contain different levels and/or types of sugar modifications, and/or internucleotidic linkages, and/or internucleotidic linkage stereochemistry, and/or patterns thereof. For example, in some embodiments, one wing comprises 2'-OR modifications wherein R is optionally substituted C_{1-6} alkyl (*e.g.*, 2-MOE), while the other wing comprises no such modifications, or lower level (*e.g.*, by number and/or percentage) of such modifications; additionally and alternatively, one wing comprises natural phosphate linkages while the other wing comprises no natural phosphate linkages or lower level (*e.g.*, by number and/or percentage) of natural phosphate linkages; additionally and alternatively, one wing may comprise a certain type of modified internucleotidic linkages (*e.g.*, phosphorothioate diester internucleotidic linkage) while the other wing comprises no natural phosphate linkages or lower level (*e.g.*, by number and/or percentage) of the type of modified internucleotidic linkages; additionally and alternatively, one wing may comprise chiral modified internucleotidic linkages comprising linkage phosphorus atoms of a particular configuration (*e.g.*, *R*p or *S*p), while the other wing comprises no or lower level of chiral modified internucleotidic linkages comprising linkage phosphorus atoms of the particular configuration; alternatively or additionally, each wing may comprise a different pattern of sugar modification, internucleotidic linkages, and/or backbone chiral centers. In some embodiments, one wing comprises one or more natural phosphate linkages and one or more 2'-OR modifications wherein R is not −H or −Me, and the other wing comprises no natural phosphate linkages and no 2'-OR modifications wherein R is not −H or −Me. In some embodiments, one wing comprises one or more natural phosphate linkages and one or more 2'-MOE modifications, and each internucleotidic linkage in the other wing is a phosphorothioate linkage and each sugar unit of the other wing comprises a 2'-OMe modification. In some embodiments, one wing comprises one or more natural phosphate linkages and one or more 2'-MOE modifications, and each internucleotidic linkage in the other wing is a *S*p phosphorothioate linkage and each sugar unit of the other wing comprises a 2'-OMe modification.

[00143] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein one wing comprises a 2'-OMe and the other wing comprises a bicyclic sugar. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein one wing comprises a 2'-OMe and the other wing comprises a bicyclic sugar, and the majority of the sugars in the core comprise a 2'-deoxy.

[00144] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-OMe and the majority of the sugars in the other wing are a bicyclic sugar. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-OMe and the majority of the sugars in the other wing are a bicyclic sugar, and the majority of the sugars in the core comprise a 2'-deoxy.

[00145] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-OMe and, in the other wing, at least one sugar is a bicyclic sugar and at least one sugar comprises a 2'-OMe. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-OMe and, in the other wing, at least one sugar is a bicyclic sugar and at least one sugar comprises a 2'-OMe, and the majority of the sugars in the core comprise a 2'-deoxy.

[00146] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing are a bicyclic sugar and, in the other wing, at least one sugar is a bicyclic sugar and at least one sugar comprises a 2'-OMe. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing are a bicyclic sugar and, in the other wing, at least one sugar is a bicyclic sugar and at least one sugar comprises a 2'-OMe, and the majority of the sugars in the core comprise a 2'-deoxy.

[00147] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-OMe and, in the other wing, at least two sugars are a bicyclic sugar and at least two sugars comprise a 2'-OMe. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-OMe and, in the other wing, at least two sugars are a bicyclic sugar and at least two sugars comprise a 2'-OMe, and the majority of the sugars in the core comprise a 2'-deoxy.

[00148] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing are a bicyclic sugar and, in the other wing, at least two sugars are a bicyclic sugar and at least two sugars comprise a 2'-OMe. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing are a bicyclic sugar and, in the other wing, at least two sugars are a bicyclic sugar and at least two sugars comprise a 2'-OMe, and the majority of the sugars in the core comprise a 2'-deoxy.

[00149] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein each sugar in one wing comprises a 2'-OMe and each sugar in the other wing comprises a bicyclic sugar. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein each sugar in one wing comprises a 2'-OMe and each sugar in the other wing comprises a bicyclic sugar, and the majority of the sugars in the core comprise a 2'-deoxy.

[00150] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein each sugar in one wing comprises a bicyclic sugar, each sugar in the other wing comprises a 2'-OMe, and each sugar in the core comprises a 2'-deoxy.

[00151] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein one wing comprises a bicyclic sugar and the other wing comprises a 2'-MOE. In some embodiments, an

oligonucleotide comprises a wing-core-wing structure, wherein one wing comprises a bicyclic sugar and the other wing comprises a 2'-MOE, and the majority of the sugars in the core comprise a 2'-deoxy.

[00152] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a bicyclic sugar and the majority of the sugars in the other wing comprise a 2'-MOE. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a bicyclic sugar and the majority of the sugars in the other wing comprise a 2'-MOE, and the majority of the sugars in the core comprise a 2'-deoxy.

[00153] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a bicyclic sugar and, in the other wing, at least one sugar comprises a 2'-MOE and at least one sugar is a bicyclic sugar. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a bicyclic sugar and, in the other wing, at least one sugar comprises a 2'-MOE and at least one sugar is a bicyclic sugar, and the majority of the sugars in the core comprise a 2'-deoxy.

[00154] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-MOE and, in the other wing, at least one sugar comprises a 2'-MOE and at least one sugar is a bicyclic sugar. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-MOE and, in the other wing, at least one sugar comprises a 2'-MOE and at least one sugar is a bicyclic sugar, and the majority of the sugars in the core comprise a 2'-deoxy.

[00155] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a bicyclic sugar and, in the other wing, at least two sugars comprise a 2'-MOE and at least two sugars is a bicyclic sugar. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a bicyclic sugar and, in the other wing, at least two sugars comprise a 2'-MOE and at least two sugars is a bicyclic sugar, and the majority of the sugars in the core comprise a 2'-deoxy.

[00156] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-MOE and, in the other wing, at least two sugars comprise a 2'-MOE and at least two sugars is a bicyclic sugar. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-MOE and, in the other wing, at least two sugars comprise a 2'-MOE and at least two sugars is a bicyclic sugar, and the majority of the sugars in the core comprise a 2'-deoxy.

[00157] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein each sugar in one wing are a bicyclic sugar and each sugar in the other wing comprises a 2'-MOE. In

some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein each sugar in one wing are a bicyclic sugar and each sugar in the other wing comprises a 2'-MOE, and the majority of the sugars in the core comprise a 2'-deoxy.

[00158] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein each sugar in one wing comprises a 2'-MOE, each sugar in the other wing are a bicyclic sugar, and each sugar in the core comprises a 2'-deoxy.

[00159] In some embodiments, a bicyclic sugar is a LNA, a cEt or BNA.

[00160] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein one wing comprises a 2'-OMe and the other wing comprises 2'-F. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein one wing comprises a 2'-OMe and the other wing comprises 2'-F, and the majority of the sugars in the core comprise a 2'-deoxy.

[00161] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-OMe and the majority of the sugars in the other wing are 2'-F. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-OMe and the majority of the sugars in the other wing are 2'-F, and the majority of the sugars in the core comprise a 2'-deoxy.

[00162] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-OMe and, in the other wing, at least one sugar is 2'-F and at least one sugar comprises a 2'-OMe. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-OMe and, in the other wing, at least one sugar is 2'-F and at least one sugar comprises a 2'-OMe, and the majority of the sugars in the core comprise a 2'-deoxy.

[00163] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing are 2'-F and, in the other wing, at least one sugar is 2'-F and at least one sugar comprises a 2'-OMe. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing are 2'-F and, in the other wing, at least one sugar is 2'-F and at least one sugar comprises a 2'-OMe, and the majority of the sugars in the core comprise a 2'-deoxy.

[00164] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-OMe and, in the other wing, at least two sugars are 2'-F and at least two sugars comprise a 2'-OMe. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-OMe and, in the other wing, at least two sugars are 2'-F and at least two sugars comprise a 2'-OMe, and the majority of the sugars in the core comprise a 2'-deoxy.

[00165] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing are 2'-F and, in the other wing, at least two sugars are 2'-F and at least two sugars comprise a 2'-OMe. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing are 2'-F and, in the other wing, at least two sugars are 2'-F and at least two sugars comprise a 2'-OMe, and the majority of the sugars in the core comprise a 2'-deoxy.

[00166] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein each sugar in one wing comprises a 2'-OMe and each sugar in the other wing comprises 2'-F. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein each sugar in one wing comprises a 2'-OMe and each sugar in the other wing comprises 2'-F, and the majority of the sugars in the core comprise a 2'-deoxy.

[00167] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein each sugar in one wing comprises 2'-F, each sugar in the other wing comprises a 2'-OMe, and each sugar in the core comprises a 2'-deoxy.

[00168] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein one wing comprises 2'-F and the other wing comprises a 2'-MOE. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein one wing comprises 2'-F and the other wing comprises a 2'-MOE, and the majority of the sugars in the core comprise a 2'-deoxy.

[00169] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise 2'-F and the majority of the sugars in the other wing comprise a 2'-MOE. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise 2'-F and the majority of the sugars in the other wing comprise a 2'-MOE, and the majority of the sugars in the core comprise a 2'-deoxy.

[00170] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise 2'-F and, in the other wing, at least one sugar comprises a 2'-MOE and at least one sugar is 2'-F. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise 2'-F and, in the other wing, at least one sugar comprises a 2'-MOE and at least one sugar is 2'-F, and the majority of the sugars in the core comprise a 2'-deoxy.

[00171] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-MOE and, in the other wing, at least one sugar comprises a 2'-MOE and at least one sugar is 2'-F. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-MOE and, in the other wing, at least one sugar comprises a 2'-MOE and at least one sugar is 2'-F, and the majority of

the sugars in the core comprise a 2'-deoxy.

[00172] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise 2'-F and, in the other wing, at least two sugars comprise a 2'-MOE and at least two sugars is 2'-F. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise 2'-F and, in the other wing, at least two sugars comprise a 2'-MOE and at least two sugars is 2'-F, and the majority of the sugars in the core comprise a 2'-deoxy.

[00173] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-MOE and, in the other wing, at least two sugars comprise a 2'-MOE and at least two sugars is 2'-F. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein the majority of the sugars in one wing comprise a 2'-MOE and, in the other wing, at least two sugars comprise a 2'-MOE and at least two sugars is 2'-F, and the majority of the sugars in the core comprise a 2'-deoxy.

[00174] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein each sugar in one wing is 2'-F and each sugar in the other wing comprises a 2'-MOE. In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein each sugar in one wing is 2'-F and each sugar in the other wing comprises a 2'-MOE, and the majority of the sugars in the core comprise a 2'-deoxy.

[00175] In some embodiments, an oligonucleotide comprises a wing-core-wing structure, wherein each sugar in one wing comprises a 2'-MOE, each sugar in the other wing are 2'-F, and each sugar in the core comprises a 2'-deoxy.

[00176] In some embodiments, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% 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.

[00177] In some embodiments, a nucleoside comprising a 2'-modification is followed by a modified internucleotidic linkage. In some embodiments, a nucleoside comprising a 2'-modification is preceded by a modified internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphorothioate. In some embodiments, a chiral internucleotidic linkage is *S*p. In some embodiments, a nucleoside comprising a 2'-modification is followed by a *S*p chiral internucleotidic linkage. In some embodiments, a nucleoside comprising a 2'-F is followed by a *S*p chiral internucleotidic linkage. In some embodiments, a nucleoside comprising a 2'-modification is preceded by a *S*p chiral internucleotidic linkage. In some embodiments, a nucleoside comprising a 2'-F is preceded by a *S*p chiral internucleotidic linkage. In some embodiments, a chiral internucleotidic linkage is *R*p. In some embodiments, a nucleoside comprising a 2'-modification is followed by an *R*p chiral internucleotidic linkage. In some embodiments, a nucleoside comprising a 2'-F is followed by an *R*p chiral internucleotidic linkage. In some embodiments, a nucleoside comprising a 2'-modification is preceded by an *R*p chiral internucleotidic linkage. In some embodiments, a nucleoside comprising a 2'-F is preceded by an *R*p chiral internucleotidic linkage.

[00178] In some embodiments, a provided oligonucleotide having an asymmetric formats has a wing-core-wing structure. In some embodiments of an oligonucleotide having an asymmetric format having an asymmetrical format, one wing differs from another. In some embodiments of an oligonucleotide having an asymmetric format having an asymmetrical format, one wing differs from another in the sugar modifications or combination or pattern thereof, or the backbone internucleotidic linkages or combination or pattern thereof, or the backbone chiral centers or combination or pattern thereof. In some embodiments of an oligonucleotide having an asymmetrical format, the core comprises 1 or more 2'-deoxy sugars. In some embodiments of an oligonucleotide having an asymmetrical format, the core comprises 5 or more consecutive 2'-deoxy sugars. In some embodiments of an oligonucleotide having an asymmetrical format, the core comprises 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more consecutive 2'-deoxy sugars. Some non-limiting examples of oligonucleotides having an asymmetrical format are shown herein. In some embodiments of an oligonucleotide having an asymmetric format having an asymmetrical format, a first wing and a second wing independently has a pattern of 2'-modifications of sugars which is or comprises F, FF, FFF, FFFF, FFFFF, FMMMF, FMMMF, LMMMm, m, M, mm, MM, mmm, mMm, MMm, MMM, mmm, mmmm, mMMm, MMMm, MMMM, mmmm, mmmmm, MMMMM, mMMMm, MMMMM, mmmmm, or any pattern of 2'-modifications of any wing

of any oligonucleotide described herein, wherein the pattern of 2'-modifications of the first and second wing are different, and wherein m = 2'-OMe; M = 2'-MOE; F = 2'-F; and L = LNA.

[00179] In some embodiments, an oligonucleotide having an asymmetric format (e.g., wherein one wing differs chemically from another wing) has an improved biological activity compared to an oligonucleotide having the same base sequence but a different structure (e.g., a symmetric format wherein both wings have the same pattern of chemical modifications; or a different asymmetric format). In some embodiments, improved biological activity includes improved decrease of the expression, activity, and/or level or a gene or gene product. In some embodiments, improved biological activity is improved delivery to a cellular nucleus. In some embodiments, improved biological activity is improved delivery to a cellular nucleus and one wing in an oligonucleotide having an asymmetric format comprises a 2'-F or two or more 2'-F. In some embodiments, improved biological activity is improved delivery to a cellular nucleus and one wing in an oligonucleotide having an asymmetric format comprises a 2'-MOE or two or more 2'-MOE. In some embodiments, improved biological activity is improved delivery to a cellular nucleus and one wing in an oligonucleotide having an asymmetric format comprises a 2'-OMe or two or more 2'-OMe. In some embodiments, improved biological activity is improved delivery to a cellular nucleus and one wing in an oligonucleotide having an asymmetric format comprises a bicyclic sugar or two or more bicyclic sugars.

[00180] In some embodiments, an oligonucleotide having an asymmetric format comprises a first wing having a particular sugar modification(s) or combination or pattern thereof, and a second wing having a different particular sugar modification(s) or combination or pattern thereof.

[00181] In some embodiments, an oligonucleotide having an asymmetric format comprises a first wing having a particular 2'-sugar modification(s) or combination or pattern thereof, and a second wing having a different particular 2'-sugar modification(s) or combination or pattern thereof.

[00182] In some embodiments, a pattern of sugar modifications of an oligonucleotide having an asymmetric format comprises any one or more of: S1-S1-S1-S1, S1-S1-S1-S2, S1-S1-S2-S1, S1-S1-S2-S2, S1-S2-S1-S1, S1-S2-S1-S2, S1-S2-S1-S2, S1-S2-S2-S1, S1-S2-S2-S2, S2-S1-S1-S1, S2-S1-S1-S2, S2-S1-S1-S2, S2-S1-S2-S1, S2-S1-S2-S2, S2-S2-S1-S1, S2-S2-S1-S2, S2-S2-S2-S1, S2-S2-S2-S2, S1-S1-S1-S1, S1-S1-S1-S3, S1-S1-S3-S1, S1-S1-S3-S3, S1-S3-S1-S1, S1-S3-S1-S3, S1-S3-S3-S1, S1-S3-S3-S3, S3-S1-S1-S1, S3-S1-S1-S3, S3-S1-S1-S3, S3-S1-S3-S1, S3-S1-S3-S1, S3-S1-S3-S3, S3-S1-S3-S3, S3-S3-S1-S1, S3-S3-S1-S1, S3-S3-S1-S3, S3-S3-S1-S3, S3-S3-S3-S1, S3-S3-S3-S1, S3-S3-S3-S3, S3-S3-S3-S3, S1-S1-S1-S1, S1-S1-S1-S4, S1-S1-S1-S4, S1-S1-S4-S1, S1-S1-S4-S1, S1-S1-S4-S4, S1-S1-S4-S4, S1-S4-S1-S1, S1-S4-S1-S1, S1-S4-S1-S4, S1-S4-S1-S4, S1-S4-S4-S1, S1-S4-S4-S1, S1-S4-S4-S4, S1-S4-S4-S4, S4-S1-S1-S1, S4-S1-S1-S1, S4-S1-S1-S4, S4-S1-S1-S4, S4-S1-S4-S1, S4-S1-S4-S1, S4-S1-S4-S4, S4-S1-S4-S4, S4-S4-S1-S1, S4-S4-S1-S1, S4-S4-S1-S4, S4-S4-S1-S4, S4-S4-S4-S1,

S4-S4-S4-S1, S4-S4-S4-S4, S4-S4-S4-S4, S1-S1-S1-S2, S1-S1-S1-S3, S1-S1-S1-S3, S1-S1-S1-S3, S1-S1-S2-S1, S1-S1-S2-S1, S1-S1-S2-S1, S1-S1-S2-S2, S1-S1-S2-S2, S1-S1-S2-S2, S1-S1-S2-S3, S1-S1-S2-S3, S1-S1-S2-S3, S1-S1-S3-S1, S1-S1-S3-S1, S1-S1-S3-S1, S1-S1-S3-S2, S1-S1-S3-S2, S1-S1-S3-S2, S1-S1-S3-S3, S1-S1-S3-S3, S1-S1-S3-S3, S1-S2-S1-S1, S1-S2-S1-S1, S1-S2-S1-S1, S1-S2-S1-S2, S1-S2-S1-S2, S1-S2-S1-S2, S1-S2-S1-S3, S1-S2-S1-S3, S1-S2-S1-S3, S1-S2-S2-S1, S1-S2-S2-S1, S1-S2-S2-S1, S1-S2-S2-S2, S1-S2-S2-S2, S1-S2-S2-S2, S1-S2-S2-S3, S1-S2-S2-S3, S1-S2-S2-S3, S1-S2-S3-S1, S1-S2-S3-S1, S1-S2-S3-S1, S1-S2-S3-S2, S1-S2-S3-S2, S1-S2-S3-S2, S1-S2-S3-S3, S1-S2-S3-S3, S1-S2-S3-S3, S1-S3-S1-S1, S1-S3-S1-S1, S1-S3-S1-S1, S1-S3-S1-S2, S1-S3-S1-S2, S1-S3-S1-S2, S1-S3-S1-S3, S1-S3-S1-S3, S1-S3-S1-S3, S1-S3-S2-S1, S1-S3-S2-S1, S1-S3-S2-S1, S1-S3-S2-S2, S1-S3-S2-S2, S1-S3-S2-S2, S1-S3-S2-S3, S1-S3-S2-S3, S1-S3-S2-S3, S1-S3-S3-S1, S1-S3-S3-S1, S1-S3-S3-S1, S1-S3-S3-S2, S1-S3-S3-S2, S1-S3-S3-S2, S1-S3-S3-S3, S1-S3-S3-S3, S1-S3-S3-S3, S2-S1-S1-S1, S2-S1-S1-S1, S2-S1-S1-S1, S2-S1-S1-S2, S2-S1-S1-S2, S2-S1-S1-S2, S2-S1-S1-S3, S2-S1-S1-S3, S2-S1-S1-S3, S2-S1-S2-S1, S2-S1-S2-S1, S2-S1-S2-S1, S2-S1-S2-S2, S2-S1-S2-S2, S2-S1-S2-S2, S2-S1-S2-S3, S2-S1-S2-S3, S2-S1-S2-S3, S2-S1-S3-S1, S2-S1-S3-S1, S2-S1-S3-S1, S2-S1-S3-S2, S2-S1-S3-S2, S2-S1-S3-S2, S2-S1-S3-S3, S2-S1-S3-S3, S2-S1-S3-S3, S2-S2-S1-S1, S2-S2-S1-S1, S2-S2-S1-S1, S2-S2-S1-S2, S2-S2-S1-S2, S2-S2-S1-S2, S2-S2-S1-S3, S2-S2-S1-S3, S2-S2-S1-S3, S2-S2-S2-S1, S2-S2-S2-S1, S2-S2-S2-S1, S2-S2-S2-S2, S2-S2-S2-S2, S2-S2-S2-S2, S2-S2-S2-S3, S2-S2-S2-S3, S2-S2-S2-S3, S2-S2-S3-S1, S2-S2-S3-S1, S2-S2-S3-S1, S2-S2-S3-S2, S2-S2-S3-S2, S2-S2-S3-S2, S2-S2-S3-S3, S2-S2-S3-S3, S2-S2-S3-S3, S2-S3-S1-S1, S2-S3-S1-S1, S2-S3-S1-S1, S2-S3-S1-S2, S2-S3-S1-S2, S2-S3-S1-S2, S2-S3-S1-S3, S2-S3-S1-S3, S2-S3-S1-S3, S2-S3-S2-S1, S2-S3-S2-S1, S2-S3-S2-S1, S2-S3-S2-S2, S2-S3-S2-S2, S2-S3-S2-S2, S2-S3-S2-S3, S2-S3-S2-S3, S2-S3-S2-S3, S2-S3-S3-S1, S2-S3-S3-S1, S2-S3-S3-S1, S2-S3-S3-S2, S2-S3-S3-S2, S2-S3-S3-S2, S2-S3-S3-S3, S2-S3-S3-S3, S2-S3-S3-S3, S3-S1-S1-S1, S3-S1-S1-S1, S3-S1-S1-S1, S3-S1-S1-S2, S3-S1-S1-S2, S3-S1-S1-S2, S3-S1-S1-S3, S3-S1-S1-S3, S3-S1-S1-S3, S3-S1-S2-S1, S3-S1-S2-S1, S3-S1-S2-S1, S3-S1-S2-S2, S3-S1-S2-S2, S3-S1-S2-S2, S3-S1-S2-S3, S3-S1-S2-S3, S3-S1-S2-S3, S3-S1-S3-S1, S3-S1-S3-S1, S3-S1-S3-S1, S3-S1-S3-S2, S3-S1-S3-S2, S3-S1-S3-S2, S3-S1-S3-S3, S3-S1-S3-S3, S3-S1-S3-S3, S3-S2-S1-S1, S3-S2-S1-S1, S3-S2-S1-S1, S3-S2-S1-S2, S3-S2-S1-S2, S3-S2-S1-S2, S3-S2-S1-S3, S3-S2-S1-S3, S3-S2-S1-S3, S3-S2-S2-S1, S3-S2-S2-S1, S3-S2-S2-S1, S3-S2-S2-S2, S3-S2-S2-S2, S3-S2-S2-S2, S3-S2-S2-S3, S3-S2-S2-S3, S3-S2-S2-S3, S3-S2-S3-S1, S3-S2-S3-S1, S3-S2-S3-S1, S3-S2-S3-S2, S3-S2-S3-S2, S3-S2-S3-S2, S3-S2-S3-S3, S3-S2-S3-S3, S3-S2-S3-S3, S3-S3-S1-S1, S3-S3-S1-S1, S3-S3-S1-S1, S3-S3-S1-S2, S3-S3-S1-S2, S3-S3-S1-S2, S3-S3-S1-S3, S3-S3-S1-S3, S3-S3-S1-S3, S3-S3-S2-S1, S3-S3-S2-S1, S3-S3-S2-S1, S3-S3-S2-S2, S3-S3-S2-S2, S3-S3-S2-S2, S3-S3-S2-S3, S3-S3-S2-S3, S3-S3-S2-S3, S3-S3-S3-S1, S3-S3-S3-S1, S3-S3-S3-S1, S3-S3-S3-S2, S3-S3-S3-S2, S3-S3-S3-S2, S3-S3-S3-S3, S3-S3-S3-S3, S3-S3-S3-S3, S1-S1-S1-S2, S1-S1-S1-S4, S1-S1-S1-S4, S1-S1-S1-S4, S1-S1-

S2-S1, S1-S1-S2-S1, S1-S1-S2-S1, S1-S1-S2-S2, S1-S1-S2-S2, S1-S1-S2-S2, S1-S1-S2-S4, S1-S1-S2-S4, S1-S1-S2-S4, S1-S1-S4-S1, S1-S1-S4-S1, S1-S1-S4-S1, S1-S1-S4-S2, S1-S1-S4-S2, S1-S1-S4-S2, S1-S1-S4-S4, S1-S1-S4-S4, S1-S1-S4-S4, S1-S2-S1-S1, S1-S2-S1-S1, S1-S2-S1-S1, S1-S2-S1-S2, S1-S2-S1-S2, S1-S2-S1-S2, S1-S2-S1-S4, S1-S2-S1-S4, S1-S2-S1-S4, S1-S2-S2-S1, S1-S2-S2-S1, S1-S2-S2-S1, S1-S2-S2-S2, S1-S2-S2-S2, S1-S2-S2-S2, S1-S2-S2-S4, S1-S2-S2-S4, S1-S2-S2-S4, S1-S2-S4-S1, S1-S2-S4-S1, S1-S2-S4-S1, S1-S2-S4-S2, S1-S2-S4-S2, S1-S2-S4-S2, S1-S2-S4-S4, S1-S2-S4-S4, S1-S2-S4-S4, S1-S4-S1-S1, S1-S4-S1-S1, S1-S4-S1-S1, S1-S4-S1-S2, S1-S4-S1-S2, S1-S4-S1-S2, S1-S4-S1-S4, S1-S4-S1-S4, S1-S4-S1-S4, S1-S4-S2-S1, S1-S4-S2-S1, S1-S4-S2-S1, S1-S4-S2-S2, S1-S4-S2-S2, S1-S4-S2-S2, S1-S4-S2-S4, S1-S4-S2-S4, S1-S4-S2-S4, S1-S4-S4-S1, S1-S4-S4-S1, S1-S4-S4-S1, S1-S4-S4-S2, S1-S4-S4-S2, S1-S4-S4-S2, S1-S4-S4-S4, S1-S4-S4-S4, S1-S4-S4-S4, S2-S1-S1-S1, S2-S1-S1-S1, S2-S1-S1-S1, S2-S1-S1-S2, S2-S1-S1-S2, S2-S1-S1-S2, S2-S1-S1-S4, S2-S1-S1-S4, S2-S1-S1-S4, S2-S1-S2-S1, S2-S1-S2-S1, S2-S1-S2-S1, S2-S1-S2-S2, S2-S1-S2-S2, S2-S1-S2-S2, S2-S1-S2-S4, S2-S1-S2-S4, S2-S1-S2-S4, S2-S1-S4-S1, S2-S1-S4-S1, S2-S1-S4-S1, S2-S1-S4-S2, S2-S1-S4-S2, S2-S1-S4-S2, S2-S1-S4-S4, S2-S1-S4-S4, S2-S1-S4-S4, S2-S2-S1-S1, S2-S2-S1-S1, S2-S2-S1-S1, S2-S2-S1-S2, S2-S2-S1-S2, S2-S2-S1-S2, S2-S2-S1-S4, S2-S2-S1-S4, S2-S2-S1-S4, S2-S2-S2-S1, S2-S2-S2-S1, S2-S2-S2-S1, S2-S2-S2-S2, S2-S2-S2-S2, S2-S2-S2-S2, S2-S2-S2-S4, S2-S2-S2-S4, S2-S2-S2-S4, S2-S2-S4-S1, S2-S2-S4-S1, S2-S2-S4-S1, S2-S2-S4-S2, S2-S2-S4-S2, S2-S2-S4-S2, S2-S2-S4-S4, S2-S2-S4-S4, S2-S2-S4-S4, S2-S4-S1-S1, S2-S4-S1-S1, S2-S4-S1-S1, S2-S4-S1-S2, S2-S4-S1-S2, S2-S4-S1-S2, S2-S4-S1-S4, S2-S4-S1-S4, S2-S4-S1-S4, S2-S4-S2-S1, S2-S4-S2-S1, S2-S4-S2-S1, S2-S4-S2-S2, S2-S4-S2-S2, S2-S4-S2-S2, S2-S4-S2-S4, S2-S4-S2-S4, S2-S4-S2-S4, S2-S4-S4-S1, S2-S4-S4-S1, S2-S4-S4-S1, S2-S4-S4-S2, S2-S4-S4-S2, S2-S4-S4-S2, S2-S4-S4-S4, S2-S4-S4-S4, S2-S4-S4-S4, S4-S1-S1-S1, S4-S1-S1-S1, S4-S1-S1-S1, S4-S1-S1-S2, S4-S1-S1-S2, S4-S1-S1-S2, S4-S1-S1-S4, S4-S1-S1-S4, S4-S1-S1-S4, S4-S1-S2-S1, S4-S1-S2-S1, S4-S1-S2-S1, S4-S1-S2-S2, S4-S1-S2-S2, S4-S1-S2-S2, S4-S1-S2-S4, S4-S1-S2-S4, S4-S1-S2-S4, S4-S1-S4-S1, S4-S1-S4-S1, S4-S1-S4-S1, S4-S1-S4-S2, S4-S1-S4-S2, S4-S1-S4-S2, S4-S1-S4-S4, S4-S1-S4-S4, S4-S1-S4-S4, S4-S2-S1-S1, S4-S2-S1-S1, S4-S2-S1-S1, S4-S2-S1-S2, S4-S2-S1-S2, S4-S2-S1-S2, S4-S2-S1-S4, S4-S2-S1-S4, S4-S2-S1-S4, S4-S2-S2-S1, S4-S2-S2-S1, S4-S2-S2-S1, S4-S2-S2-S2, S4-S2-S2-S2, S4-S2-S2-S2, S4-S2-S2-S4, S4-S2-S2-S4, S4-S2-S2-S4, S4-S2-S4-S1, S4-S2-S4-S1, S4-S2-S4-S1, S4-S2-S4-S2, S4-S2-S4-S2, S4-S2-S4-S2, S4-S2-S4-S4, S4-S2-S4-S4, S4-S2-S4-S4, S4-S4-S1-S1, S4-S4-S1-S1, S4-S4-S1-S1, S4-S4-S1-S2, S4-S4-S1-S2, S4-S4-S1-S2, S4-S4-S1-S4, S4-S4-S1-S4, S4-S4-S1-S4, S4-S4-S2-S1, S4-S4-S2-S1, S4-S4-S2-S1, S4-S4-S2-S2, S4-S4-S2-S2, S4-S4-S2-S2, S4-S4-S2-S4, S4-S4-S2-S4, S4-S4-S2-S4, S4-S4-S4-S1, S4-S4-S4-S1, S4-S4-S4-S1, S4-S4-S4-S2, S4-S4-S4-S2, S4-S4-S4-S2, S4-S4-S4-S4, S4-S4-S4-S4, S4-S4-S4-S4, or S4-S4-S4-S4, wherein S1, S2, S3 and S4 are different types of sugar modifications. In some embodiments, S1, S2, S3 and S4 are different types of 2'-sugar modifications. In

some embodiments, such a pattern of sugar modifications is in a first wing, a second wing, and/or a core of an oligonucleotide having an asymmetric format.

[00183] In some embodiments, a pattern of sugar modifications of an oligonucleotide having an asymmetric format comprises any one or more of: S1-S1-S1-S1-S1, S1-S1-S1-S1-S2, S1-S1-S1-S2-S1, S1-S1-S1-S2-S2, S1-S1-S2-S1-S1, S1-S1-S2-S1-S2, S1-S1-S2-S2-S1, S1-S1-S2-S2-S2, S1-S2-S1-S1-S1, S1-S2-S1-S1-S2, S1-S2-S1-S2-S1, S1-S2-S1-S2-S2, S1-S2-S2-S1-S1, S1-S2-S2-S1-S2, S1-S2-S2-S2-S1, S1-S2-S2-S2-S2, S2-S1-S1-S1-S1, S2-S1-S1-S1-S2, S2-S1-S1-S2-S1, S2-S1-S1-S2-S2, S2-S1-S2-S1-S1, S2-S1-S2-S1-S2, S2-S1-S2-S2-S1, S2-S1-S2-S2-S2, S2-S2-S1-S1-S1, S2-S2-S1-S1-S2, S2-S2-S1-S2-S1, S2-S2-S1-S2-S2, S2-S2-S2-S1-S1, S2-S2-S2-S1-S2, S2-S2-S2-S2-S1, S2-S2-S2-S2-S2, S1-S1-S1-S1-S1, S1-S1-S1-S1-S3, S1-S1-S1-S3-S1, S1-S1-S1-S3-S3, S1-S1-S3-S1-S1, S1-S1-S3-S1-S3, S1-S1-S3-S3-S1, S1-S1-S3-S3-S3, S1-S3-S1-S1-S1, S1-S3-S1-S1-S3, S1-S3-S1-S3-S1, S1-S3-S1-S3-S3, S1-S3-S3-S1-S1, S1-S3-S3-S1-S3, S1-S3-S3-S3-S1, S1-S3-S3-S3-S3, S3-S1-S1-S1-S1, S3-S1-S1-S1-S3, S3-S1-S1-S3-S1, S3-S1-S1-S3-S3, S3-S1-S3-S1-S1, S3-S1-S3-S1-S3, S3-S1-S3-S3-S1, S3-S1-S3-S3-S3, S3-S3-S1-S1-S1, S3-S3-S1-S1-S3, S3-S3-S1-S3-S1, S3-S3-S1-S3-S3, S3-S3-S3-S1-S1, S3-S3-S3-S1-S3, S3-S3-S3-S3-S1, S3-S3-S3-S3-S3, S1-S1-S1-S1-S4, S1-S1-S1-S4-S1, S1-S1-S1-S4-S4, S1-S1-S4-S1-S1, S1-S1-S4-S1-S4, S1-S1-S4-S4-S1, S1-S1-S4-S4-S4, S1-S4-S1-S1-S1, S1-S4-S1-S1-S4, S1-S4-S1-S4-S1, S1-S4-S1-S4-S4, S1-S4-S4-S1-S1, S1-S4-S4-S1-S4, S1-S4-S4-S4-S1, S1-S4-S4-S4-S4, S4-S1-S1-S1-S1, S4-S1-S1-S1-S4, S4-S1-S1-S4-S1, S4-S1-S1-S4-S4, S4-S1-S4-S1-S1, S4-S1-S4-S1-S4, S4-S1-S4-S4-S1, S4-S1-S4-S4-S4, S4-S4-S1-S1-S1, S4-S4-S1-S1-S4, S4-S4-S1-S4-S1, S4-S4-S1-S4-S4, S4-S4-S4-S1-S1, S4-S4-S4-S1-S4, S4-S4-S4-S4-S1, S4-S4-S4-S4-S4, S1-S1-S1-S2-S3, S1-S1-S1-S3-S1, S1-S1-S1-S3-S2, S1-S1-S1-S3-S3, S1-S1-S2-S1-S1, S1-S1-S2-S1-S2, S1-S1-S2-S1-S3, S1-S1-S2-S2-S1, S1-S1-S2-S2-S2, S1-S1-S2-S2-S3, S1-S1-S2-S3-S1, S1-S1-S2-S3-S2, S1-S1-S2-S3-S3, S1-S1-S3-S1-S1, S1-S1-S3-S1-S2, S1-S1-S3-S1-S3, S1-S1-S3-S2-S1, S1-S1-S3-S2-S2, S1-S1-S3-S2-S3, S1-S1-S3-S3-S1, S1-S1-S3-S3-S2, S1-S1-S3-S3-S3, S1-S2-S1-S1-S1, S1-S2-S1-S1-S2, S1-S2-S1-S1-S3, S1-S2-S1-S2-S1, S1-S2-S1-S2-S2, S1-S2-S1-S2-S3, S1-S2-S1-S3-S1, S1-S2-S1-S3-S2, S1-S2-S1-S3-S3, S1-S2-S2-S1-S1, S1-S2-S2-S1-S2, S1-S2-S2-S1-S3, S1-S2-S2-S2-S1, S1-S2-S2-S2-S2, S1-S2-S2-S2-S3, S1-S2-S2-S3-S1, S1-S2-S2-S3-S2, S1-S2-S2-S3-S3, S1-S2-S3-S1-S1, S1-S2-S3-S1-S2, S1-S2-S3-S1-S3, S1-S2-S3-S2-S1, S1-S2-S3-S2-S2, S1-S2-S3-S2-S3, S1-S2-S3-S3-S1, S1-S2-S3-S3-S2, S1-S2-S3-S3-S3, S1-S3-S1-S1-S1, S1-S3-S1-S1-S2, S1-S3-S1-S1-S3, S1-S3-S1-S2-S1, S1-S3-S1-S2-S2, S1-S3-S1-S2-S3, S1-S3-S1-S3-S1, S1-S3-S1-S3-S2, S1-S3-S1-S3-S3, S1-S3-S2-S1-S1, S1-S3-S2-S1-S2, S1-S3-S2-S1-S3, S1-S3-S2-S2-S1, S1-S3-S2-S2-S2, S1-S3-S2-S2-S3, S1-S3-S2-S3-S1, S1-S3-S2-S3-S2, S1-S3-S2-S3-S3, S1-S3-S3-S1-S1, S1-S3-S3-S1-S2, S1-S3-S3-S1-S3, S1-S3-S3-S2-S1, S1-S3-S3-S2-S2, S1-S3-S3-S2-S3, S1-S3-S3-S3-S1, S1-S3-S3-S3-S2, S1-S3-S3-S3-S3, S2-S1-S1-S1-S1, S2-S1-S1-S1-S2, S2-S1-S1-S1-S3, S2-S1-S1-S2-S1, S2-S1-S1-S2-S2, S2-S1-S1-S2-S3, S2-S1-S1-S3-S1, S2-S1-S1-S3-S2, S2-S1-S1-S3-S3, S2-S1-S2-S1-S1, S2-S1-S2-S1-S2, S2-S1-S2-S1-S3,

S2-S1-S2-S2-S1, S2-S1-S2-S2-S2, S2-S1-S2-S2-S3, S2-S1-S2-S3-S1, S2-S1-S2-S3-S2, S2-S1-S2-S3-S3, S2-S1-S3-S1-S1, S2-S1-S3-S1-S2, S2-S1-S3-S1-S3, S2-S1-S3-S2-S1, S2-S1-S3-S2-S2, S2-S1-S3-S2-S3, S2-S1-S3-S3-S1, S2-S1-S3-S3-S2, S2-S1-S3-S3-S3, S2-S2-S1-S1-S1, S2-S2-S1-S1-S2, S2-S2-S1-S1-S3, S2-S2-S1-S2-S1, S2-S2-S1-S2-S2, S2-S2-S1-S2-S3, S2-S2-S1-S3-S1, S2-S2-S1-S3-S2, S2-S2-S1-S3-S3, S2-S2-S2-S1-S1, S2-S2-S2-S1-S2, S2-S2-S2-S1-S3, S2-S2-S2-S2-S1, S2-S2-S2-S2-S2, S2-S2-S2-S2-S3, S2-S2-S2-S3-S1, S2-S2-S2-S3-S2, S2-S2-S2-S3-S3, S2-S2-S3-S1-S1, S2-S2-S3-S1-S2, S2-S2-S3-S1-S3, S2-S2-S3-S2-S1, S2-S2-S3-S2-S2, S2-S2-S3-S2-S3, S2-S2-S3-S3-S1, S2-S2-S3-S3-S2, S2-S2-S3-S3-S3, S2-S3-S1-S1-S1, S2-S3-S1-S1-S2, S2-S3-S1-S1-S3, S2-S3-S1-S2-S1, S2-S3-S1-S2-S2, S2-S3-S1-S2-S3, S2-S3-S1-S3-S1, S2-S3-S1-S3-S2, S2-S3-S1-S3-S3, S2-S3-S2-S1-S1, S2-S3-S2-S1-S2, S2-S3-S2-S1-S3, S2-S3-S2-S2-S1, S2-S3-S2-S2-S2, S2-S3-S2-S2-S3, S2-S3-S2-S3-S1, S2-S3-S2-S3-S2, S2-S3-S2-S3-S3, S2-S3-S3-S1-S1, S2-S3-S3-S1-S2, S2-S3-S3-S1-S3, S2-S3-S3-S2-S1, S2-S3-S3-S2-S2, S2-S3-S3-S2-S3, S2-S3-S3-S3-S1, S2-S3-S3-S3-S2, S2-S3-S3-S3-S3, S3-S1-S1-S1-S1, S3-S1-S1-S1-S2, S3-S1-S1-S1-S3, S3-S1-S1-S2-S1, S3-S1-S1-S2-S2, S3-S1-S1-S2-S3, S3-S1-S1-S3-S1, S3-S1-S1-S3-S2, S3-S1-S1-S3-S3, S3-S1-S2-S1-S1, S3-S1-S2-S1-S2, S3-S1-S2-S1-S3, S3-S1-S2-S2-S1, S3-S1-S2-S2-S2, S3-S1-S2-S2-S3, S3-S1-S2-S3-S1, S3-S1-S2-S3-S2, S3-S1-S2-S3-S3, S3-S1-S3-S1-S1, S3-S1-S3-S1-S2, S3-S1-S3-S1-S3, S3-S1-S3-S2-S1, S3-S1-S3-S2-S2, S3-S1-S3-S2-S3, S3-S1-S3-S3-S1, S3-S1-S3-S3-S2, S3-S1-S3-S3-S3, S3-S2-S1-S1-S1, S3-S2-S1-S1-S2, S3-S2-S1-S1-S3, S3-S2-S1-S2-S1, S3-S2-S1-S2-S2, S3-S2-S1-S2-S3, S3-S2-S1-S3-S1, S3-S2-S1-S3-S2, S3-S2-S1-S3-S3, S3-S2-S2-S1-S1, S3-S2-S2-S1-S2, S3-S2-S2-S1-S3, S3-S2-S2-S2-S1, S3-S2-S2-S2-S2, S3-S2-S2-S2-S3, S3-S2-S2-S3-S1, S3-S2-S2-S3-S2, S3-S2-S2-S3-S3, S3-S2-S3-S1-S1, S3-S2-S3-S1-S2, S3-S2-S3-S1-S3, S3-S2-S3-S2-S1, S3-S2-S3-S2-S2, S3-S2-S3-S2-S3, S3-S2-S3-S3-S1, S3-S2-S3-S3-S2, S3-S2-S3-S3-S3, S3-S3-S1-S1-S1, S3-S3-S1-S1-S2, S3-S3-S1-S1-S3, S3-S3-S1-S2-S1, S3-S3-S1-S2-S2, S3-S3-S1-S2-S3, S3-S3-S1-S3-S1, S3-S3-S1-S3-S2, S3-S3-S1-S3-S3, S3-S3-S2-S1-S1, S3-S3-S2-S1-S2, S3-S3-S2-S1-S3, S3-S3-S2-S2-S1, S3-S3-S2-S2-S2, S3-S3-S2-S2-S3, S3-S3-S2-S3-S1, S3-S3-S2-S3-S2, S3-S3-S2-S3-S3, S3-S3-S3-S1-S1, S3-S3-S3-S1-S2, S3-S3-S3-S1-S3, S3-S3-S3-S2-S1, S3-S3-S3-S2-S2, S3-S3-S3-S2-S3, S3-S3-S3-S3-S1, S3-S3-S3-S3-S2, S3-S3-S3-S3-S3, S3-S3-S3-S3-S3, S1-S1-S1-S2-S4, S1-S1-S1-S4-S1, S1-S1-S1-S4-S2, S1-S1-S1-S4-S4, S1-S1-S2-S1-S1, S1-S1-S2-S1-S2, S1-S1-S2-S1-S4, S1-S1-S2-S2-S1, S1-S1-S2-S2-S2, S1-S1-S2-S2-S4, S1-S1-S2-S4-S1, S1-S1-S2-S4-S2, S1-S1-S2-S4-S4, S1-S1-S4-S1-S1, S1-S1-S4-S1-S2, S1-S1-S4-S1-S4, S1-S1-S4-S2-S1, S1-S1-S4-S2-S2, S1-S1-S4-S2-S4, S1-S1-S4-S4-S1, S1-S1-S4-S4-S2, S1-S1-S4-S4-S4, S1-S2-S1-S1-S1, S1-S2-S1-S1-S2, S1-S2-S1-S1-S4, S1-S2-S1-S2-S1, S1-S2-S1-S2-S2, S1-S2-S1-S2-S4, S1-S2-S1-S4-S1, S1-S2-S1-S4-S2, S1-S2-S1-S4-S4, S1-S2-S2-S1-S1, S1-S2-S2-S1-S2, S1-S2-S2-S1-S4, S1-S2-S2-S2-S1, S1-S2-S2-S2-S2, S1-S2-S2-S2-S4, S1-S2-S2-S4-S1, S1-S2-S2-S4-S2, S1-S2-S2-S4-S4, S1-S2-S4-S1-S1, S1-S2-S4-S1-S2, S1-S2-S4-S1-S4, S1-S2-S4-S2-S1, S1-S2-S4-S2-S2, S1-S2-S4-S2-S4, S1-S2-S4-S4-S1, S1-S2-S4-S4-S2, S1-S2-S4-S4-S4, S1-S4-S1-S1-S1, S1-S4-S1-S1-S2, S1-S4-S1-S1-S4, S1-S4-S1-S2-S1,

S1-S4-S1-S2-S2, S1-S4-S1-S2-S4, S1-S4-S1-S4-S1, S1-S4-S1-S4-S2, S1-S4-S1-S4-S4, S1-S4-S2-S1-S1, S1-S4-S2-S1-S2, S1-S4-S2-S1-S4, S1-S4-S2-S2-S1, S1-S4-S2-S2-S2, S1-S4-S2-S2-S4, S1-S4-S2-S4-S1, S1-S4-S2-S4-S2, S1-S4-S2-S4-S4, S1-S4-S4-S1-S1, S1-S4-S4-S1-S2, S1-S4-S4-S1-S4, S1-S4-S4-S2-S1, S1-S4-S4-S2-S2, S1-S4-S4-S2-S4, S1-S4-S4-S4-S1, S1-S4-S4-S4-S2, S1-S4-S4-S4-S4, S2-S1-S1-S1-S1, S2-S1-S1-S1-S2, S2-S1-S1-S1-S4, S2-S1-S1-S2-S1, S2-S1-S1-S2-S2, S2-S1-S1-S2-S4, S2-S1-S1-S4-S1, S2-S1-S1-S4-S2, S2-S1-S1-S4-S4, S2-S1-S2-S1-S1, S2-S1-S2-S1-S2, S2-S1-S2-S1-S4, S2-S1-S2-S2-S1, S2-S1-S2-S2-S2, S2-S1-S2-S2-S4, S2-S1-S2-S4-S1, S2-S1-S2-S4-S2, S2-S1-S2-S4-S4, S2-S1-S4-S1-S1, S2-S1-S4-S1-S2, S2-S1-S4-S1-S4, S2-S1-S4-S2-S1, S2-S1-S4-S2-S2, S2-S1-S4-S2-S4, S2-S1-S4-S4-S1, S2-S1-S4-S4-S2, S2-S1-S4-S4-S4, S2-S2-S1-S1-S1, S2-S2-S1-S1-S2, S2-S2-S1-S1-S4, S2-S2-S1-S2-S1, S2-S2-S1-S2-S2, S2-S2-S1-S2-S4, S2-S2-S1-S4-S1, S2-S2-S1-S4-S2, S2-S2-S1-S4-S4, S2-S2-S2-S1-S1, S2-S2-S2-S1-S2, S2-S2-S2-S1-S4, S2-S2-S2-S2-S1, S2-S2-S2-S2-S2, S2-S2-S2-S2-S4, S2-S2-S2-S4-S1, S2-S2-S2-S4-S2, S2-S2-S2-S4-S4, S2-S2-S4-S1-S1, S2-S2-S4-S1-S2, S2-S2-S4-S1-S4, S2-S2-S4-S2-S1, S2-S2-S4-S2-S2, S2-S2-S4-S2-S4, S2-S2-S4-S4-S1, S2-S2-S4-S4-S2, S2-S2-S4-S4-S4, S2-S4-S1-S1-S1, S2-S4-S1-S1-S2, S2-S4-S1-S1-S4, S2-S4-S1-S2-S1, S2-S4-S1-S2-S2, S2-S4-S1-S2-S4, S2-S4-S1-S4-S1, S2-S4-S1-S4-S2, S2-S4-S1-S4-S4, S2-S4-S2-S1-S1, S2-S4-S2-S1-S2, S2-S4-S2-S1-S4, S2-S4-S2-S2-S1, S2-S4-S2-S2-S2, S2-S4-S2-S2-S4, S2-S4-S2-S4-S1, S2-S4-S2-S4-S2, S2-S4-S2-S4-S4, S2-S4-S4-S1-S1, S2-S4-S4-S1-S2, S2-S4-S4-S1-S4, S2-S4-S4-S2-S1, S2-S4-S4-S2-S2, S2-S4-S4-S2-S4, S2-S4-S4-S4-S1, S2-S4-S4-S4-S2, S2-S4-S4-S4-S4, S4-S1-S1-S1-S1, S4-S1-S1-S1-S2, S4-S1-S1-S1-S4, S4-S1-S1-S2-S1, S4-S1-S1-S2-S2, S4-S1-S1-S2-S4, S4-S1-S1-S4-S1, S4-S1-S1-S4-S2, S4-S1-S1-S4-S4, S4-S1-S2-S1-S1, S4-S1-S2-S1-S2, S4-S1-S2-S1-S4, S4-S1-S2-S2-S1, S4-S1-S2-S2-S2, S4-S1-S2-S2-S4, S4-S1-S2-S4-S1, S4-S1-S2-S4-S2, S4-S1-S2-S4-S4, S4-S1-S4-S1-S1, S4-S1-S4-S1-S2, S4-S1-S4-S1-S4, S4-S1-S4-S2-S1, S4-S1-S4-S2-S2, S4-S1-S4-S2-S4, S4-S1-S4-S4-S1, S4-S1-S4-S4-S2, S4-S1-S4-S4-S4, S4-S2-S1-S1-S1, S4-S2-S1-S1-S2, S4-S2-S1-S1-S4, S4-S2-S1-S2-S1, S4-S2-S1-S2-S2, S4-S2-S1-S2-S4, S4-S2-S1-S4-S1, S4-S2-S1-S4-S2, S4-S2-S1-S4-S4, S4-S2-S2-S1-S1, S4-S2-S2-S1-S2, S4-S2-S2-S1-S4, S4-S2-S2-S2-S1, S4-S2-S2-S2-S2, S4-S2-S2-S2-S4, S4-S2-S2-S4-S1, S4-S2-S2-S4-S2, S4-S2-S2-S4-S4, S4-S2-S4-S1-S1, S4-S2-S4-S1-S2, S4-S2-S4-S1-S4, S4-S2-S4-S2-S1, S4-S2-S4-S2-S2, S4-S2-S4-S2-S4, S4-S2-S4-S4-S1, S4-S2-S4-S4-S2, S4-S2-S4-S4-S4, S4-S4-S1-S1-S1, S4-S4-S1-S1-S2, S4-S4-S1-S1-S4, S4-S4-S1-S2-S1, S4-S4-S1-S2-S2, S4-S4-S1-S2-S4, S4-S4-S1-S4-S1, S4-S4-S1-S4-S2, S4-S4-S1-S4-S4, S4-S4-S2-S1-S1, S4-S4-S2-S1-S2, S4-S4-S2-S1-S4, S4-S4-S2-S2-S1, S4-S4-S2-S2-S2, S4-S4-S2-S2-S4, S4-S4-S2-S4-S1, S4-S4-S2-S4-S2, S4-S4-S2-S4-S4, S4-S4-S4-S1-S1, S4-S4-S4-S1-S2, S4-S4-S4-S1-S4, S4-S4-S4-S2-S1, S4-S4-S4-S2-S2, S4-S4-S4-S2-S4, S4-S4-S4-S4-S1, S4-S4-S4-S4-S2, S4-S4-S4-S4-S4, or S4-S4-S4-S4-S4, wherein S1, S2, S3 and S4 are different types of sugar modifications. In some embodiments, S1, S2, S3 and S4 are different types of 2'-sugar modifications. In some embodiments, such a pattern of sugar

modifications is in a first wing, a second wing, and/or a core of an oligonucleotide having an asymmetric format.

[00184] In some embodiments, a pattern of sugar modifications of an oligonucleotide having an asymmetric format comprises any one or more of: LLLLL, LLLLD, LLLDL, LLLDD, LLDLL, LLDLD, LLDDL, LLDDD, LDLLL, LDLLD, LDLDL, LDLDD, LDDLL, LDDLD, LDDDL, LDDDD, DLLLL, DLLLD, DLLDL, DLLDD, DLDLL, DLDLD, DLDDL, DLDDD, DDLLL, DDLLD, DDLDL, DDLDD, DDDLL, DDDLD, DDDDL, DDDDD, LLLLL, LLLLM, LLLML, LLLMM, LLMLL, LLMLM, LLMML, LLMMM, LMLLL, LMLLM, LMLML, LMLMM, LMMLL, LMMLM, LMMML, LMMMM, MLLLL, MLLLM, MLLML, MLLMM, MLMLL, MLMLM, MLMML, MLMMM, MMLLL, MMLLM, MMLML, MMLMM, MMMLL, MMMLM, MMMML, MMMMM, LLLLm, LLLmL, LLLmm, LLmLL, LLmLm, LLmmL, LLmmm, LmLLL, LmLLm, LmLmL, LmLmm, LmmLL, LmmLm, LmmmL, Lmmmm, mLLLL, mLLLm, mLLmL, mLLmm, mLmLL, mLmLm, mLmmL, mLmmm, mmLLL, mmLLm, mmLmL, mmLmm, mmmLL, mmmLm, mmmmL, mmmmm, LLLDM, LLLML, LLLMD, LLLMM, LLDLL, LLDLD, LLDLM, LLDDL, LLDDD, LLDDM, LLDML, LLDMD, LLDMM, LLMLL, LLMLD, LLMLM, LLMDL, LLMDD, LLMDM, LLMML, LLMMD, LLMMM, LDLLL, LDLLD, LDLLM, LDLDL, LDLDD, LDLDM, LDLML, LDLMD, LDLMM, LDDLL, LDDLD, LDDLM, LDDDL, LDDDD, LDDDM, LDDML, LDDMD, LDDMM, LDMLL, LDMLD, LDMLM, LDMDL, LDMDD, LDMDM, LDMML, LDMMD, LDMMM, LMLLL, LMLLD, LMLLM, LMLDL, LMLDD, LMLDM, LMLML, LMLMD, LMLMM, LMDLL, LMDLD, LMDLM, LMDDL, LMDDD, LMDDM, LMDML, LMDMD, LMDMM, LMMLL, LMMLD, LMMLM, LMMDL, LMMDD, LMMDM, LMMML, LMMMD, LMMMM, DLLLL, DLLLD, DLLLM, DLLDL, DLLDD, DLLDM, DLLML, DLLMD, DLLMM, DLDLL, DLDLD, DLDLM, DLDDL, DLDDD, DLDDM, DLDML, DLDMD, DLDMM, DLMLL, DLMLD, DLMLM, DLMDL, DLMDD, DLMDM, DLMML, DLMMD, DLMMM, DDLLL, DDLLD, DDLLM, DDLDL, DDLDD, DDLDM, DDLML, DDLMD, DDLMM, DDDLL, DDDLD, DDDLM, DDDDL, DDDDD, DDDDM, DDDML, DDDMD, DDDMM, DDMLL, DDMLD, DDMLM, DDMDL, DDMDD, DDMDM, DDMML, DDMMD, DDMMM, DMLLL, DMLLD, DMLLM, DMLDL, DMLDD, DMLDM, DMLML, DMLMD, DMLMM, DMDLL, DMDLD, DMDLM, DMDDL, DMDDD, DMDDM, DMDML, DMDMD, DMDMM, DMMLL, DMMLD, DMMLM, DMMDL, DMMDD, DMMDM, DMMML, DMMMD, DMMMM, MLLLL, MLLLD, MLLLM, MLLDL, MLLDD, MLLDM, MLLML, MLLMD, MLLMM, MLDLL, MLDLD, MLDLM, MLDDL, MLDDD, MLDDM, MLDML, MLDMD, MLDMM, MLMLL, MLMLD, MLMLM, MLMDL, MLMDD, MLMDM, MLMML, MLMMD, MLMMM, MDLLL, MDLLD, MDLLM, MDLDL, MDLDD, MDLDM, MDLML, MDLMD, MDLMM, MDDLL, MDDLD, MDDLM, MDDDL, MDDDD, MDDDM, MDDML, MDDMD, MDDMM, MDMLL, MDMLD, MDMLM, MDMDL, MDMDD,

MDMDM, MDMML, MDMMD, MDMMM, MMLLL, MMLLD, MMLLM, MMLDL, MMLDD, MMLDM, MMLML, MMLMD, MMLMM, MMDLL, MMDLD, MMDLM, MMDDL, MMDDD, MMDDM, MMDML, MMDMD, MMDMM, MMMLL, MMMLD, MMMLM, MMMDL, MMMDD, MMMDM, MMMML, MMMMD, MMMMM, MMMMM, LLLDm, LLLmL, LLLmD, LLLmm, LLDLL, LLDLD, LLDLm, LLDDL, LLDDD, LLDDm, LLDmL, LLDmD, LLDmm, LLmLL, LLmLD, LLmLm, LLmDL, LLmDD, LLmDm, LLmmL, LLmmD, LLmmm, LDLLL, LDLLD, LDLLm, LDLDL, LDLDD, LDLDm, LDLmL, LDLmD, LDLmm, LDDLL, LDDLD, LDDLm, LDDDL, LDDDD, LDDDm, LDDmL, LDDmD, LDDmm, LDmLL, LDmLD, LDmLm, LDmDL, LDmDD, LDmDm, LDmmL, LDmmD, LDmmm, LmLLL, LmLLD, LmLLm, LmLDL, LmLDD, LmLDm, LmLmL, LmLmD, LmLmm, LmDLL, LmDLD, LmDLm, LmDDL, LmDDD, LmDDm, LmDmL, LmDmD, LmDmm, LmmLL, LmmLD, LmmLm, LmmDL, LmmDD, LmmDm, LmmmL, LmmmD, Lmmmm, DLLLL, DLLLD, DLLLm, DLLDL, DLLDD, DLLDm, DLLmL, DLLmD, DLLmm, DLDLL, DLDLD, DLDLm, DLDDL, DLDDD, DLDDm, DLDmL, DLDmD, DLDmm, DLmLL, DLmLD, DLmLm, DLmDL, DLmDD, DLmDm, DLmmL, DLmmD, DLmmm, DDLLL, DDLLD, DDLLm, DDLDL, DDLDD, DDLDm, DDLmL, DDLmD, DDLmm, DDDLL, DDDLD, DDDLm, DDDDL, DDDDD, DDDDm, DDDmL, DDDmD, DDDmm, DDmLL, DDmLD, DDmLm, DDmDL, DDmDD, DDmDm, DDmmL, DDmmD, DDmmm, DmLLL, DmLLD, DmLLm, DmLDL, DmLDD, DmLDm, DmLmL, DmLmD, DmLmm, DmDLL, DmDLD, DmDLm, DmDDL, DmDDD, DmDDm, DmDmL, DmDmD, DmDmm, DmmLL, DmmLD, DmmLm, DmmDL, DmmDD, DmmDm, DmmmL, DmmmD, Dmmmm, mLLLL, mLLLD, mLLLm, mLLDL, mLLDD, mLLDm, mLLmL, mLLmD, mLLmm, mLDLL, mLDLD, mLDLm, mLDDL, mLDDD, mLDDm, mLDmL, mLDmD, mLDmm, mLmLL, mLmLD, mLmLm, mLmDL, mLmDD, mLmDm, mLmmL, mLmmD, mLmmm, mDLLL, mDLLD, mDLLm, mDLDL, mDLDD, mDLDm, mDLmL, mDLmD, mDLmm, mDDLL, mDDLD, mDDLm, mDDDL, mDDDD, mDDDm, mDDmL, mDDmD, mDDmm, mDmLL, mDmLD, mDmLm, mDmDL, mDmDD, mDmDm, mDmmL, mDmmD, mDmmm, mmLLL, mmLLD, mmLLm, mmLDL, mmLDD, mmLDm, mmLmL, mmLmD, mmLmm, mmDLL, mmDLD, mmDLm, mmDDL, mmDDD, mmDDm, mmDmL, mmDmD, mmDmm, mmmLL, mmmLD, mmmLm, mmmDL, mmmDD, mmmDm, mmmmL, mmmmD, mmmmm, or mmmmm, wherein L = LNA, D = deoxy, M = 2'-MOE, and m = 2'-OMe. In some embodiments, such a pattern of sugar modifications is in a first wing, a second wing, and/or a core of an oligonucleotide having an asymmetric format.

[00185] Various non-limiting examples of asymmetric formats for oligonucleotides are described herein. Also described herein are various non-limiting examples of oligonucleotides having such formats.

[00186] In some embodiments of an oligonucleotide having an asymmetric format, a core comprises any sugar or sugar modification described herein or known in the art, or any pattern or combination of two or more different sugars and/or sugar modifications.

[00187] In some embodiments of an oligonucleotide having an asymmetric format: a core comprises: D. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, WV-8664.

[00188] In some embodiments of an oligonucleotide having an asymmetric format: a core comprises: DD. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, WV-8664.

[00189] In some embodiments of an oligonucleotide having an asymmetric format: a core comprises: DDD. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, WV-8664.

[00190] In some embodiments of an oligonucleotide having an asymmetric format: a core comprises: DDDD. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, WV-8664.

[00191] In some embodiments of an oligonucleotide having an asymmetric format: a core comprises: DDDDD. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, WV-8664.

[00192] In some embodiments of an oligonucleotide having an asymmetric format: a core comprises: DDDDDD. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, WV-8664.

[00193] In some embodiments of an oligonucleotide having an asymmetric format: a core comprises: DDDDDDD. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, WV-8664.

[00194] In some embodiments of an oligonucleotide having an asymmetric format: a core comprises: DDDDDDDD. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, WV-8664.

[00195] In some embodiments of an oligonucleotide having an asymmetric format: a core comprises: DDDDDDDDD. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, WV-8664.

[00196] In some embodiments of an oligonucleotide having an asymmetric format: a core comprises: DDDDDDDDDD. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, WV-8664.

[00197] In some embodiments of an oligonucleotide having an asymmetric format: a core comprises: 5'BrdU.

[00198] In some embodiments of an oligonucleotide having an asymmetric format: a core comprises: 5'BrdU and D.

[00199] In some embodiments of an oligonucleotide having an asymmetric format: a core comprises: 5'BrdU and two or more D.

[00200] In some embodiments of an oligonucleotide having an asymmetric format: a core comprises: 5'BrdU and two or more consecutive D.

[00201] In some embodiments, an oligonucleotide having an asymmetric format can comprise a first wing; and a second wing, wherein the first and second wing differ chemically from each other and from the core.

[00202] Non-limiting examples of formats of an oligonucleotide having an asymmetric format, wherein the first and second wing differ chemically from each other and from the core are illustrated in Figure 1A and Figure 1B, with a legend to Figure 1A and Figure 1B provided in Figure 1D.

[00203] In some embodiments, an oligonucleotide having an asymmetric format can comprise a first wing; and a second wing, wherein the first and second wing differ chemically from each other and from the core, wherein the first and/or second wing can comprise M, m and/or L, wherein M is (at least one) 2'-MOE (or, if the base is C, optionally methyl-C 2'-MOE); m is (at least one) 2'-OMe, and L is (at least one) LNA, and wherein either the first or second wing can be at the 5' end end, and the other wing is at the 3' end of the wing-core-wing format.

[00204] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive M; and a second wing comprises: 2 or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV- 8852, and WV-8856.

[00205] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive m; and a second wing comprises: 2 or more consecutive M. Non-limiting example(s) of such an oligonucleotide include: WV- 8043-8048.

[00206] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mmmmm; and a second wing comprises: MMMMM. Non-limiting example(s) of such an oligonucleotide include: WV- 8043-8048.

[00207] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: MMMMM; and a second wing comprises: mmmmm. Non-limiting example(s) of such an oligonucleotide include: WV- 8852, and WV-8856.

[00208] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and M in a particular order and number; and a second wing comprises: m and M in a different order and/or different number. Non-limiting example(s) of such an oligonucleotide include: WV- 8248.

[00209] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMmMm; and a second wing comprises: mMmmm. Non-limiting example(s) of such an oligonucleotide include: WV- 8248.

[00210] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and 2 or more consecutive M; and a second wing comprises: M and 2 or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV- 9894-9896.

[00211] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMM; and a second wing comprises: Mmmmm. Non-limiting example(s) of such an oligonucleotide include: WV- 9894-9896, and WV-10253 to 10254.

[00212] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and M in a particular order and number; and a second wing comprises: 2 or more consecutive M.

[00213] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMMMM; and a second wing comprises: MMMMMMM. Non-limiting example(s) of such an oligonucleotide include: WV- 12099, WV-12101, WV-12103, WV-12105, WV-12107, and WV-12109.

[00214] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMM; and a second wing comprises: MMMMM. Non-limiting example(s) of such an oligonucleotide include: WV- 10250, and WV-9869 to WV-9870.

[00215] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: all M. Non-limiting example(s) of such an oligonucleotide include: WV- 9441-9445.

[00216] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: MMMMM. Non-limiting example(s) of such an oligonucleotide include: WV- 9441-9445.

[00217] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and M in a particular order and number; and a second wing comprises: 2 or more consecutive m.

[00218] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive m; and a second wing comprises: m and M in a particular order and number.

[00219] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive M; and a second wing comprises: m and M in a particular order and number.

[00220] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: L, m and M in a particular order and number; and a second wing comprises: L, m and M in a different order and/or different number. Non-limiting example(s) of such an oligonucleotide include: WV- 8250.

[00221] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: LMmMm; and a second wing comprises: mMmmL. Non-limiting example(s) of such an oligonucleotide include: WV- 8250.

[00222] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: L, m and M; and a second wing comprises: m and L. Non-limiting example(s) of such an oligonucleotide include: WV- 8246.

[00223] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: LMmMm; and a second wing comprises: mmmmL. Non-limiting example(s) of such an oligonucleotide include: WV- 8246.

[00224] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: L and M; and a second wing comprises: m and L. Non-limiting example(s) of such an oligonucleotide include: WV- 11958, and WV-11960, and WV-11962.

[00225] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: L and 2 or more consecutive M; and a second wing comprises: 2 or more consecutive m and L. Non-limiting example(s) of such an oligonucleotide include: WV- 11958, WV-11960, and WV-11962.

[00226] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: LMMMM; and a second wing comprises: mmmmL. Non-limiting example(s) of such an oligonucleotide include: WV- 11958, WV-11960, and WV-11962.

[00227] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: only one type of sugar modification. Non-limiting example(s) of such an oligonucleotide include: WV-11114, WV-11533, WV-12503, WV-12504, WV-12505, WV-8553, WV-8555, WV-8556, WV-8557, WV-8582, WV-8583,

WV-8584, WV-8585, WV-8586, WV-8587, WV-8588, WV-8589, WV-8590, WV-8591, WV-8592, WV-8593, WV-9058, WV-9059, WV-9060, WV-9061, WV-9696, WV-9697, and WV-9698.

[00228] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a pattern of m and M; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-11114, WV-11533, WV-12503, WV-12504, WV-12505, WV-8553, WV-8555, WV-8556, WV-8557, WV-8582, WV-8583, WV-8584, WV-8585, WV-8586, WV-8587, WV-8588, WV-8589, WV-8590, WV-8591, WV-8592, WV-8593, WV-9058, WV-9059, WV-9060, WV-9061, WV-9696, WV-9697, and WV-9698.

[00229] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-11114, WV-11533, WV-12503, WV-12504, WV-12505, WV-8553, WV-8555, WV-8556, WV-8557, WV-8582, WV-8583, WV-8584, WV-8585, WV-8586, WV-8587, WV-8588, WV-8589, WV-8590, WV-8591, WV-8592, WV-8593, WV-9058, WV-9059, WV-9060, WV-9061, WV-9696, WV-9697, and WV-9698.

[00230] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a pattern of two different types of sugar modifications; and a second wing comprises: a different pattern of the same two different types of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8097, WV-8098, WV-8099, WV-8100, WV-8101, WV-8102, and WV-8109.

[00231] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a pattern of m and M; and a second wing comprises: a different pattern of m and M. Non-limiting example(s) of such an oligonucleotide include: WV-8097, WV-8098, WV-8099, WV-8100, WV-8101, WV-8102, and WV-8109.

[00232] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mmMMm; and a second wing comprises: mmMmm. Non-limiting example(s) of such an oligonucleotide include: WV-8097, WV-8098, WV-8099, WV-8100, WV-8101, WV-8102, and WV-8109.

[00233] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and two or more consecutive M; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-12110, WV-12111, WV-12112, WV-12113, and WV-12114.

[00234] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMM; and a second wing comprises: two or more consecutive m. Non-limiting

example(s) of such an oligonucleotide include: WV-12110, WV-12111, WV-12112, WV-12113, and WV-12114.

[00235] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-13303, WV-13304, WV-13809, WV-14087, WV-14349, WV-14556, WV-14557, WV-14558, WV-14559, WV-14560, WV-14561, WV-14562, WV-14563, WV-14564, WV-14733, WV-14734, WV-14735, WV-14736, WV-14737, WV-14771, WV-15310, WV-15311, WV-15312, WV-15313, WV-15314, WV-15315, WV-15316, WV-15317, WV-15318, WV-15319, WV-15320, WV-15321, WV-15351, WV-15352, WV-15353, WV-15354, WV-15355, WV-15356, WV-15357, WV-15358, WV-15359, WV-15360, WV-15361, WV-15362, WV-15363, WV-15364, WV-15365, WV-15562, WV-15563, WV-15863, WV-15864, and WV-15887.

[00236] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8552, WV-8554, WV-8570, WV-8571, WV-8572, WV-8573, WV-8574, WV-8575, WV-8576, WV-8577, WV-8578, WV-8579, WV-8580, and WV-8581.

[00237] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: two different types of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-14552, WV-14553, WV-14554, and WV-14555.

[00238] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: two different types of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8456.

[00239] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8005, WV-8006, WV-8007, WV-8008, WV-8466, WV-8467, WV-8468, WV-8469, WV-8470, WV-8471, WV-8547, WV-8548, WV-8594, WV-13305, WV-13306, WV-13307, WV-13308, WV-13309, WV-13310, WV-13311, WV-13313, WV-13803, WV-13804, and WV-13805.

[00240] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: two different types of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8125.

[00241] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: two or more consecutive M. Non-limiting example(s) of such an oligonucleotide include: WV-8314.

[00242] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: a third type of sugar modification. Non-limiting example(s) of such an oligonucleotide include: WV-9508, WV-9509, and WV-9510.

[00243] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: two or more consecutive F. Non-limiting example(s) of such an oligonucleotide include: WV-9508, WV-9509, and WV-9510.

[00244] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8595, WV-8691, WV-8692, WV-8693, WV-8694, WV-8695, WV-8696, WV-9062, WV-9063, WV-9285, WV-9286, WV-9380, WV-9381, WV-9394, WV-9395, WV-9396, WV-9397, WV-9398, WV-9399, WV-9421, WV-9421, WV-9486, and WV-9487.

[00245] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-9488, WV-9489, WV-9490, WV-9491, WV-9492, WV-9494, WV-9505, WV-9506, WV-9507, WV-8452, WV-8453, WV-8009, WV-8010, WV-8011, WV-8012, WV-8454, and WV-8455.

[00246] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8549, WV-8550, WV-8551, WV-8568, WV-8569, WV-13312, WV-14758, WV-14772, WV-15049, WV-15050, and WV-15051.

[00247] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a particular pattern of two different types of sugar modifications; and a second wing comprises: a different pattern of two different types of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8121, WV-8129, WV-8118, WV-8126, WV-8472, WV-8473, WV-8474, WV-8475, and WV-8476.

[00248] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a particular pattern of two different types of sugar modifications; and a second wing

comprises: a different pattern of two different types of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8119 and WV-8127.

[00249] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: a only one type of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8115 and WV-8123.

[00250] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a particular pattern of two different types of sugar modifications; and a second wing comprises: a different pattern of two different types of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8120 and WV-8128.

[00251] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: one type of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8116 and WV-8124.

[00252] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: M and two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-14552, WV-14553, WV-14554, and WV-14555.

[00253] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: MmMmm. Non-limiting example(s) of such an oligonucleotide include: WV-8456.

[00254] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8005, WV-8006, WV-8007, WV-8008, WV-8466, WV-8467, WV-8468, WV-8469, WV-8470, WV-8471, WV-8547, WV-8548, WV-8594, WV-13305, WV-13306, WV-13307, WV-13308, WV-13309, WV-13310, WV-13311, WV-13313, WV-13803, WV-13804, and WV-13805.

[00255] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: M and two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8125.

[00256] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: two or more consecutive M. Non-limiting example(s) of such an oligonucleotide include: WV-8314.

[00257] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modification; and a second wing comprises: a third type of sugar

modification. Non-limiting example(s) of such an oligonucleotide include: WV-9508, WV-9509, WV-9510.

[00258] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: two or more consecutive F. Non-limiting example(s) of such an oligonucleotide include: WV-9508, WV-9509, WV-9510.

[00259] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8595, WV-8691, WV-8692, WV-8693, WV-8694, WV-8695, WV-8696, WV-9062, WV-9063, WV-9285, WV-9286, WV-9380, WV-9381, WV-9394, WV-9395, WV-9396, WV-9397, WV-9398, WV-9399, WV-9421, WV-9421, WV-9486, and WV-9487.

[00260] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-9488, WV-9489, WV-9490, WV-9491, WV-9492, WV-9494, WV-9505, WV-9506, and WV-9507.

[00261] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a particular pattern of two different types of sugar modification; and a second wing comprises: a different pattern of two different types of sugar modification. Non-limiting example(s) of such an oligonucleotide include: WV-8452 and WV-8453.

[00262] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: MmMmm. Non-limiting example(s) of such an oligonucleotide include: WV-8452 and WV-8453.

[00263] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8009, WV-8010, WV-8011, WV-8012, WV-8454, and WV-8455.

[00264] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8549, WV-8550, WV-8551, WV-8568, WV-8569, WV-13312, WV-14758, WV-14772, WV-15049, WV-15050, and WV-15051.

[00265] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMmm; and a second wing comprises: M and two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8121 and WV-8129.

[00266] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: only one type of

sugar modification. Non-limiting example(s) of such an oligonucleotide include: WV-8118, WV-8126, WV-8472, WV-8473, WV-8474, WV-8475, and WV-8476.

[00267] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMmm; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8118, WV-8126, WV-8472, WV-8473, WV-8474, WV-8475, and WV-8476.

[00268] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMmmm; and a second wing comprises: M and two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8119 and WV-8127.

[00269] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMmmm; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8115 and WV-8123.

[00270] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mmMmm; and a second wing comprises: M and two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8120 and WV-8128.

[00271] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mmMmm; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8116 and WV-8124.

[00272] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: DMMD. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, and WV-8664.

[00273] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: MMD. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, and WV-8664.

[00274] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: DDMMD. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, and WV-8664.

[00275] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8637, WV-8638, WV-8639, WV-8640, WV-8653, WV-8654, WV-8655, WV-8656, WV-8665, WV-8666, WV-8667, WV-8668, WV-8669, WV-

8670, WV-8671, WV-8672, WV-12947, WV-12948, WV-12949, WV-12950, WV-12951, WV-12952, WV-12953, WV-12954, WV-12955, WV-12956, WV-12957, WV-12958, WV-12959, WV-12960, WV-12961, WV-12962, WV-12963, WV-12964, WV-12965, WV-12966, WV-12967, WV-12968, WV-12969, WV-12970, WV-12971, WV-12972, WV-12973, WV-12974, WV-12975, and WV-12976.

[00276] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: two or more consecutive M. Non-limiting example(s) of such an oligonucleotide include: WV-12977, WV-12978, WV-12979, WV-12980, WV-12981, WV-12982, WV-12983, WV-12984, WV-12985, WV-12986, WV-12987, WV-12988, WV-12989, WV-12990, WV-12991, WV-12992, WV-12993, WV-12994, WV-12995, WV-12996, WV-12997, WV-12998, WV-12999, WV-13000, WV-13001, WV-13002, WV-13003, WV-13004, WV-13005, WV-13006, WV-13007, and WV-13008.

[00277] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMM; and a second wing comprises: M and two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-9887, WV-9888, WV-10245, and WV-10246.

[00278] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMM; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-9871 and WV-9872.

[00279] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMMMM; and a second wing comprises: mmmmmmm. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00280] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMM; and a second wing comprises: M and two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-9873 and WV-9874.

[00281] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMM; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-9885, WV-9886, WV-10243, and WV-10244.

[00282] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: two or more consecutive F. Non-limiting example(s) of such an oligonucleotide include: WV-9526, WV-9527, WV-9528, WV-9529, WV-9530, WV-9531, WV-9532, WV-9533, WV-9590, WV-9591, WV-9592, and WV-9593.

[00283] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: two or more consecutive m. Non-limiting example(s) of such an oligonucleotide include: WV-8610, WV-8611, WV-8612, WV-8613, WV-8614, WV-8615, WV-8616, WV-8617, WV-8618, WV-8619, WV-8629, WV-8632, WV-8673, WV-8674, WV-

8675, WV-8676, WV-8677, WV-8678, WV-8679, WV-8680, WV-8681, WV-8682, WV-8683, WV-8684, WV-8685, WV-8686, WV-8687, and WV-8688.

[00284] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8852, and WV-8856.

[00285] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8043-8048.

[00286] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: MMMMM; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8043-8048.

[00287] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mmmmm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8852, and WV-8856.

[00288] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and M in a different order and/or different number; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8248.

[00289] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMmmm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8248.

[00290] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: M and 2 or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 9894-9896.

[00291] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: Mmmmm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 9894-9896, and WV-10253 to 10254.

[00292] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications.

[00293] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: MMMMMMM; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 12099, WV-12101, WV-12103, WV-12105, WV-12107, and WV-12109.

[00294] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: MMMMM; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 10250, and WV-9869 to WV-9870.

[00295] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: all M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9441-9445.

[00296] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: MMMMM; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 9441-9445.

[00297] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications.

[00298] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and M in a particular order and number; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications.

[00299] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and M in a particular order and number; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications.

[00300] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: L, m and M in a different order and/or different number; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8250.

[00301] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMmmL; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8250.

[00302] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and L; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8246.

[00303] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mmmmL; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8246.

[00304] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and L; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 11958, and WV-11960, and WV-11962.

[00305] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive m and L; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 11958, WV-11960, and WV-11962.

[00306] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mmmmL; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 11958, WV-11960, and WV-11962.

[00307] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: only one type of sugar modification; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-11114, WV-11533, WV-12503, WV-12504, WV-12505, WV-8553, WV-8555, WV-8556, WV-8557, WV-8582, WV-8583, WV-8584, WV-8585, WV-8586, WV-8587, WV-8588, WV-8589, WV-8590, WV-8591, WV-8592, WV-8593, WV-9058, WV-9059, WV-9060, WV-9061, WV-9696, WV-9697, and WV-9698.

[00308] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an

oligonucleotide include: WV-11114, WV-11533, WV-12503, WV-12504, WV-12505, WV-8553, WV-8555, WV-8556, WV-8557, WV-8582, WV-8583, WV-8584, WV-8585, WV-8586, WV-8587, WV-8588, WV-8589, WV-8590, WV-8591, WV-8592, WV-8593, WV-9058, WV-9059, WV-9060, WV-9061, WV-9696, WV-9697, and WV-9698.

[00309] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-11114, WV-11533, WV-12503, WV-12504, WV-12505, WV-8553, WV-8555, WV-8556, WV-8557, WV-8582, WV-8583, WV-8584, WV-8585, WV-8586, WV-8587, WV-8588, WV-8589, WV-8590, WV-8591, WV-8592, WV-8593, WV-9058, WV-9059, WV-9060, WV-9061, WV-9696, WV-9697, and WV-9698.

[00310] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a different pattern of the same two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8097, WV-8098, WV-8099, WV-8100, WV-8101, WV-8102, and WV-8109.

[00311] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a different pattern of m and M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8097, WV-8098, WV-8099, WV-8100, WV-8101, WV-8102, and WV-8109.

[00312] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mmMmm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8097, WV-8098, WV-8099, WV-8100, WV-8101, WV-8102, and WV-8109.

[00313] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-12110, WV-12111, WV-12112, WV-12113, and WV-12114.

[00314] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-12110, WV-12111, WV-12112, WV-12113, and WV-12114.

[00315] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-13303, WV-13304, WV-13809, WV-14087, WV-14349, WV-14556, WV-14557, WV-14558, WV-14559, WV-14560, WV-14561, WV-14562, WV-14563, WV-14564, WV-14733, WV-14734, WV-14735, WV-14736, WV-14737, WV-14771, WV-15310, WV-15311, WV-15312, WV-15313, WV-15314, WV-15315, WV-15316, WV-15317, WV-15318, WV-15319, WV-15320, WV-15321, WV-15351, WV-15352, WV-15353, WV-15354, WV-15355, WV-15356, WV-15357, WV-15358, WV-15359, WV-15360, WV-15361, WV-15362, WV-15363, WV-15364, WV-15365, WV-15562, WV-15563, WV-15863, WV-15864, and WV-15887.

[00316] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8552, WV-8554, WV-8570, WV-8571, WV-8572, WV-8573, WV-8574, WV-8575, WV-8576, WV-8577, WV-8578, WV-8579, WV-8580, and WV-8581.

[00317] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-14552, WV-14553, WV-14554, and WV-14555.

[00318] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8456.

[00319] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8005, WV-8006, WV-8007, WV-8008, WV-8466, WV-8467, WV-8468, WV-8469, WV-8470, WV-8471, WV-8547, WV-8548, WV-8594, WV-13305, WV-13306, WV-13307, WV-13308, WV-13309, WV-13310, WV-13311, WV-13313, WV-13803, WV-13804, and WV-13805.

[00320] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8125.

[00321] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8314.

[00322] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a third type of sugar modification; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9508, WV-9509, and WV-9510.

[00323] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive F; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9508, WV-9509, and WV-9510.

[00324] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8595, WV-8691, WV-8692, WV-8693, WV-8694, WV-8695, WV-8696, WV-9062, WV-9063, WV-9285, WV-9286, WV-9380, WV-9381, WV-9394, WV-9395, WV-9396, WV-9397, WV-9398, WV-9399, WV-9421, WV-9421, WV-9486, and WV-9487.

[00325] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9488, WV-9489, WV-9490, WV-9491, WV-9492, WV-9494, WV-9505, WV-9506, WV-9507, WV-8452, WV-8453, WV-8009, WV-8010, WV-8011, WV-8012, WV-8454, and WV-8455.

[00326] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8549, WV-8550, WV-8551, WV-8568, WV-8569, WV-13312, WV-14758, WV-14772, WV-15049, WV-15050, and WV-15051.

[00327] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a different pattern of two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8121, WV-8129, WV-8118, WV-8126, WV-8472, WV-8473, WV-8474, WV-8475, and WV-8476.

[00328] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a different pattern of two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8119 and WV-8127.

[00329] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a only one type of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8115 and WV-8123.

[00330] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a different pattern of two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8120 and WV-8128.

[00331] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: one type of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8116 and WV-8124.

[00332] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: M and two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-14552, WV-14553, WV-14554, and WV-14555.

[00333] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: MmMmm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8456.

[00334] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8005, WV-8006, WV-8007, WV-8008, WV-8466, WV-8467, WV-8468, WV-8469, WV-8470, WV-8471, WV-8547, WV-8548, WV-8594, WV-13305, WV-13306, WV-13307, WV-13308, WV-13309, WV-13310, WV-13311, WV-13313, WV-13803, WV-13804, and WV-13805.

[00335] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: M and two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8125.

[00336] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8314.

[00337] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a third type of sugar modification; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9508, WV-9509, WV-9510.

[00338] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive F; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9508, WV-9509, WV-9510.

[00339] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8595, WV-8691, WV-8692, WV-8693, WV-8694, WV-8695, WV-8696, WV-9062, WV-9063, WV-9285, WV-9286, WV-9380, WV-9381, WV-9394, WV-9395, WV-9396, WV-9397, WV-9398, WV-9399, WV-9421, WV-9421, WV-9486, and WV-9487.

[00340] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9488, WV-9489, WV-9490, WV-9491, WV-9492, WV-9494, WV-9505, WV-9506, and WV-9507.

[00341] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a different pattern of two different types of sugar modification; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8452 and WV-8453.

[00342] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: MmMmm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8452 and WV-8453.

[00343] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a

different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8009, WV-8010, WV-8011, WV-8012, WV-8454, and WV-8455.

[00344] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8549, WV-8550, WV-8551, WV-8568, WV-8569, WV-13312, WV-14758, WV-14772, WV-15049, WV-15050, and WV-15051.

[00345] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: M and two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8121 and WV-8129.

[00346] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: only one type of sugar modification; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8118, WV-8126, WV-8472, WV-8473, WV-8474, WV-8475, and WV-8476.

[00347] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8118, WV-8126, WV-8472, WV-8473, WV-8474, WV-8475, and WV-8476.

[00348] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: M and two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8119 and WV-8127.

[00349] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8115 and WV-8123.

[00350] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: M and two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8120 and WV-8128.

[00351] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8116 and WV-8124.

[00352] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: DMMD; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, and WV-8664.

[00353] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: MMD; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, and WV-8664.

[00354] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: DDMMD; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, and WV-8664.

[00355] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8637, WV-8638, WV-8639, WV-8640, WV-8653, WV-8654, WV-8655, WV-8656, WV-8665, WV-8666, WV-8667, WV-8668, WV-8669, WV-8670, WV-8671, WV-8672, WV-12947, WV-12948, WV-12949, WV-12950, WV-12951, WV-12952, WV-12953, WV-12954, WV-12955, WV-12956, WV-12957, WV-12958, WV-12959, WV-12960, WV-12961, WV-12962, WV-12963, WV-12964, WV-12965, WV-12966, WV-12967, WV-12968, WV-12969, WV-12970, WV-12971, WV-12972, WV-12973, WV-12974, WV-12975, and WV-12976.

[00356] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-12977, WV-12978, WV-12979, WV-12980, WV-12981, WV-12982, WV-12983, WV-12984, WV-12985, WV-12986, WV-12987, WV-12988, WV-12989, WV-12990, WV-12991, WV-12992, WV-12993, WV-12994, WV-12995, WV-12996, WV-12997, WV-12998, WV-12999, WV-13000, WV-13001, WV-13002, WV-13003, WV-13004, WV-13005, WV-13006, WV-13007, and WV-13008.

[00357] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: M and two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9887, WV-9888, WV-10245, and WV-10246.

[00358] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9871 and WV-9872.

[00359] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mmmmmmm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00360] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: M and two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9873 and WV-9874.

[00361] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9885, WV-9886, WV-10243, and WV-10244.

[00362] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive F; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9526, WV-9527, WV-9528, WV-9529, WV-9530, WV-9531, WV-9532, WV-9533, WV-9590, WV-9591, WV-9592, and WV-9593.

[00363] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8610, WV-8611, WV-8612, WV-8613, WV-8614, WV-8615, WV-8616, WV-8617, WV-8618, WV-8619, WV-8629, WV-8632, WV-8673, WV-8674, WV-8675, WV-8676, WV-8677, WV-8678, WV-8679, WV-8680, WV-8681, WV-8682, WV-8683, WV-8684, WV-8685, WV-8686, WV-8687, and WV-8688.

[00364] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive M; and a second wing comprises: a different sugar modification or a

different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8852, and WV-8856.

[00365] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8043-8048.

[00366] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mmmmm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8043-8048.

[00367] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: MMMMM; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8852, and WV-8856.

[00368] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and M in a particular order and number; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8248.

[00369] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMmMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8248.

[00370] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and 2 or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 9894-9896.

[00371] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMM; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 9894-9896, and WV-10253 to 10254.

[00372] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and M in a particular order and number; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications.

[00373] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMMMM; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 12099, WV-12101, WV-12103, WV-12105, WV-12107, and WV-12109.

[00374] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMM; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 10250, and WV-9869 to WV-9870.

[00375] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 9441-9445.

[00376] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 9441-9445.

[00377] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and M in a particular order and number; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications.

[00378] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications.

[00379] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications.

[00380] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: L, m and M in a particular order and number; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8250.

[00381] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: LMmMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8250.

[00382] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: L, m and M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8246.

[00383] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: LMmMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 8246.

[00384] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: L and M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 11958, and WV-11960, and WV-11962.

[00385] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: L and 2 or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 11958, WV-11960, and WV-11962.

[00386] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: LMMMM; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV- 11958, WV-11960, and WV-11962.

[00387] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-11114, WV-11533, WV-12503, WV-12504, WV-12505, WV-8553, WV-8555, WV-8556, WV-8557, WV-8582, WV-8583, WV-8584, WV-8585, WV-8586, WV-8587, WV-8588, WV-8589, WV-8590, WV-8591, WV-8592, WV-8593, WV-9058, WV-9059, WV-9060, WV-9061, WV-9696, WV-9697, and WV-9698.

[00388] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a pattern of m and M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-11114, WV-11533, WV-12503, WV-12504, WV-12505, WV-8553, WV-8555, WV-8556, WV-8557, WV-8582, WV-8583, WV-8584, WV-8585, WV-8586, WV-8587, WV-8588, WV-8589, WV-8590, WV-8591, WV-8592, WV-8593, WV-9058, WV-9059, WV-9060, WV-9061, WV-9696, WV-9697, and WV-9698.

[00389] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-11114, WV-11533, WV-12503, WV-12504, WV-12505, WV-8553, WV-8555, WV-8556, WV-8557, WV-8582, WV-8583, WV-8584, WV-8585, WV-8586, WV-8587, WV-8588, WV-8589, WV-8590, WV-8591, WV-8592, WV-8593, WV-9058, WV-9059, WV-9060, WV-9061, WV-9696, WV-9697, and WV-9698.

[00390] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a pattern of two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8097, WV-8098, WV-8099, WV-8100, WV-8101, WV-8102, and WV-8109.

[00391] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a pattern of m and M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8097, WV-8098, WV-8099, WV-8100, WV-8101, WV-8102, and WV-8109.

[00392] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mmMMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8097, WV-8098, WV-8099, WV-8100, WV-8101, WV-8102, and WV-8109.

[00393] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: m and two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-12110, WV-12111, WV-12112, WV-12113, and WV-12114.

[00394] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMM; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-12110, WV-12111, WV-12112, WV-12113, and WV-12114.

[00395] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-13303, WV-13304, WV-13809, WV-14087, WV-14349, WV-14556, WV-14557, WV-14558, WV-14559, WV-14560, WV-14561, WV-14562, WV-14563, WV-14564, WV-14733, WV-

14734, WV-14735, WV-14736, WV-14737, WV-14771, WV-15310, WV-15311, WV-15312, WV-15313, WV-15314, WV-15315, WV-15316, WV-15317, WV-15318, WV-15319, WV-15320, WV-15321, WV-15351, WV-15352, WV-15353, WV-15354, WV-15355, WV-15356, WV-15357, WV-15358, WV-15359, WV-15360, WV-15361, WV-15362, WV-15363, WV-15364, WV-15365, WV-15562, WV-15563, WV-15863, WV-15864, and WV-15887.

[00396] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8552, WV-8554, WV-8570, WV-8571, WV-8572, WV-8573, WV-8574, WV-8575, WV-8576, WV-8577, WV-8578, WV-8579, WV-8580, and WV-8581.

[00397] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-14552, WV-14553, WV-14554, and WV-14555.

[00398] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8456.

[00399] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8005, WV-8006, WV-8007, WV-8008, WV-8466, WV-8467, WV-8468, WV-8469, WV-8470, WV-8471, WV-8547, WV-8548, WV-8594, WV-13305, WV-13306, WV-13307, WV-13308, WV-13309, WV-13310, WV-13311, WV-13313, WV-13803, WV-13804, and WV-13805.

[00400] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8125.

[00401] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8314.

[00402] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: a different sugar

modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9508, WV-9509, and WV-9510.

[00403] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9508, WV-9509, and WV-9510.

[00404] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8595, WV-8691, WV-8692, WV-8693, WV-8694, WV-8695, WV-8696, WV-9062, WV-9063, WV-9285, WV-9286, WV-9380, WV-9381, WV-9394, WV-9395, WV-9396, WV-9397, WV-9398, WV-9399, WV-9421, WV-9421, WV-9486, and WV-9487.

[00405] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9488, WV-9489, WV-9490, WV-9491, WV-9492, WV-9494, WV-9505, WV-9506, WV-9507, WV-8452, WV-8453, WV-8009, WV-8010, WV-8011, WV-8012, WV-8454, and WV-8455.

[00406] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8549, WV-8550, WV-8551, WV-8568, WV-8569, WV-13312, WV-14758, WV-14772, WV-15049, WV-15050, and WV-15051.

[00407] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a particular pattern of two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8121, WV-8129, WV-8118, WV-8126, WV-8472, WV-8473, WV-8474, WV-8475, and WV-8476.

[00408] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a particular pattern of two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8119 and WV-8127.

[00409] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: a different sugar

modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8115 and WV-8123.

[00410] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a particular pattern of two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8120 and WV-8128.

[00411] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8116 and WV-8124.

[00412] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-14552, WV-14553, WV-14554, and WV-14555.

[00413] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8456.

[00414] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8005, WV-8006, WV-8007, WV-8008, WV-8466, WV-8467, WV-8468, WV-8469, WV-8470, WV-8471, WV-8547, WV-8548, WV-8594, WV-13305, WV-13306, WV-13307, WV-13308, WV-13309, WV-13310, WV-13311, WV-13313, WV-13803, WV-13804, and WV-13805.

[00415] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8125.

[00416] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8314.

[00417] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modification; and a second wing comprises: a different sugar

modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9508, WV-9509, WV-9510.

[00418] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9508, WV-9509, WV-9510.

[00419] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8595, WV-8691, WV-8692, WV-8693, WV-8694, WV-8695, WV-8696, WV-9062, WV-9063, WV-9285, WV-9286, WV-9380, WV-9381, WV-9394, WV-9395, WV-9396, WV-9397, WV-9398, WV-9399, WV-9421, WV-9421, WV-9486, and WV-9487.

[00420] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9488, WV-9489, WV-9490, WV-9491, WV-9492, WV-9494, WV-9505, WV-9506, and WV-9507.

[00421] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: a particular pattern of two different types of sugar modification; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8452 and WV-8453.

[00422] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8452 and WV-8453.

[00423] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8009, WV-8010, WV-8011, WV-8012, WV-8454, and WV-8455.

[00424] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8549, WV-8550, WV-8551, WV-8568, WV-8569, WV-13312, WV-14758, WV-14772, WV-15049, WV-15050, and WV-15051.

[00425] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMmm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8121 and WV-8129.

[00426] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two different types of sugar modifications; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8118, WV-8126, WV-8472, WV-8473, WV-8474, WV-8475, and WV-8476.

[00427] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMmm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8118, WV-8126, WV-8472, WV-8473, WV-8474, WV-8475, and WV-8476.

[00428] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMmmm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8119 and WV-8127.

[00429] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMmmm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8115 and WV-8123.

[00430] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mmMmm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8120 and WV-8128.

[00431] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mmMmm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8116 and WV-8124.

[00432] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, and WV-8664.

[00433] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, and WV-8664.

[00434] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8645, WV-8646, WV-8647, WV-8648, WV-8661, WV-8662, WV-8663, and WV-8664.

[00435] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive M; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8637, WV-8638, WV-8639, WV-8640, WV-8653, WV-8654, WV-8655, WV-8656, WV-8665, WV-8666, WV-8667, WV-8668, WV-8669, WV-8670, WV-8671, WV-8672, WV-12947, WV-12948, WV-12949, WV-12950, WV-12951, WV-12952, WV-12953, WV-12954, WV-12955, WV-12956, WV-12957, WV-12958, WV-12959, WV-12960, WV-12961, WV-12962, WV-12963, WV-12964, WV-12965, WV-12966, WV-12967, WV-12968, WV-12969, WV-12970, WV-12971, WV-12972, WV-12973, WV-12974, WV-12975, and WV-12976.

[00436] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive m; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-12977, WV-12978, WV-12979, WV-12980, WV-12981, WV-12982, WV-12983, WV-12984, WV-12985, WV-12986, WV-12987, WV-12988, WV-12989, WV-12990, WV-12991, WV-12992, WV-12993, WV-12994, WV-12995, WV-12996, WV-12997, WV-12998, WV-12999, WV-13000, WV-13001, WV-13002, WV-13003, WV-13004, WV-13005, WV-13006, WV-13007, and WV-13008.

[00437] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMM; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9887, WV-9888, WV-10245, and WV-10246.

[00438] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMM; and a second wing comprises: a different sugar modification or a different

combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9871 and WV-9872.

[00439] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMMMM; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00440] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMM; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9873 and WV-9874.

[00441] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMM; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9885, WV-9886, WV-10243, and WV-10244.

[00442] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-9526, WV-9527, WV-9528, WV-9529, WV-9530, WV-9531, WV-9532, WV-9533, WV-9590, WV-9591, WV-9592, and WV-9593.

[00443] In some embodiments of an oligonucleotide having an asymmetric format: a first wing comprises: mMMMm; and a second wing comprises: a different sugar modification or a different combination or pattern of sugar modifications. Non-limiting example(s) of such an oligonucleotide include: WV-8610, WV-8611, WV-8612, WV-8613, WV-8614, WV-8615, WV-8616, WV-8617, WV-8618, WV-8619, WV-8629, WV-8632, WV-8673, WV-8674, WV-8675, WV-8676, WV-8677, WV-8678, WV-8679, WV-8680, WV-8681, WV-8682, WV-8683, WV-8684, WV-8685, WV-8686, WV-8687, and WV-8688.

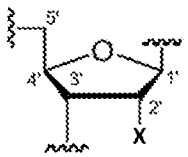
[00444] In some embodiments, two or more consecutive m is mm. In some embodiments, two or more consecutive m is mmm. In some embodiments, two or more consecutive m is mmmm. In some embodiments, two or more consecutive m is mmmmm. In some embodiments, two or more consecutive m is mmmmmm. In some embodiments, two or more consecutive m is mmmmmmm.

[00445] In some embodiments, two or more consecutive M is MM. In some embodiments, two or more consecutive M is MMM. In some embodiments, two or more consecutive M is MMMM. In some embodiments, two or more consecutive M is MMMMM. In some embodiments, two or more consecutive M is MMMMMM. In some embodiments, two or more consecutive M is MMMMMMM.

[00446] In some embodiments, two or more consecutive F is FF. In some embodiments, two or more consecutive F is FFF. In some embodiments, two or more consecutive F is FFFF. In some embodiments, two or more consecutive F is FFFFF. In some embodiments, two or more consecutive F is FFFFFF. In some embodiments, two or more consecutive F is FFFFFFF.

[00447] In some embodiments, oligonucleotides of the present disclosure comprise sugar modifications. In some embodiments, oligonucleotides can comprise any sugar described herein or known in the art. In some embodiments, a first wing of an oligonucleotide having an asymmetric format can comprise any sugar described herein or known in the art, and a second wing of the oligonucleotide does not comprise the sugar. In some embodiments, a first wing of an oligonucleotide having an asymmetric format can comprise any sugar described herein or known in the art, and a second wing of the oligonucleotide comprises a different sugar.

[00448] In some embodiments, a sugar has a structure of:



X= H, OH, F, OMe or MOE

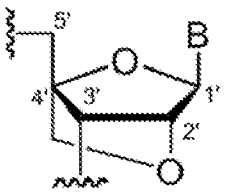
[00449] Modified sugars can be incorporated into a provided oligonucleotide. In some embodiments, a modified sugar contains one or more substituents at the 2' position including one of the following: –F; $-CF_3$, –CN, $-N_3$, –NO, $-NO_2$, –OR', –SR', or $-N(R')_2$, wherein each R' is independently described 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, DMAEOE. Also contemplated herein are modified sugars described in WO 2001/088198; 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 a nucleic acid, a group for improving the pharmacodynamic properties of a nucleic acid, 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 the sugar or modified

sugar, including the 3' position of the sugar on the 3'-terminal nucleotide or in the 5' position of the 5'-terminal nucleotide.

[00450] In some embodiments, a 2'-modification is 2'-F.

[00451] In some embodiments, the 2'-OH of a ribose is replaced with a substituent 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 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. 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 $–OCH_2CH_2OMe$.

[00452] Modified sugars also include 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(Et)−. In some embodiments, −L− is between C2 and C4 of a sugar moiety. In some embodiments, a locked nucleic acid has the structure indicated below. A locked nucleic acid of the structure below is indicated, wherein B represents a nucleobase or modified nucleobase as described herein, and wherein, *e.g.,* R^{2s} and R^{4s} are R taken together with their intervening atoms to form a ring. In some embodiments, a modified nucleoside has a structure of:



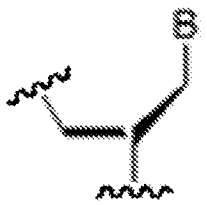
wherein B is a base.

[00453] In some embodiments, a modified sugar is an ENA 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.

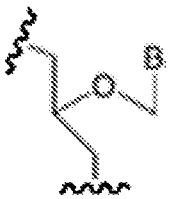
[00454] Modified sugars include cyclobutyl or cyclopentyl moieties in place of the pentofuranosyl sugar. Representative United States patents that teach the preparation of such modified sugar structures include, but are not limited to, US Patent Nos.: 4,981,957; 5,118,800; 5,319,080; and 5,359,044. Some modified sugars that are contemplated include 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).

[00455] Non-limiting examples of modified sugars include glycerol, which form glycerol nucleic acid (GNA). One example of a GNA is shown below and 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. In some embodiments, a nucleoside has a structure of:



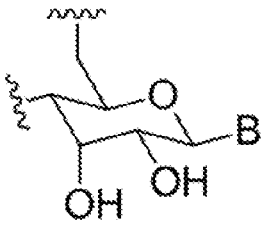
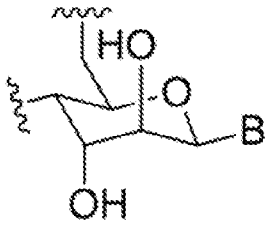
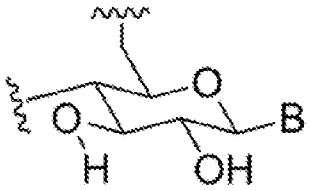
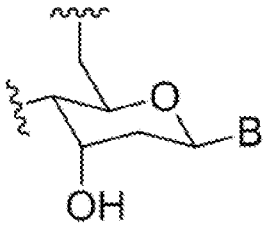
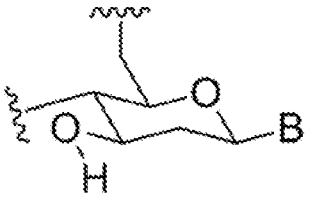
Wherein B is a base.

[00456] A 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. In some embodiments, a nucleoside has a structure of:



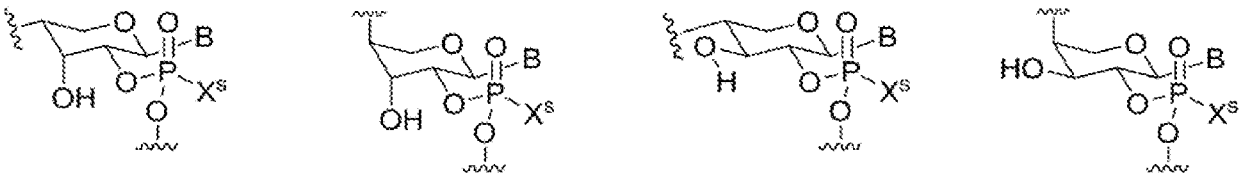
Wherein B is a base.

[00457] Additional non-limiting examples of modified sugars and/or modified nucleosides and/or modified nucleotides include hexopyranosyl (6' to 4'), pentopyranosyl (4' to 2'), pentopyranosyl (4' to 3'), 5'-deoxy-5'-C-malonyl, squaryldiamide, and tetrofuranosyl (3' to 2') sugars. In some embodiments, a modified nucleoside comprises a hexopyranosyl (6' to 4') sugar and has the structure of any one in the following formulae:

wherein X^s corresponds to the P-modification group "-XLR^1" described herein wherein XLR^1 is equivalent to X-L-R^1 and X, L, and R^1 are as defined in Formula **I**, disclosed herein, and B is a base.

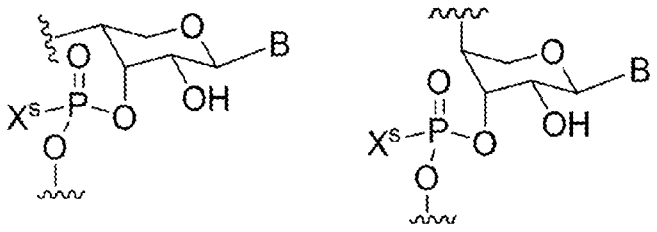
[00458] In some embodiments, a modified nucleotide comprises a pentopyranosyl (4' to 2') sugar and has a structure of any one in the following formulae:



,

wherein X^s corresponds to the P-modification group "-XLR^1" described herein, wherein XLR^1 is equivalent to X-L-R^1 and X, L, and R^1 are as defined in Formula **I**, disclosed herein, and B is a base.

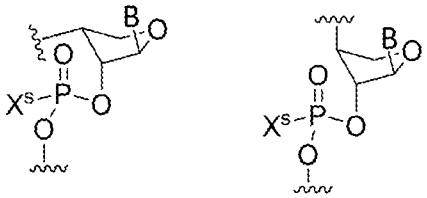
[00459] In some embodiments, a modified nucleotide comprises a pentopyranosyl (4' to 3') sugar and is of any one in the following formulae:



,

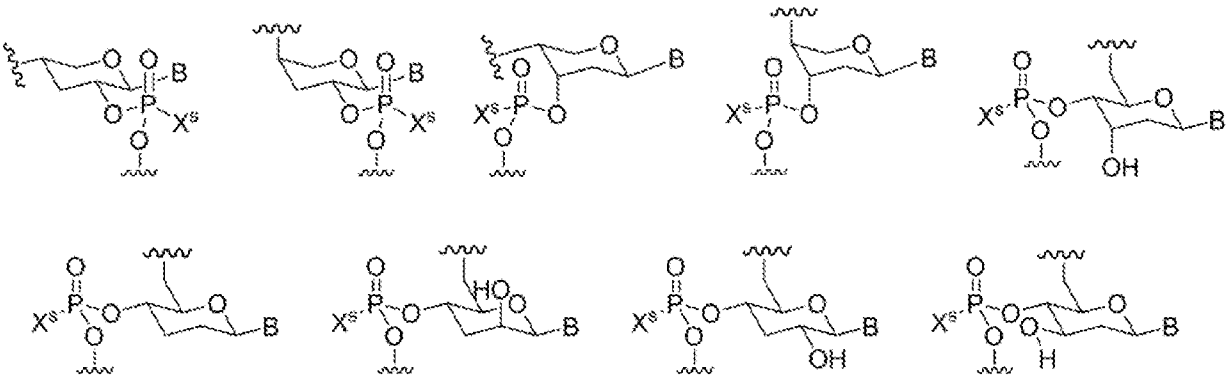
wherein X^s corresponds to the P-modification group "-XLR^1" described herein, wherein XLR^1 is equivalent to X-L-R^1 and X, L, and R^1 are as defined in Formula **I**, disclosed herein, and B is a base.

[00460] In some embodiments, a modified nucleotide comprises a tetrofuranosyl (3' to 2') sugar and is of either in the following formulae:



wherein X^s corresponds to the P-modification group "-XLR^1" described herein, wherein XLR^1 is equivalent to X-L-R^1 and X, L, and R^1 are as defined in Formula **I**, disclosed herein, and B is a base.

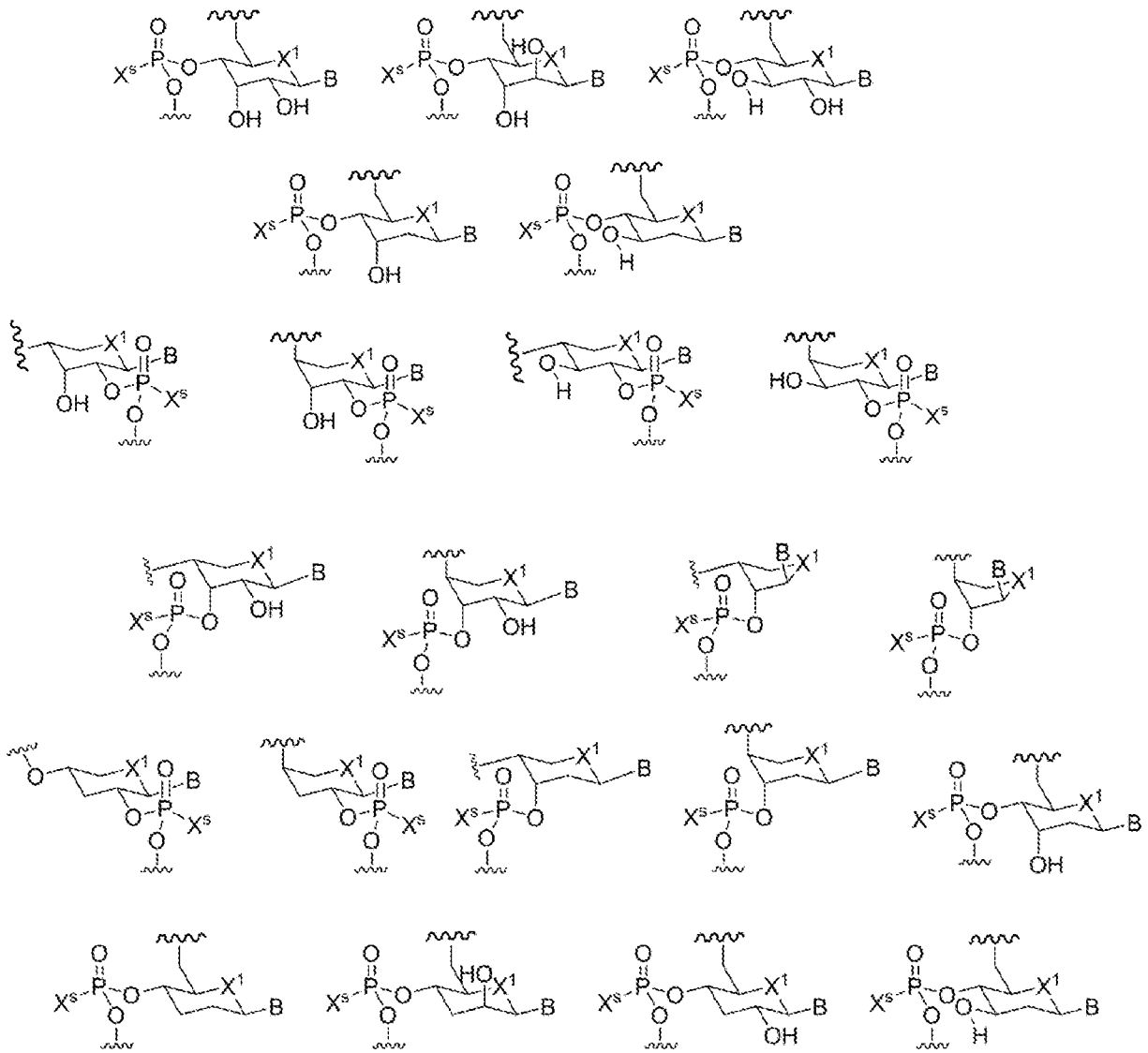
[00461] In some embodiments, a modified nucleotide comprises a modified sugar and is of any one in the following formulae:



wherein X^s corresponds to the P-modification group "-XLR^1" described herein, wherein XLR^1 is equivalent to X-L-R^1 and X, L, and R^1 are as defined in Formula **I**, disclosed herein, and B is a base.

[00462] 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 described in the present disclosure.

[00463] In some embodiments, a modified nucleotide is as illustrated below, wherein X^s corresponds to the P-modification group "-XLR^1" described herein, wherein XLR^1 is equivalent to X-L-R^1 and X, L, and R^1 are as defined in Formula **I**, disclosed herein, B is a base, and X^1 is selected from –S–, –Se–, $-CH_2-$, –NMe–, –NEt– and –N*i*Pr–



[00464] 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 having an asymmetric format are modified. In some embodiments, only purine residues 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 residues are modified). In some embodiments, only pyrimidine residues are modified (*e.g.*, about 1%, 2%, 3%, 4%,

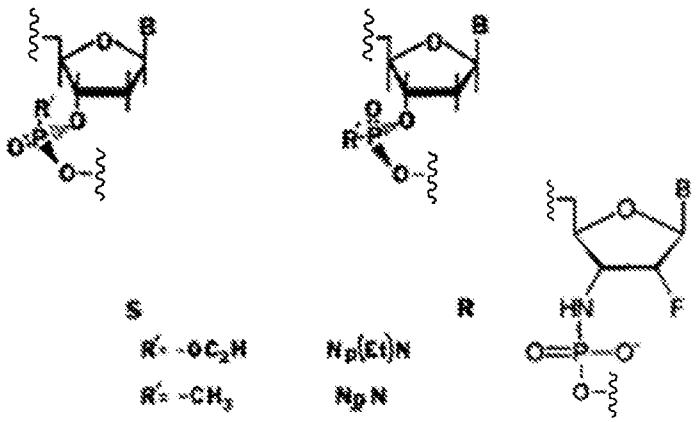
5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50% or more [*e.g.*, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more] of the pyridimine residues are modified). In some embodiments, both purine and pyrimidine residues are modified.

[00465] Modified sugars can be prepared by methods known in the art, including, but not limited to: 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. Specific modifications to the ribose can be found in the following references: 2'-fluoro (Kawasaki et. al., J. Med. Chem., 1993, 36, 831- 841), 2'-MOE (Martin, P. Helv. Chim. Acta 1996, 79, 1930-1938), "LNA" (Wengel, J. Acc. Chem. Res. 1999, 32, 301-310). In some embodiments, a modified sugar is any of those described in PCT Publication No. WO2012/030683, incorporated herein by reference, and/or depicted herein. 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

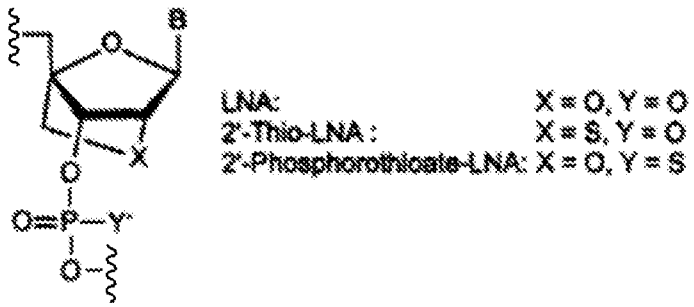
(2008), 52(1), 553-554; Singh et al. 1998 Chem. Comm. 1247-1248; Singh et al. 1998 J. Org. Chem. 63: 10035-39; Singh et al. 1998 J. Org. Chem. 63: 6078-6079; Sorensen 2003 Chem. Comm. 2130-2131; Ts'o et al. Ann. N. Y. Acad. Sci. 1988, 507, 220; Van Aerschot et al. 1995 Angew. Chem. Int. Ed. Engl. 34: 1338; Vasseur et al. J. Am. Chem. Soc. 1992, 114, 4006; WO 20070900071; WO 20070900071; or WO 2016/079181.

[00466] 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.

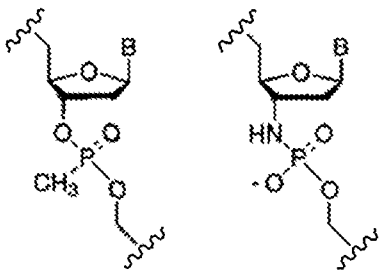
[00467] In some embodiments, an example modified nucleotide is selected from:



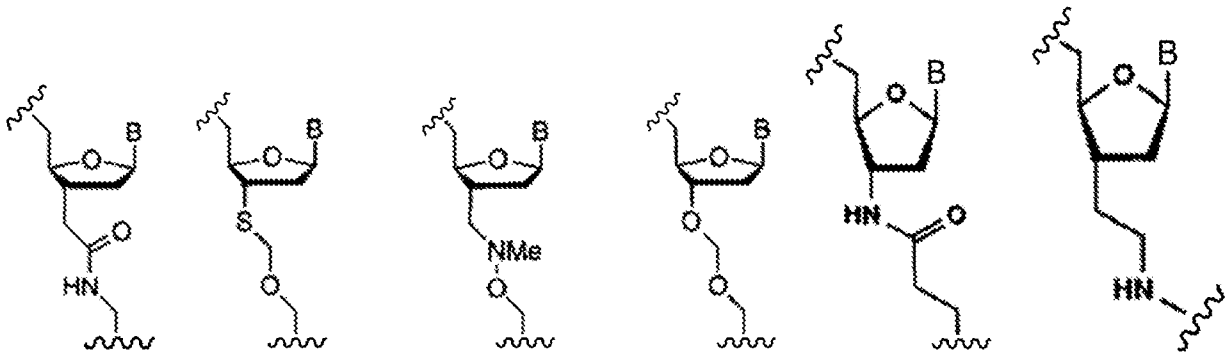
2'-Fluoro N3'-P5'-phosphoramidate

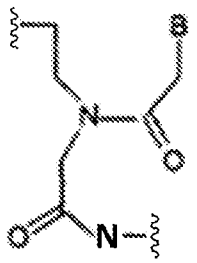


PS-LNA



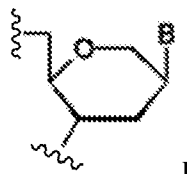
In some embodiments, a nucleotide has a structure selected from any of:



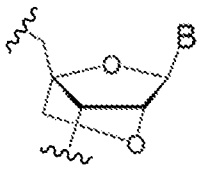


PNA

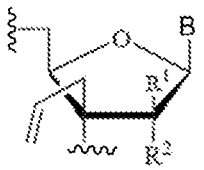
In some embodiments, a modified nucleoside has a structure selected from:

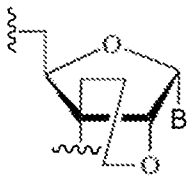


HNA



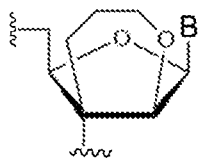
beta-D-oxy-LNA

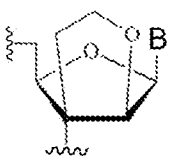




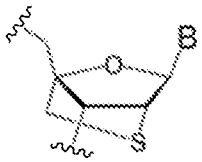
Wherein

R^1 and R^2 are independently -H, -F, -OMe, -MOE or substituted or unsubstituted C_{1-6} alkyl;

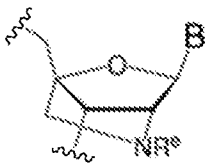




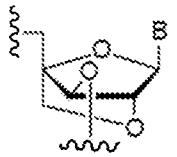
2'-O,3'-C-linked bicyclic



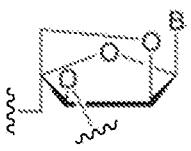
beta-D-thio-LNA

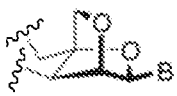


beta-D-amino-LNA where R^e is substituted or unsubstituted C_{1-6} alkyl or H,



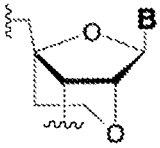
, xylo-LNA [c]

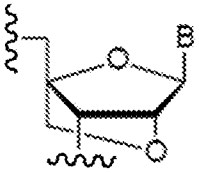


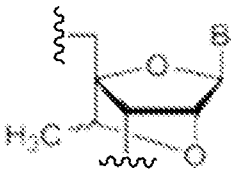


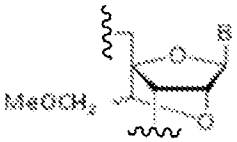
alpha-L-LNA

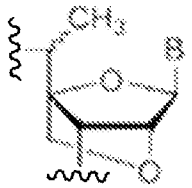

ENA


beta-D-ENA

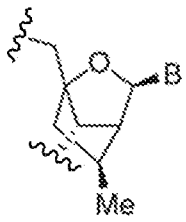

methylphosphonate-LNA

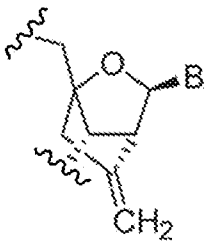

(*R*, *S*)-cEt

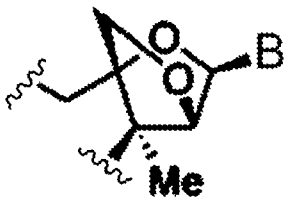

(*R*,*S*)-cMOE

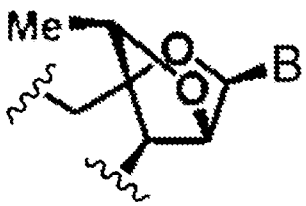

(*R*, *S*)-cMOE

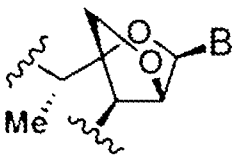
(*R*, *S*)-5'-Me-LNA

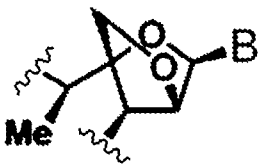

S-Me cLNA

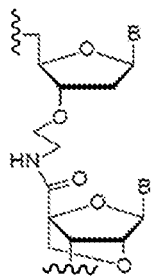

Methylene-cLNA


3'-Me-alpha-L-LNA


R-6'-Me-alpha-L-LNA


S-5'-Me-alpha-L-LNA


R-5'-Me-alpha-L-LNA. Additional chemically modified sugars are described in WO 2008/101157, WO 2007/134181, WO 2016/167780, and published US Patent Application US2005-0130923. In some embodiments, a nucleotide and adjacent nucleoside have the structure of:


amide-linked LNA.

[00468] In some embodiments, a locked nucleic acid or LNA or LNA nucleoside or LNA nucleotide is or comprises a nucleic acid monomer having a bridge connecting two carbon atoms between

the 4' and 2' position of the nucleoside sugar unit, thereby forming a bicyclic sugar. Examples of such a bicyclic sugar include but are not limited to alpha-L-Methyleneoxy (4'-CH_2-O-2') LNA, beta-D-Methyleneoxy (4'-CH_2-O-2') LNA, Ethyleneoxy (4' -$(CH_2)_2$-O-2') LNA, Aminooxy (4' -CH_2-O-N(R)-2') LNA, and Oxyamino (4'-CH_2-N(R)-O-2') LNA. In some embodiments, R is R_1 or R_2.

[00469] Examples of nucleosides having modified sugar moieties include without limitation nucleosides comprising 5'-vinyl, 5'-methyl group (*R* or *S*), 4'-S, 2'-F, 2'-OCH_3, 2'-OCH_2CH_3, 2'-OCH_2CH_2F and 2'-$O(CH_2)_{20}CH_3$ substituent groups. The substituent at the 2' position can also be selected from allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, OCF_3, OCH_2F, $O(CH_2)_2SCH_3$, $O(CH_2)_2$-O-N(R_m)(R_n), O-CH_2-C(=O)-N(R_m)(R_n), and O-CH_2-C(=O)-N(R_1)-$(CH_2)_2$-N(R_m)(R_n), where each R_l, R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl.

[00470] In some embodiments, a bicyclic nucleoside includes any modified nucleoside comprising a bicyclic sugar moiety. Examples of bicyclic nucleic acids (BNAs) include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In some embodiments, antisense compounds provided herein include one or more BNA nucleosides wherein the bridge comprises one of the formulas: 4'-(CH_2)-O-2' (LNA); 4'-(CH_2)-S-2'; 4,-$(CH_2)_2$-O-2' (ENA); 4'-$CH(CH_3)$-O-2' and 4'-$CH(CH_2OCH_3)$-O-2' (and analogs thereof; see U.S. Patent 7,399,845); 4'-$C(CH_3)(CH_3)$-O-2' (and analogs thereof; see PCT/US2008/068922 published as WO/2009/006478); 4'-CH_2-N(OCH_3)-2' (and analogs thereof; see PCT/US2008/064591 published as WO/2008/150729); 4'-CH_2-O-N(CH_3)-2' (see published U.S. Patent Application US2004-0171570); 4'-CH_2-N(R)-O-2', wherein R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Patent 7,427,672); 4'-CH_2-C(H)(CH_3)-2' (see Chattopadhyaya et al, J. Org. Chem., 2009, 74, 118-134); and 4,-CH_2-C(=CH_2)-2' (and analogs thereof; see PCT/US2008/066154 published as WO 2008/154401).

[00471] Further bicyclic nucleosides have been reported in the literature (see for example: Srivastava et al, J. Am. Chem. Soc., 2007, 129(26) 8362-8379; Frieden et al, Nucleic Acids Research, 2003, 21, 6365-6372; Elayadi et al, Curr. Opinion Inverts. Drugs, 2001, 2, 558-561; Braasch et al, Chem. Biol, 2001, 8, 1-7; Oram et al, Curr. Opinion Mol Ther., 2001, 3, 239-243; Wahlestedt et al, Proc. Natl Acad. Sci. U. S. A., 2000, 97, 5633-5638; Singh et al, Chem. Commun., 1998, 4, 455-456; Koshkin et al, Tetrahedron, 1998, 54, 3607-3630; Kumar et al, Bioorg. Med. Chem. Lett., 1998, 8, 2219-2222; Singh et al, J. Org. Chem., 1998, 63, 10035-10039; U.S. Patents Nos.: 7,399,845; 7,053,207; 7,034,133; 6,794,499; 6,770,748; 6,670,461; 6,525,191; 6,268,490; U.S. Patent Publication Nos.: US2008-0039618; US2007-0287831; US2004-0171570; U.S. Patent Applications, Serial Nos.: 12/129,154; 61/099,844; 61/097,787; 61/086,231; 61/056,564; 61/026,998; 61/026,995; 60/989,574; International applications WO 2007/134181; WO 2005/021570; WO 2004/106356; and PCT International Applications Nos.: PCT/US2008/068922; PCT/US2008/066154; and PCT/US2008/064591).

[00472] In some embodiments, a bicyclic nucleoside can be prepared having one or more stereochemical sugar configurations including for example alpha-L-ribofuranose and beta-D-ribofuranose (see PCT international application PCT/DK98/00393, published as WO 99/14226). In some embodiments, a monocyclic nucleosides is a nucleoside comprising a modified sugar moiety that is not a bicyclic sugar moiety. In some embodiments, the sugar moiety, or sugar moiety analogue, of a nucleoside may be modified or substituted at any position. In some embodiments, a 4'-2' bicyclic nucleoside or 4' to 2' bicyclic nucleoside is a bicyclic nucleoside comprising a furanose ring comprising a bridge connecting two carbon atoms of the furanose ring connects the 2' carbon atom and the 4' carbon atom of the sugar ring. In some embodiments, bicyclic sugar moieties of BNA nucleosides include, but are not limited to, compounds having at least one bridge between the 4' and the 2' carbon atoms of the pentofuranosyl sugar moiety including without limitation, bridges comprising 1 or from 1 to 4 linked groups independently selected from $-[C(R_a)(R_b)]_n-$, $-C(R_a)=C(R_b)-$, $-C(R_a)=N-$, $-C(=NR_a)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-Si(R_a)_2-$, $-S(=O)x-$, and $-N(R_a)-$; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O)-H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl (S(=O)-J_1); and each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(=O)-H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12} aminoalkyl, substituted C_1-C_{12} aminoalkyl or a protecting group.

[00473] In some embodiments, the bridge of a bicyclic sugar moiety is $-[C(R_a)(R_b)]_n-$, $-[C(R_a)(R_b)]_n-O-$, $-C(R_aR_b)-N(R)-O-$ or $-C(R_aR_b)-O-N(R)-$. In some embodiments, the bridge is 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2', 4'-$(CH_2)_2$-O-2', 4'-CH_2-O-N(R)-2' and 4'-CH_2-N(R)-O-2'- wherein each R is, independently, H, a protecting group or C_1-C_{12} alkyl.

[00474] In some embodiments, bicyclic nucleosides are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-(CH_2)-O-2' bridge, may be in the alpha-L configuration or in the beta-D configuration. alpha-L-methyleneoxy (4'-CH_2-O-2') BNA's have been incorporated into antisense oligonucleotides that showed antisense activity (Frieden et al., Nucleic Acids Research, 2003, 21, 6365-6372).

[00475] In some embodiments, bicyclic nucleosides include those having a 4' to 2' bridge wherein such bridges include without limitation, a-L-4'-(CH_2)-O-2', P-D-4'-CH_2-O-2', 4'-$(CH_2)_2$-O-2', 4'-CH_2-O-N(R)-2', 4'-CH_2-N(R)-O-2', 4'-$CH(CH_3)$-O-2', 4'-CH_2-S-2', 4'-CH_2-N(R)-2', 4'-CH_2-$CH(CH_3)$-2', and 4'-$(CH_2)_3$-2', wherein R is H, a protecting group or C_1-C_{12} alkyl.

[00476] Analogs of various bicyclic nucleosides that have 4' to 2' bridging groups such as 4'-CH_2-O-2' and 4'-CH_2-S-2', have also been prepared (Kumar et al, Bioorg. Med. Chem. Lett., 1998, 8, 2219-2222). Preparation of oligodeoxyribonucleotide duplexes comprising bicyclic nucleosides for use as substrates for nucleic acid polymerases has also been described (Wengel et al, WO 99/14226). Furthermore, synthesis of 2'-amino-BNA, a novel conformationally restricted high-affinity oligonucleotide analog has been described in the art (Singh et al, J. Org. Chem., 1998, 63, 10035-10039). In addition, 2'-amino- and 2'-methylamino-BNA's have been prepared and the thermal stability of their duplexes with complementary RNA and DNA strands has been previously reported.

[00477] One carbocyclic bicyclic nucleoside having a 4'-$(CH_2)_3$-2' bridge and the alkenyl analog bridge 4'-CH=CH-CH_2-2' have been described (Frier et al., Nucleic Acids Research, 1997, 25(22), 4429-4443 and Albaek et al., J. Org. Chem., 2006, 71, 7731-7740). The synthesis and preparation of carbocyclic bicyclic nucleosides along with their oligomerization and biochemical studies have also been described (Srivastava et al, J. Am. Chem. Soc. 2007, 129(26), 8362-8379).

[00478] In some embodiments, bicyclic nucleosides include, but are not limited to, alpha-L-methyleneoxy (4'-CH_2-O-2') BNA, beta-D-methyleneoxy (4'-CH_2-O-2') BNA, ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA, aminooxy (4'-CH_2-O-N(R)-2') BNA, oxyamino (4'-CH_2-N(R)-O-2') BNA, methyl(methyleneoxy) (4'-$CH(CH_3)$-O-2') BNA (also referred to as constrained ethyl or cEt), methylene-thio (4'-CH_2-S-2') BNA, methylene-amino (4'-CH_2-N(R)-2') BNA, methyl carbocyclic (4'-CH_2-$CH(CH_3)$-2') BNA, propylene carbocyclic (4'-$(CH_2)_3$-2') BNA, and vinyl BNA.

[00479] In some embodiments, LNA compounds include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the sugar wherein each of the bridges independently comprises 1 or from 2 to 4 linked groups independently selected from -$[C(R_1)(R_2)]_n$-, -$C(R_1)$=$C(R_2)$-, -$C(R_1)$=N-, -$C(=NR_1)$-, -C(=O)-, -C(=S)-, -O-, -$Si(R_1)_2$-, -$S(=O)_x$- and -$N(R_1)$-; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each R_1 and R_2 is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, a heterocycle radical, a substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O)-H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl (S(=O)-J_1); and each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(=O)-H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12} aminoalkyl, substituted C_1-C_{12} aminoalkyl or a protecting group. Non-limiting examples of 4' - 2' bridging groups encompassed within the definition of LNA include, but are not limited to one of formulae: -$[C(R_1)(R_2)]_n$-, -$[C(R_1)(R_2)]_n$-O-, -$C(R_1R_2)$-$N(R_1)$-O- or $C(R_1R_2)$-O-$N(R_1)$-. Furthermore, other bridging groups

encompassed with the definition of LNA are 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2', 4'-$(CH_2)_2$-O-2', 4'-CH_2-O-N(R_1)-2' and 4'-CH_2-N(R_1)-O-2'- bridges, wherein each R_1 and R_2 is, independently, H, a protecting group or C_1-C_{12} alkyl. Also included within the definition of LNA are LNAs in which the 2'-hydroxyl group of the ribosyl sugar ring is connected to the 4' carbon atom of the sugar ring, thereby forming a methyleneoxy (4'-CH_2-O-2') bridge to form the bicyclic sugar moiety. The bridge can also be a methylene (-CH_2-) group connecting the 2' oxygen atom and the 4' carbon atom, for which the term methyleneoxy (4'-CH_2-O-2') LNA is used. In some embodiments, in the case of the bicylic sugar moiety having an ethylene bridging group in this position, the term ethyleneoxy (4'-CH_2CH_2-O-2') LNA is used. alpha-L-methyleneoxy (4'-CH_2-O-2'), an isomer of methyleneoxy (4'-CH_2-O-2') LNA, is also encompassed within the definition of LNA, as used herein.

[00480] In some embodiments, a 2'-modification is −F. In some embodiments, a 2'-modification is FANA. In some embodiments, a 2'-modification is FRNA.

[00481] In some embodiments, a sugar modification is a 5'-modification, *e.g.*, *R*-5'-Me, *S*-5'-Me, etc.

[00482] In some embodiments, a sugar modification changes the size of the sugar ring. In some embodiments, a sugar modification is the sugar moiety in FHNA.

[00483] 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 (optionally with its phosphorodiamidate linkage), glycol nucleic acids, etc.

[00484] In some embodiments, a modified tetrahydropyran nucleoside or modified THP nucleoside is a nucleoside having a six-membered tetrahydropyran "sugar" substituted for the pentofuranosyl residue in normal nucleosides and can be referred to as a sugar surrogate. Modified THP nucleosides include, but are not limited to, what is referred to in the art as hexitol nucleic acid (HNA), anitol nucleic acid (ANA), manitol nucleic acid (MNA) (see Leumann, Bioorg. Med. Chem., 2002, 10, 841-854) or fluoro HNA (F-HNA) having a tetrahydropyranyl ring system as illustrated below.

[00485] In some embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example nucleosides comprising morpholino sugar moieties and their use in oligomeric compounds has been reported (see for example: Braasch et al., Biochemistry, 2002, 41, 4503-4510; and U.S. Patents 5,698,685; 5,166,315; 5,185,444; and 5,034,506).

[00486] Combinations of modifications are also provided without limitation, such as 2'-F-5'-methyl substituted nucleosides (see PCT International Application WO 2008/101157 for other disclosed 5', 2'-bis substituted nucleosides) and replacement of the ribosyl ring oxygen atom with S and further substitution at the 2'-position (see published U.S. Patent Application US2005-0130923) or alternatively 5'-substitution of a bicyclic nucleic acid (see PCT International Application WO 2007/134181, wherein a

4'-CH_2-O-2' bicyclic nucleoside is further substituted at the 5' position with a 5'-methyl or a 5'-vinyl group). The synthesis and preparation of carbocyclic bicyclic nucleosides along with their oligomerization and biochemical studies have also been described (see, e.g., Srivastava et al, J. Am. Chem. Soc. 2007, 129(26), 8362-8379).

[00487] In some embodiments, antisense compounds comprise one or more modified cyclohexenyl nucleosides, which is a nucleoside having a six-membered cyclohexenyl in place of the pentofuranosyl residue in naturally occurring nucleosides. Modified cyclohexenyl nucleosides include, but are not limited to those described in the art (see for example commonly owned, published PCT Application WO 2010/036696, Robeyns et al, J. Am. Chem. Soc., 2008, 130(6), 1979-1984; Horvath et al, Tetrahedron Letters, 2007, 48, 3621-3623; Nauwelaerts et al, J. Am. Chem. Soc., 2007, 129(30), 9340-9348; Gu et al., Nucleosides, Nucleotides & Nucleic Acids, 2005, 24(5-7), 993-998; Nauwelaerts et al, Nucleic Acids Research, 2005, 33(8), 2452-2463; Robeyns et al., Acta Crystallographica, Section F: Structural Biology and Crystallization Communications, 2005, F61(6), 585-586; Gu et al, Tetrahedron, 2004, 60(9), 2111-2123; Gu et al, Oligonucleotides, 2003, 13(6), 479-489; Wang et al, J. Org. Chem., 2003, 68, 4499-4505; Verbeure et al, Nucleic Acids Research, 2001, 29(24), 4941-4947; Wang et al, J. Org. Chem., 2001, 66, 8478-82; Wang et al, Nucleosides, Nucleotides & Nucleic Acids, 2001, 20(4-7), 785-788; Wang et al, J. Am. Chem., 2000, 122, 8595-8602; Published PCT application, WO 06/047842; and Published PCT Application WO 01/049687.

[00488] Many other monocyclic, bicyclic and tricyclic ring systems are known in the art and are suitable as sugar surrogates that can be used to modify nucleosides for incorporation into oligomeric compounds as provided herein (see for example review article: Leumann, Christian J. Bioorg. & Med. Chem., 2002, 10, 841-854). Such ring systems can undergo various additional substitutions to further enhance their activity. In some embodiments, a 2'-modified sugar is a furanosyl sugar modified at the 2' position. In some embodiments, such modifications include substituents selected from: a halide, including, but not limited to substituted and unsubstituted alkoxy, substituted and unsubstituted thioalkyl, substituted and unsubstituted amino alkyl, substituted and unsubstituted alkyl, substituted and unsubstituted allyl, and substituted and unsubstituted alkynyl. In some embodiments, 2' modifications are selected from substituents including, but not limited to: $O[(CH_2)_nO]_mCH$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nF$, $O(CH_2)_nONH_2$, $OCH_2C(=O)N(H)CH_3$, and $O(CH_2)_nON[(CH_2)_nCH_3]_2$, where n and m are from 1 to about 10. Other 2'- substituent groups can also be selected from: C_1-C_{12} alkyl, substituted alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, F, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an R A cleaving group, a reporter group, an intercalator, a group for improving pharmacokinetic properties, or a group for improving the pharmacodynamic properties of an

antisense compound, and other substituents having similar properties. In some embodiments, modified nucleosides comprise a 2'-MOE side chain (Baker et al, J. Biol. Chem., 1997, 272, 11944-12000). Such 2'-MOE substitution have been described as having improved binding affinity compared to unmodified nucleosides and to other modified nucleosides, such as 2'- O-methyl, O-propyl, and O-aminopropyl. Oligonucleotides having the 2'-MOE substituent also have been shown to be antisense inhibitors of gene expression with promising features for in vivo use (Martin, Helv. Chim. Acta, 1995, 78, 486-504; Altmann et al., Chimia, 1996, 50, 168-176; Altmann et al., Biochem. Soc. Trans., 1996, 24, 630-637; and Altmann et al., Nucleosides Nucleotides, 1997, 16, 917-926).

[00489] In some embodiments, a 2'-modified" or 2'-substituted nucleoside is a nucleoside comprising a sugar comprising a substituent at the 2' position other than H or OH. In some embodiments, 2'-modified nucleosides, include, but are not limited to, bicyclic nucleosides wherein the bridge connecting two carbon atoms of the sugar ring connects the 2' carbon and another carbon of the sugar ring; and nucleosides with non-bridging 2' substituents, such as allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-O$(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N$(R_m)(R_n)$, or O-CH_2-C(=O)-N$(R_m)(R_{,,})$, where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl.

[00490] Methods for the preparations of modified sugars are well known to those skilled in the art. Some representative U.S. patents that teach the preparation of such modified sugars include without limitation, U.S.: 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,670,633; 5,700,920; 5,792,847 and 6,600,032 and International Application PCT/US2005/019219 published as WO 2005/121371.

[00491] In some embodiments, R^1 is R as defined and described. In some embodiments, R^2 is R. In some embodiments, R^e is R. In some embodiments, R^e is H, CH_3, Bn, $COCF_3$, benzoyl, benzyl, pyren-1-ylcarbonyl, pyren-1-ylmethyl, 2-aminoethyl. In some embodiments, a non-limiting example internucleotidic linkage or sugar is or comprises a component of any of: N-methanocarba, C3-amide, Formacetal, Thioformacetal, MMI, PMO (phosphorodiamidate linked morpholino), PNA (peptide nucleic acid), LNA, cMOE BNA, cEt BNA, α-L-NA or a related analog, HNA, Me-ANA, MOE-ANA, Ara-FHNA, FHNA, R-6'-Me-FHNA, S-6'-Me-FHNA, ENA, or c-ANA. In some embodiments, a non-limiting example internucleotidic linkage or sugar is or comprises a component of any of those described in Allerson et al. 2005 J. Med. Chem. 48: 901-4; BMCL 2011 21: 1122; BMCL 2011 21: 588; BMCL 2012 22: 296; Chattopadhyaya et al. 2007 J. Am. Chem. Soc. 129: 8362; Chem. Bio. Chem. 2013 14: 58; Curr. Prot. Nucl. Acids Chem. 2011 1.24.1; Egli et al. 2011 J. Am. Chem. Soc. 133: 16642; Hendrix et al. 1997 Chem. Eur. J. 3: 110; Hyrup et al. 1996 Bioorg. Med. Chem. 4: 5; Imanishi 1997 Tet. Lett. 38: 8735; J. Am. Chem. Soc. 1994, 116, 3143; J. Med. Chem. 2009 52: 10; J. Org. Chem. 2010 75: 1589; Jepsen et al.

2004 Oligo. 14: 130-146; Jones et al. J. Org. Chem. 1993, 58, 2983; Jung et al. 2014 ACIEE 53: 9893; Kodama et al. 2014 AGDS; Koizumi 2003 BMC 11: 2211; 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; Lima et al. 2012 Cell 150: 883-894; Mesmaeker et al. Angew. Chem., Int. Ed. Engl. 1994, 33, 226; Migawa et al. 2013 Org. Lett. 15: 4316; Mol. Ther. Nucl. Acids 2012 1: e47; 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; Murray et al. 2012 Nucl. Acids Res. 40: 6135; 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; Obika et al. 2008 J. Am. Chem. Soc. 130: 4886; Obika et al. 2011 Org. Lett. 13: 6050; Oestergaard et al. 2014 JOC 79: 8877; Pallan et al. 2012 Biochem. 51: 7; Pallan et al. 2012 Chem. Comm. 48: 8195-8197; Petersen et al. 2003 TRENDS Biotech. 21: 74-81; Prakash et al. 2010 J. Med. Chem. 53: 1636; Prakash et al. 2015 Nucl. Acids Res. 43: 2993-3011; Prakash et al. 2016 Bioorg. Med. Chem. Lett. 26: 2817-2820; Rajwanshi et al. 1999 Chem. Commun. 1395-1396; Schultz et al. 1996 Nucleic Acids Res. 24: 2966; Seth et al. 2008 Nucl. Acid Sym. Ser. 52: 553; Seth et al. 2009 J. Med. Chem. 52: 10-13; Seth et al. 2010 J. Am. Chem. Soc. 132: 14942; Seth et al. 2010 J. Med. Chem. 53: 8309-8318; Seth et al. 2010 J. Org. Chem. 75: 1569-1581; Seth et al. 2011 BMCL 21: 4690; Seth et al. 2012 Bioo. Med. Chem. Lett. 22: 296-299; Seth et al. 2012 Mol. Ther-Nuc. Acids. 1, e47; Seth et al., 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; Starrup et al. 2010 Nucl. Acids Res. 38: 7100; Swayze et al. 2007 Nucl. Acids Res. 35: 687; 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 2016/079181; US 6,326,199; US 6,066,500; and US 6,440,739, the base and sugar modifications of each of which is herein incorporated by reference.

[00492] 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 a sugar and/or moiety. For example, in some embodiments, a modification is a modification described in US9006198, WO2014/012081 and WO/2015/107425, the sugar and base modifications of each of which are incorporated herein by reference.

[00493] In some embodiments, a sugar modification is a 5'-modification, *e.g.*, *R*-5'-Me, *S*-5'-Me,

etc.

[00494] In some embodiments, a sugar modification changes the size of the sugar ring. In some embodiments, a sugar modification is the sugar moiety in FHNA.

[00495] 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 (optionally with its phosphorodiamidate linkage), glycol nucleic acids, etc.

[00496] In some embodiments, an oligonucleotide having an asymmetric format can comprise any sugar described herein or known in the art. In some embodiments, an oligonucleotide can comprise any sugar described herein or known in the art in combination with any other structural element or modification described herein, including but not limited to, base sequence or portion thereof, base; internucleotidic linkage; stereochemistry or combination or pattern thereof; additional chemical moiety, including but not limited to, a targeting moiety, etc.; pattern of modifications of sugars, bases or internucleotidic linkages; format or any structural element thereof, and/or any other structural element or modification described herein; and in some embodiments, the present disclosure pertains to multimers of any such oligonucleotides.

Certain Internucleotidic Linkages, Stereochemistry of Linkage Phosphorus, and Patterns Thereof

[00497] In some embodiments, provided oligonucleotides comprise one or more modified internucleotidic linkages. In some embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkage. In some embodiments, a chiral internucleotidic linkage is a chirally controlled internucleotidic linkage. Various internucleotidic linkages including modified internucleotidic linkages can be utilized in accordance with the present disclosure, for example, those described in WO2017/062862, US20180216108, US20170037399, and US9982257, the internucleotidic linkages of each of which is incorporated herein by reference.

[00498] In some embodiments, an oligonucleotide having an asymmetric format comprises a first wing having a particular internucleotidic linkage(s) or combination or pattern thereof, and a second wing having a different particular internucleotidic linkage(s) or combination or pattern thereof.

[00499] In some embodiments, an oligonucleotide having an asymmetric format comprises a first wing having a particular stereochemistry of internucleotidic linkage(s) or combination or pattern thereof, and a second wing having a different particular stereochemistry of internucleotidic linkage(s) or combination or pattern thereof.

[00500] In some embodiments, an oligonucleotide having an asymmetrical format comprises a first and a second wing which each independently comprise R, S, O, X, and/or nX, wherein R = PS (phosphorothioate) in the Rp configuration, S = PS in the Sp configuration, O = PO (phosphodiester), and X is a stereorandom (not chirally controlled) PS, and nX = a non-negatively charged (e.g., neutral)

internucleotidic linkage. In some embodiments, such a pattern of internucleotidic linkages is in a first wing, a second wing, and/or a core of an oligonucleotide having an asymmetric format.

[00501] In some embodiments, an oligonucleotide having an asymmetric format comprises one or more internucleotidic linkages which comprise an asymmetric P atom.

[00502] In some embodiments, an oligonucleotide having an asymmetric format comprises one or more internucleotidic linkages which comprise an asymmetric P atom, including but not limited to a phosphorothioate.

[00503] In some embodiments, the present disclosure pertains to a composition of an oligonucleotide having an asymmetric format and comprising one or more internucleotidic linkages which comprise an asymmetric P atom, including but not limited to a phosphorothioate, wherein the composition is stereorandom. In some embodiments, the present disclosure pertains to a composition of an oligonucleotide having an asymmetric format and comprising one or more phosphorothioates, wherein the composition is stereorandom. In some embodiments, the present disclosure pertains to a composition of an oligonucleotide having an asymmetric format, wherein every internucleotidic linkage is a phosphorothioate and wherein the composition is stereorandom.

[00504] In some embodiments, the present disclosure pertains to a composition of an oligonucleotide having an asymmetric format and comprising two or more internucleotidic linkages which comprise an asymmetric P atom, including but not limited to a phosphorothioate, wherein the composition is stereorandom at at least one said internucleotidic linkage and the composition is stereocontrolled (e.g., chirally controlled) at at least one other said internucleotidic linkage. In some embodiments, the present disclosure pertains to a composition of an oligonucleotide having an asymmetric format and comprising two or more phosphorothioates, wherein the composition is stereorandom at at least one phosphorothioate and stereocontrolled (e.g., chirally controlled) at at least one other phosphorothioate. In some embodiments, the present disclosure pertains to a composition of an oligonucleotide having an asymmetric format, wherein all of the internucleotidic linkages are a phosphorothioate and wherein the composition is stereorandom at at least one phosphorothioate and stereocontrolled (e.g., chirally controlled) at at least one other phosphorothioate.

[00505] In some embodiments, the present disclosure pertains to a composition of an oligonucleotide having an asymmetric format and comprising one or more internucleotidic linkages which comprise an asymmetric P atom, including but not limited to a phosphorothioate, wherein the composition is stereocontrolled (e.g., chirally controlled). In some embodiments, the present disclosure pertains to a composition of an oligonucleotide having an asymmetric format and comprising one or more phosphorothioates, wherein the composition is stereocontrolled (e.g., chirally controlled). In some embodiments, the present disclosure pertains to a composition of an oligonucleotide having an

asymmetric format, wherein every internucleotidic linkage is a phosphorothioate and wherein the composition is stereocontrolled (e.g., chirally controlled).

[00506] In some embodiments, a wing comprises one or more natural phosphate linkages. In some embodiments, a wing comprises one or more consecutive natural phosphate linkages. In some embodiments, a wing comprises one or more natural phosphate linkages and one or more modified internucleotidic linkages. In some embodiments, a modified internucleotidic linkage is a phosphorothioate diester linkage. In some embodiments, a modified internucleotidic linkage is a *Sp* phosphorothioate diester linkage.

[00507] In some embodiments, a wing comprises no natural phosphate linkages, and each internucleotidic linkage of the wing is independently a modified internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is chiral and chirally controlled. In some embodiments, a modified internucleotidic linkage is a phosphorothioate diester linkage. In some embodiments, a modified internucleotidic linkage is a *Sp* phosphorothioate diester linkage.

[00508] In some embodiments, for an oligonucleotide comprising or is a wing-core-wing structure, the two wings are different in that they contain different levels and/or types of chemical modifications, backbone chiral center stereochemistry, and/or patterns thereof.

[00509] In some embodiments of an oligonucleotide having an asymmetrical format, a first wing and a second wing independently has a pattern of internucleotidic linkages which is or comprises PS, PO, PS-PS, PS-PO, PO-PS, PO-PO, PO-PS-PS, PS-PO-PO-PO-PS, PS-PO-PO-PS, PS-PS-PS-PS, PS-PS-PS-PS-PS, PS-Xn-Xn-Xn-PS, or any pattern of internucleotidic linkages of any wing of any oligonucleotide described herein, wherein the pattern of internucleotidic linkages of the first and second wing are different, and wherein PS = Phosphorothioate; PO = phosphodiester; Xn = any neutral internucleotidic linkage. In some embodiments of an oligonucleotide having an asymmetrical format, a first wing and a second wing independently has a pattern of stereochemistry of internucleotidic linkages which is or comprises PO, SR, Sp, Rp, Sp-PO, Rp-PO, PO-Sp, PO-Rp, PO-PO-PO, Sp-PO-PO, Rp-PO-PO, Rp-PO-PO-PO-Rp, Rp-PO-PO-Rp-Rp, Rp-PO-Rp-PO-Rp, Rp-Rp-PO-PO-Rp, Sp-PO-PO-PO-Sp, Sp-Sp-Sp-Sp, Sp-Sp-Sp-Sp, Sp-Sp-Sp-Sp-Sp, Sp-Xn-Xn-Xn-Sp, SR-PO-PO-PO-SR, SR-SR-SR-SR, SR-SR-SR-SR-SR, SR-Xn-Xn-Xn-SR, or any pattern of stereochemistry of internucleotidic linkages of any wing of any oligonucleotide described herein, wherein the pattern of stereochemistry of internucleotidic linkages of the first and second wing are different, and wherein SR = internucleotidic linkage which is stereorandom (e.g., not chirally controlled); PO = phosphodiester (which lacks a chiral center); Sp = internucleotidic linkage in the Sp configuration; Rp = internucleotidic linkage in the Rp configuration; Xn = a neutral internucleotidic linkage, which can be independently stereocontrolled (in the Rp or Sp configuration) or stereorandom. In some embodiments of an oligonucleotide having an asymmetrical format, the first wing

is the 5' wing (the wing closer to the 5'-end of the oligonucleotide) and the second wing is the 3'-wing (the wing closer to the 3'-end of the oligonucleotide). In some embodiments of an oligonucleotide having an asymmetrical format, the first wing is the 3' wing (the wing closer to the 3'-end of the oligonucleotide) and the second wing is the 5'-wing (the wing closer to the 5'-end of the oligonucleotide). In some embodiments, the first and second wings are the same or different lengths.

[00510] In some embodiments, no less than 70%, 80%, 90% or 100% of internucleotidic linkages in a core is a modified internucleotidic linkage. In some embodiments, no less than 70%, 80%, or 90% of internucleotidic linkages in a core is independently a modified internucleotidic linkage of *Sp* configuration, and the core also contains 1, 2, 3, 4, or 5 internucleotidic linkages selected from modified internucleotidic linkages of *Rp* configuration and natural phosphate linkages. In some embodiments, the core also contains 1 or 2 internucleotidic linkages selected from modified internucleotidic linkages of *Rp* configuration and natural phosphate linkages. In some embodiments, the core also contains 1 and no more than 1 internucleotidic linkage selected from a modified internucleotidic linkage of *Rp* configuration and a natural phosphate linkage, and the rest internucleotidic linkages are independently modified internucleotidic linkages of *Sp* configuration. In some embodiments, the core also contains 2 and no more than 2 internucleotidic linkage each independently selected from a modified internucleotidic linkage of *Rp* configuration and a natural phosphate linkage, and the rest internucleotidic linkages are independently modified internucleotidic linkages of *Sp* configuration. In some embodiments, the core also contains 1 and no more than 1 natural phosphate linkage, and the rest internucleotidic linkages are independently modified internucleotidic linkages of *Sp* configuration. In some embodiments, the core also contains 2 and no more than 2 natural phosphate linkages, and the rest internucleotidic linkages are independently modified internucleotidic linkages of *Sp* configuration. In some embodiments, the core also contains 1 and no more than 1 modified internucleotidic linkage of *Rp* configuration, and the rest internucleotidic linkages are independently modified internucleotidic linkages of *Sp* configuration. In some embodiments, the core also contains 2 and no more than 2 modified internucleotidic linkages of *Rp* configuration, and the rest internucleotidic linkages are independently modified internucleotidic linkages of *Sp* configuration. In some embodiments, the two natural phosphate linkages, or the two modified internucleotidic linkages of *Rp* configuration, are separated by two or more modified internucleotidic linkages of *Sp* configuration. In some embodiments, a modified internucleotidic linkage is of Formula **I**, disclosed herein. In some embodiments, a modified internucleotidic linkage is a phosphorothioate diester linkage.

[00511] In some embodiments, an oligonucleotide composition or an internucleotidic linkage in an oligonucleotide composition has a particular diastereomeric purity.

[00512] In some embodiments, a provided oligonucleotide composition has a diastereomeric purity of 60%-100%. In some embodiments, a diastereomeric purity is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. In some embodiments, a chiral element, *e.g.*, a chiral center (carbon, phosphorus, *etc.*) of a provided compound, e.g. a provided oligonucleotide, has a diastereomeric purity of 60%-100%. In some embodiments, a chiral element, *e.g.*, a chiral center (carbon, phosphorus, *etc.*) has a diastereomeric purity of at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. In some embodiments, a diastereomeric purity is at least 60%. In some embodiments, a diastereomeric purity is at least 70%. In some embodiments, a diastereomeric purity is at least 80%. In some embodiments, a diastereomeric purity is at least 85%. In some embodiments, a diastereomeric purity is at least 90%. In some embodiments, a diastereomeric purity is at least 91%. In some embodiments, a diastereomeric purity is at least 92%. In some embodiments, a diastereomeric purity is at least 93%. In some embodiments, a diastereomeric purity is at least 94%. In some embodiments, a diastereomeric purity is at least 95%. In some embodiments, a diastereomeric purity is at least 96%. In some embodiments, a diastereomeric purity is at least 97%. In some embodiments, a diastereomeric purity is at least 98%. In some embodiments, a diastereomeric purity is at least 99%. In some embodiments, a diastereomeric purity is at least 99.5%.

[00513] In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or more chiral elements of a provided compound each independently have a diastereomeric purity as described herein. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or more chiral carbon centers of a provided compound each independently have a diastereomeric purity as described herein. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or more chiral phosphorus centers of a provided compound each independently have a diastereomeric purity as described herein.

[00514] In some embodiments, at least 5%-100% of all chiral elements of a provided compound each independently have a diastereomeric purity as described herein. In some embodiments, at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of all chiral elements of a provided compound each independently have a diastereomeric purity as described herein. In some embodiments, at least 5%-100% of all chiral phosphorus centers of a provided compound each independently have a diastereomeric purity as described herein. In some embodiments, at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of all chiral phosphorus centers of a provided compound each independently have a diastereomeric purity as described herein.

[00515] In some embodiments, each chiral element independently has a diastereomeric purity as described herein. In some embodiments, each chiral center independently has a diastereomeric purity as

described herein. In some embodiments, each chiral carbon center independently has a diastereomeric purity as described herein. In some embodiments, each chiral phosphorus center independently has a diastereomeric purity as described herein.

[00516] The present disclosure provides chirally controlled oligonucleotides, and chirally controlled oligonucleotide compositions which are of high crude purity and of high diastereomeric purity. 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.

[00517] In some embodiments, an oligonucleotide having an asymmetric format 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.

[00518] In some embodiments, a single oligonucleotide having an asymmetric format in a provided composition has at least about 25% of its internucleotidic linkages in *S*p configuration. In some embodiments, a single oligonucleotide in a provided composition has at least about 30% of its internucleotidic linkages in *S*p configuration. In some embodiments, a single oligonucleotide in a provided composition has at least about 35% of its internucleotidic linkages in *S*p configuration. In some embodiments, a single oligonucleotide in a provided composition has at least about 40% of its internucleotidic linkages in *S*p configuration. In some embodiments, a single oligonucleotide in a provided composition has at least about 45% of its internucleotidic linkages in *S*p configuration. In some embodiments, a single oligonucleotide in a provided composition has at least about 50% of its internucleotidic linkages in *S*p configuration. In some embodiments, a single oligonucleotide in a provided composition has at least about 55% of its internucleotidic linkages in *S*p configuration. In some embodiments, a single oligonucleotide in a provided composition has at least about 60% of its internucleotidic linkages in *S*p configuration. In some embodiments, a single oligonucleotide in a provided composition has at least about 65% of its internucleotidic linkages in *S*p configuration. In some embodiments, a single oligonucleotide in a provided composition has at least about 70% of its internucleotidic linkages in *S*p configuration. In some embodiments, a single oligonucleotide in a provided composition has at least about 75% of its internucleotidic linkages in *S*p configuration. In some embodiments, a single oligonucleotide in a provided composition has at least about 80% of its internucleotidic linkages in *S*p configuration. In some embodiments, a single oligonucleotide in a provided composition has at least about 85% of its internucleotidic linkages in *S*p configuration. In some embodiments, a single oligonucleotide in a provided composition has at least about 90% of its

internucleotidic linkages in *Sp* configuration.

[00519] In some embodiments, the present disclosure provides oligonucleotides having an asymmetric format and comprising one or more diastereomerically pure internucleotidic linkages with respect to the chiral linkage phosphorus. In some embodiments, the present disclosure provides oligonucleotides comprising one or more diastereomerically pure internucleotidic linkages having the structure of Formula **I**, disclosed herein. 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 phosphate diester linkages. In some embodiments, the present disclosure provides oligonucleotides comprising one or more diastereomerically pure internucleotidic linkages having the structure of Formula **I**, and one or more phosphate diester 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 pre-designed diastereomerically pure internucleotidic linkages with respect to the chiral linkage phosphorus. Example internucleotidic linkages, including those having structures of Formula **I**, are further described herein.

[00520] In some embodiments, the present disclosure provides oligonucleotides and oligonucleotide compositions that are chirally controlled. For instance, in some embodiments, a provided composition contains non-random or 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, a particular oligonucleotide type may be defined by 1A) base identity; 1B) pattern of base modification; 1C) pattern of sugar modification; 2) pattern of backbone linkages; 3) pattern of backbone chiral centers; and 4) pattern of backbone P-modifications, wherein the oligonucleotide has an asymmetrical format. In some embodiments, oligonucleotides of the same oligonucleotide type are identical. In some embodiments, the present disclosure provides chirally controlled oligonucleotide compositions of oligonucleotides, wherein the composition comprises a non-random or controlled level of a plurality of oligonucleotides, wherein oligonucleotides of the plurality share a common base sequence, and comprise the same configuration of linkage phosphorus at 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, or 25 chiral internucleotidic linkages (chirally controlled internucleotidic linkages). In some embodiments, oligonucleotides of a predetermined level and/or a provided plurality, e.g., those of formula **O-I**, 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)$_b$, comprise 1-30 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides having an asymmetric format comprise 2-30 chirally controlled internucleotidic

linkages. In some embodiments, provided oligonucleotides comprise 5-30 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides comprise 10-30 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides comprise 1 chirally controlled internucleotidic linkage. In some embodiments, provided oligonucleotides comprise 2 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides comprise 3 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides comprise 4 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides comprise 5 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides comprise 6 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides comprise 7 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides comprise 8 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides comprise 9 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides comprise 10 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides comprise 11 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides comprise 12 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides comprise 13 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides comprise 14 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides have 15 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides have 16 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides have 17 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides have 18 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides have 19 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides have 20 chirally controlled internucleotidic linkages. In some embodiments, about 1-100% of all internucleotidic linkages are chirally controlled internucleotidic linkages. In some embodiments, a percentage is about 5%-100%. In some embodiments, a percentage is at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 965, 96%, 98%, or 99%. In some embodiments, a percentage is about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 965, 96%, 98%, or 99%.

[00521] In some embodiments, a provided oligonucleotide is a unimer. In some embodiments, a provided oligonucleotide is a P-modification unimer. In some embodiments, a provided oligonucleotide is a stereounimer. In some embodiments, a provided oligonucleotide is a stereounimer where each chiral linkage phosphorus is *R*p. In some embodiments, a provided oligonucleotide is a stereounimer where each chiral linkage phosphorus is *S*p.

[00522] In some embodiments, a pattern of internucleotidic linkages comprises any one or more of: IL1-IL1-IL1-IL1, IL1-IL1-IL1-IL2, IL1-IL1-IL2-IL1, IL1-IL1-IL2-IL2, IL1-IL2-IL1-IL1, IL1-IL2-IL1-IL2, IL1-IL2-IL1-IL2, IL1-IL2-IL2-IL1, IL1-IL2-IL2-IL2, IL2-IL1-IL1-IL1, IL2-IL1-IL1-IL2, IL2-IL1-IL1-IL2, IL2-IL1-IL2-IL1, IL2-IL1-IL2-IL2, IL2-IL2-IL1-IL1, IL2-IL2-IL1-IL2, IL2-IL2-IL2-IL1, IL2-IL2-IL2-IL2, IL1-IL1-IL1-IL1, IL1-IL1-IL1-IL3, IL1-IL1-IL3-IL1, IL1-IL1-IL3-IL3, IL1-IL3-IL1-IL1, IL1-IL3-IL1-IL3, IL1-IL3-IL3-IL1, IL1-IL3-IL3-IL3, IL3-IL1-IL1-IL1, IL3-IL1-IL1-IL3, IL3-IL1-IL1-IL3, IL3-IL1-IL3-IL1, IL3-IL1-IL3-IL1, IL3-IL1-IL3-IL3, IL3-IL1-IL3-IL3, IL3-IL3-IL1-IL1, IL3-IL3-IL1-IL1, IL3-IL3-IL1-IL3, IL3-IL3-IL1-IL3, IL3-IL3-IL3-IL1, IL3-IL3-IL3-IL1, IL3-IL3-IL3-IL3, IL3-IL3-IL3-IL3, IL1-IL1-IL1-IL1, IL1-IL1-IL1-IL4, IL1-IL1-IL1-IL4, IL1-IL1-IL4-IL1, IL1-IL1-IL4-IL1, IL1-IL1-IL4-IL4, IL1-IL1-IL4-IL4, IL1-IL4-IL1-IL1, IL1-IL4-IL1-IL1, IL1-IL4-IL1-IL4, IL1-IL4-IL1-IL4, IL1-IL4-IL4-IL1, IL1-IL4-IL4-IL1, IL1-IL4-IL4-IL4, IL1-IL4-IL4-IL4, IL4-IL1-IL1-IL1, IL4-IL1-IL1-IL1, IL4-IL1-IL1-IL4, IL4-IL1-IL1-IL4, IL4-IL1-IL4-IL1, IL4-IL1-IL4-IL1, IL4-IL1-IL4-IL4, IL4-IL1-IL4-IL4, IL4-IL4-IL1-IL1, IL4-IL4-IL1-IL1, IL4-IL4-IL1-IL4, IL4-IL4-IL1-IL4, IL4-IL4-IL4-IL1, IL4-IL4-IL4-IL1, IL4-IL4-IL4-IL4, IL4-IL4-IL4-IL4, IL1-IL1-IL1-IL2, IL1-IL1-IL1-IL3, IL1-IL1-IL1-IL3, IL1-IL1-IL1-IL3, IL1-IL1-IL2-IL1, IL1-IL1-IL2-IL1, IL1-IL1-IL2-IL1, IL1-IL1-IL2-IL2, IL1-IL1-IL2-IL2, IL1-IL1-IL2-IL2, IL1-IL1-IL2-IL3, IL1-IL1-IL2-IL3, IL1-IL1-IL2-IL3, IL1-IL1-IL3-IL1, IL1-IL1-IL3-IL1, IL1-IL1-IL3-IL1, IL1-IL1-IL3-IL2, IL1-IL1-IL3-IL2, IL1-IL1-IL3-IL2, IL1-IL1-IL3-IL3, IL1-IL1-IL3-IL3, IL1-IL1-IL3-IL3, IL1-IL2-IL1-IL1, IL1-IL2-IL1-IL1, IL1-IL2-IL1-IL1, IL1-IL2-IL1-IL2, IL1-IL2-IL1-IL2, IL1-IL2-IL1-IL2, IL1-IL2-IL1-IL3, IL1-IL2-IL1-IL3, IL1-IL2-IL1-IL3, IL1-IL2-IL2-IL1, IL1-IL2-IL2-IL1, IL1-IL2-IL2-IL1, IL1-IL2-IL2-IL2, IL1-IL2-IL2-IL2, IL1-IL2-IL2-IL2, IL1-IL2-IL2-IL3, IL1-IL2-IL2-IL3, IL1-IL2-IL2-IL3, IL1-IL2-IL3-IL1, IL1-IL2-IL3-IL1, IL1-IL2-IL3-IL1, IL1-IL2-IL3-IL2, IL1-IL2-IL3-IL2, IL1-IL2-IL3-IL2, IL1-IL2-IL3-IL3, IL1-IL2-IL3-IL3, IL1-IL2-IL3-IL3, IL1-IL3-IL1-IL1, IL1-IL3-IL1-IL1, IL1-IL3-IL1-IL1, IL1-IL3-IL1-IL2, IL1-IL3-IL1-IL2, IL1-IL3-IL1-IL2, IL1-IL3-IL1-IL3, IL1-IL3-IL1-IL3, IL1-IL3-IL1-IL3, IL1-IL3-IL2-IL1, IL1-IL3-IL2-IL1, IL1-IL3-IL2-IL1, IL1-IL3-IL2-IL2, IL1-IL3-IL2-IL2, IL1-IL3-IL2-IL2, IL1-IL3-IL2-IL3, IL1-IL3-IL2-IL3, IL1-IL3-IL2-IL3, IL1-IL3-IL3-IL1, IL1-IL3-IL3-IL1, IL1-IL3-IL3-IL1, IL1-IL3-IL3-IL2, IL1-IL3-IL3-IL2, IL1-IL3-IL3-IL2, IL1-IL3-IL3-IL3, IL1-IL3-IL3-IL3, IL1-IL3-IL3-IL3, IL2-IL1-IL1-IL1, IL2-IL1-IL1-IL1, IL2-IL1-IL1-IL1, IL2-IL1-IL1-IL2, IL2-IL1-IL1-IL2, IL2-IL1-IL1-IL2, IL2-IL1-IL1-IL3, IL2-IL1-IL1-IL3, IL2-IL1-IL1-IL3, IL2-IL1-IL2-IL1, IL2-IL1-IL2-IL1, IL2-IL1-IL2-IL1, IL2-IL1-IL2-IL2, IL2-IL1-IL2-IL2, IL2-IL1-IL2-IL2, IL2-IL1-IL2-IL3, IL2-IL1-IL2-IL3, IL2-IL1-IL2-IL3, IL2-IL1-IL3-IL1, IL2-IL1-IL3-IL1, IL2-IL1-IL3-IL1, IL2-IL1-IL3-IL2, IL2-IL1-IL3-IL2, IL2-IL1-IL3-IL2, IL2-IL1-IL3-IL3, IL2-IL1-IL3-IL3, IL2-IL1-IL3-IL3, IL2-IL2-IL1-IL1, IL2-IL2-IL1-IL1, IL2-IL2-IL1-IL1, IL2-IL2-IL1-IL2, IL2-IL2-IL1-IL2, IL2-IL2-IL1-IL2, IL2-IL2-IL1-IL3, IL2-IL2-IL1-IL3, IL2-IL2-IL1-IL3, IL2-IL2-IL2-IL1, IL2-IL2-IL2-IL1, IL2-IL2-IL2-IL1, IL2-IL2-IL2-IL2, IL2-IL2-IL2-IL2, IL2-

IL2-IL2-IL2, IL2-IL2-IL2-IL3, IL2-IL2-IL2-IL3, IL2-IL2-IL2-IL3, IL2-IL2-IL3-IL1, IL2-IL2-IL3-IL1, IL2-IL2-IL3-IL1, IL2-IL2-IL3-IL2, IL2-IL2-IL3-IL2, IL2-IL2-IL3-IL2, IL2-IL2-IL3-IL3, IL2-IL2-IL3-IL3, IL2-IL2-IL3-IL3, IL2-IL3-IL1-IL1, IL2-IL3-IL1-IL1, IL2-IL3-IL1-IL1, IL2-IL3-IL1-IL2, IL2-IL3-IL1-IL2, IL2-IL3-IL1-IL2, IL2-IL3-IL1-IL3, IL2-IL3-IL1-IL3, IL2-IL3-IL1-IL3, IL2-IL3-IL2-IL1, IL2-IL3-IL2-IL1, IL2-IL3-IL2-IL1, IL2-IL3-IL2-IL2, IL2-IL3-IL2-IL2, IL2-IL3-IL2-IL2, IL2-IL3-IL2-IL3, IL2-IL3-IL2-IL3, IL2-IL3-IL2-IL3, IL2-IL3-IL3-IL1, IL2-IL3-IL3-IL1, IL2-IL3-IL3-IL1, IL2-IL3-IL3-IL2, IL2-IL3-IL3-IL2, IL2-IL3-IL3-IL2, IL2-IL3-IL3-IL3, IL2-IL3-IL3-IL3, IL2-IL3-IL3-IL3, IL3-IL1-IL1-IL1, IL3-IL1-IL1-IL1, IL3-IL1-IL1-IL1, IL3-IL1-IL1-IL2, IL3-IL1-IL1-IL2, IL3-IL1-IL1-IL2, IL3-IL1-IL1-IL3, IL3-IL1-IL1-IL3, IL3-IL1-IL1-IL3, IL3-IL1-IL2-IL1, IL3-IL1-IL2-IL1, IL3-IL1-IL2-IL1, IL3-IL1-IL2-IL2, IL3-IL1-IL2-IL2, IL3-IL1-IL2-IL2, IL3-IL1-IL2-IL3, IL3-IL1-IL2-IL3, IL3-IL1-IL2-IL3, IL3-IL1-IL3-IL1, IL3-IL1-IL3-IL1, IL3-IL1-IL3-IL1, IL3-IL1-IL3-IL2, IL3-IL1-IL3-IL2, IL3-IL1-IL3-IL2, IL3-IL1-IL3-IL3, IL3-IL1-IL3-IL3, IL3-IL1-IL3-IL3, IL3-IL2-IL1-IL1, IL3-IL2-IL1-IL1, IL3-IL2-IL1-IL1, IL3-IL2-IL1-IL2, IL3-IL2-IL1-IL2, IL3-IL2-IL1-IL2, IL3-IL2-IL1-IL3, IL3-IL2-IL1-IL3, IL3-IL2-IL1-IL3, IL3-IL2-IL2-IL1, IL3-IL2-IL2-IL1, IL3-IL2-IL2-IL1, IL3-IL2-IL2-IL2, IL3-IL2-IL2-IL2, IL3-IL2-IL2-IL2, IL3-IL2-IL2-IL3, IL3-IL2-IL2-IL3, IL3-IL2-IL2-IL3, IL3-IL2-IL3-IL1, IL3-IL2-IL3-IL1, IL3-IL2-IL3-IL1, IL3-IL2-IL3-IL2, IL3-IL2-IL3-IL2, IL3-IL2-IL3-IL2, IL3-IL2-IL3-IL3, IL3-IL2-IL3-IL3, IL3-IL2-IL3-IL3, IL3-IL3-IL1-IL1, IL3-IL3-IL1-IL1, IL3-IL3-IL1-IL1, IL3-IL3-IL1-IL2, IL3-IL3-IL1-IL2, IL3-IL3-IL1-IL2, IL3-IL3-IL1-IL3, IL3-IL3-IL1-IL3, IL3-IL3-IL1-IL3, IL3-IL3-IL2-IL1, IL3-IL3-IL2-IL1, IL3-IL3-IL2-IL1, IL3-IL3-IL2-IL2, IL3-IL3-IL2-IL2, IL3-IL3-IL2-IL2, IL3-IL3-IL2-IL3, IL3-IL3-IL2-IL3, IL3-IL3-IL2-IL3, IL3-IL3-IL3-IL1, IL3-IL3-IL3-IL1, IL3-IL3-IL3-IL1, IL3-IL3-IL3-IL2, IL3-IL3-IL3-IL2, IL3-IL3-IL3-IL2, IL3-IL3-IL3-IL3, IL3-IL3-IL3-IL3, IL3-IL3-IL3-IL3, IL3-IL3-IL3-IL3, IL1-IL1-IL1-IL2, IL1-IL1-IL1-IL4, IL1-IL1-IL1-IL4, IL1-IL1-IL1-IL4, IL1-IL1-IL2-IL1, IL1-IL1-IL2-IL1, IL1-IL1-IL2-IL1, IL1-IL1-IL2-IL2, IL1-IL1-IL2-IL2, IL1-IL1-IL2-IL2, IL1-IL1-IL2-IL4, IL1-IL1-IL2-IL4, IL1-IL1-IL2-IL4, IL1-IL1-IL4-IL1, IL1-IL1-IL4-IL1, IL1-IL1-IL4-IL1, IL1-IL1-IL4-IL2, IL1-IL1-IL4-IL2, IL1-IL1-IL4-IL2, IL1-IL1-IL4-IL4, IL1-IL1-IL4-IL4, IL1-IL1-IL4-IL4, IL1-IL2-IL1-IL1, IL1-IL2-IL1-IL1, IL1-IL2-IL1-IL1, IL1-IL2-IL1-IL2, IL1-IL2-IL1-IL2, IL1-IL2-IL1-IL2, IL1-IL2-IL1-IL4, IL1-IL2-IL1-IL4, IL1-IL2-IL1-IL4, IL1-IL2-IL2-IL1, IL1-IL2-IL2-IL1, IL1-IL2-IL2-IL1, IL1-IL2-IL2-IL2, IL1-IL2-IL2-IL2, IL1-IL2-IL2-IL2, IL1-IL2-IL2-IL4, IL1-IL2-IL2-IL4, IL1-IL2-IL2-IL4, IL1-IL2-IL4-IL1, IL1-IL2-IL4-IL1, IL1-IL2-IL4-IL1, IL1-IL2-IL4-IL2, IL1-IL2-IL4-IL2, IL1-IL2-IL4-IL2, IL1-IL2-IL4-IL4, IL1-IL2-IL4-IL4, IL1-IL2-IL4-IL4, IL1-IL4-IL1-IL1, IL1-IL4-IL1-IL1, IL1-IL4-IL1-IL1, IL1-IL4-IL1-IL2, IL1-IL4-IL1-IL2, IL1-IL4-IL1-IL2, IL1-IL4-IL1-IL4, IL1-IL4-IL1-IL4, IL1-IL4-IL1-IL4, IL1-IL4-IL2-IL1, IL1-IL4-IL2-IL1, IL1-IL4-IL2-IL1, IL1-IL4-IL2-IL2, IL1-IL4-IL2-IL2, IL1-IL4-IL2-IL2, IL1-IL4-IL2-IL4, IL1-IL4-IL2-IL4, IL1-IL4-IL2-IL4, IL1-IL4-IL4-IL1, IL1-IL4-IL4-IL1, IL1-IL4-IL4-IL1, IL1-IL4-IL4-IL2, IL1-IL4-IL4-IL2, IL1-IL4-IL4-IL2, IL1-IL4-IL4-

IL4, IL1-IL4-IL4-IL4, IL1-IL4-IL4-IL4, IL2-IL1-IL1-IL1, IL2-IL1-IL1-IL1, IL2-IL1-IL1-IL1, IL2-IL1-IL1-IL2, IL2-IL1-IL1-IL2, IL2-IL1-IL1-IL2, IL2-IL1-IL1-IL4, IL2-IL1-IL1-IL4, IL2-IL1-IL1-IL4, IL2-IL1-IL2-IL1, IL2-IL1-IL2-IL1, IL2-IL1-IL2-IL1, IL2-IL1-IL2-IL2, IL2-IL1-IL2-IL2, IL2-IL1-IL2-IL2, IL2-IL1-IL2-IL4, IL2-IL1-IL2-IL4, IL2-IL1-IL2-IL4, IL2-IL1-IL4-IL1, IL2-IL1-IL4-IL1, IL2-IL1-IL4-IL1, IL2-IL1-IL4-IL2, IL2-IL1-IL4-IL2, IL2-IL1-IL4-IL2, IL2-IL1-IL4-IL4, IL2-IL1-IL4-IL4, IL2-IL1-IL4-IL4, IL2-IL2-IL1-IL1, IL2-IL2-IL1-IL1, IL2-IL2-IL1-IL1, IL2-IL2-IL1-IL2, IL2-IL2-IL1-IL2, IL2-IL2-IL1-IL2, IL2-IL2-IL1-IL4, IL2-IL2-IL1-IL4, IL2-IL2-IL1-IL4, IL2-IL2-IL2-IL1, IL2-IL2-IL2-IL1, IL2-IL2-IL2-IL1, IL2-IL2-IL2-IL2, IL2-IL2-IL2-IL2, IL2-IL2-IL2-IL2, IL2-IL2-IL2-IL4, IL2-IL2-IL2-IL4, IL2-IL2-IL2-IL4, IL2-IL2-IL4-IL1, IL2-IL2-IL4-IL1, IL2-IL2-IL4-IL1, IL2-IL2-IL4-IL2, IL2-IL2-IL4-IL2, IL2-IL2-IL4-IL2, IL2-IL2-IL4-IL4, IL2-IL2-IL4-IL4, IL2-IL2-IL4-IL4, IL2-IL4-IL1-IL1, IL2-IL4-IL1-IL1, IL2-IL4-IL1-IL1, IL2-IL4-IL1-IL2, IL2-IL4-IL1-IL2, IL2-IL4-IL1-IL2, IL2-IL4-IL1-IL4, IL2-IL4-IL1-IL4, IL2-IL4-IL1-IL4, IL2-IL4-IL2-IL1, IL2-IL4-IL2-IL1, IL2-IL4-IL2-IL1, IL2-IL4-IL2-IL2, IL2-IL4-IL2-IL2, IL2-IL4-IL2-IL2, IL2-IL4-IL2-IL4, IL2-IL4-IL2-IL4, IL2-IL4-IL2-IL4, IL2-IL4-IL4-IL1, IL2-IL4-IL4-IL1, IL2-IL4-IL4-IL1, IL2-IL4-IL4-IL2, IL2-IL4-IL4-IL2, IL2-IL4-IL4-IL2, IL2-IL4-IL4-IL4, IL2-IL4-IL4-IL4, IL2-IL4-IL4-IL4, IL4-IL1-IL1-IL1, IL4-IL1-IL1-IL1, IL4-IL1-IL1-IL1, IL4-IL1-IL1-IL2, IL4-IL1-IL1-IL2, IL4-IL1-IL1-IL2, IL4-IL1-IL1-IL4, IL4-IL1-IL1-IL4, IL4-IL1-IL1-IL4, IL4-IL1-IL2-IL1, IL4-IL1-IL2-IL1, IL4-IL1-IL2-IL1, IL4-IL1-IL2-IL2, IL4-IL1-IL2-IL2, IL4-IL1-IL2-IL2, IL4-IL1-IL2-IL4, IL4-IL1-IL2-IL4, IL4-IL1-IL2-IL4, IL4-IL1-IL4-IL1, IL4-IL1-IL4-IL1, IL4-IL1-IL4-IL1, IL4-IL1-IL4-IL2, IL4-IL1-IL4-IL2, IL4-IL1-IL4-IL2, IL4-IL1-IL4-IL4, IL4-IL1-IL4-IL4, IL4-IL1-IL4-IL4, IL4-IL2-IL1-IL1, IL4-IL2-IL1-IL1, IL4-IL2-IL1-IL1, IL4-IL2-IL1-IL2, IL4-IL2-IL1-IL2, IL4-IL2-IL1-IL2, IL4-IL2-IL1-IL4, IL4-IL2-IL1-IL4, IL4-IL2-IL1-IL4, IL4-IL2-IL2-IL1, IL4-IL2-IL2-IL1, IL4-IL2-IL2-IL1, IL4-IL2-IL2-IL2, IL4-IL2-IL2-IL2, IL4-IL2-IL2-IL2, IL4-IL2-IL2-IL4, IL4-IL2-IL2-IL4, IL4-IL2-IL2-IL4, IL4-IL2-IL4-IL1, IL4-IL2-IL4-IL1, IL4-IL2-IL4-IL1, IL4-IL2-IL4-IL2, IL4-IL2-IL4-IL2, IL4-IL2-IL4-IL2, IL4-IL2-IL4-IL4, IL4-IL2-IL4-IL4, IL4-IL2-IL4-IL4, IL4-IL4-IL1-IL1, IL4-IL4-IL1-IL1, IL4-IL4-IL1-IL1, IL4-IL4-IL1-IL2, IL4-IL4-IL1-IL2, IL4-IL4-IL1-IL2, IL4-IL4-IL1-IL4, IL4-IL4-IL1-IL4, IL4-IL4-IL1-IL4, IL4-IL4-IL2-IL1, IL4-IL4-IL2-IL1, IL4-IL4-IL2-IL1, IL4-IL4-IL2-IL2, IL4-IL4-IL2-IL2, IL4-IL4-IL2-IL2, IL4-IL4-IL2-IL4, IL4-IL4-IL2-IL4, IL4-IL4-IL2-IL4, IL4-IL4-IL4-IL1, IL4-IL4-IL4-IL1, IL4-IL4-IL4-IL1, IL4-IL4-IL4-IL2, IL4-IL4-IL4-IL2, IL4-IL4-IL4-IL2, IL4-IL4-IL4-IL4, IL4-IL4-IL4-IL4, IL4-IL4-IL4-IL4, or IL4-IL4-IL4-IL4, wherein IL1, IL2, IL3 and IL4 are different types of internucleotidic linkages. In some embodiments, IL1, IL2, IL3 and IL4 are different types of internucleotidic linkages that differ in chemistry and/or stereochemistry. In some embodiments, such a pattern of internucleotidic linkages is in a first wing, a second wing, and/or a core of an oligonucleotide having an asymmetric format.

[00523] In some embodiments, a pattern of internucleotidic linkages of an oligonucleotide comprises any one or more of: IL1-IL1-IL1-IL1-IL1, IL1-IL1-IL1-IL1-IL2, IL1-IL1-IL1-IL2-IL1, IL1-IL1-IL1-IL2-IL2, IL1-IL1-IL2-IL1-IL1, IL1-IL1-IL2-IL1-IL2, IL1-IL1-IL2-IL2-IL1, IL1-IL1-IL2-IL2-IL2, IL1-IL2-IL1-IL1-IL1, IL1-IL2-IL1-IL1-IL2, IL1-IL2-IL1-IL2-IL1, IL1-IL2-IL1-IL2-IL2, IL1-IL2-IL2-IL1-IL1, IL1-IL2-IL2-IL1-IL2, IL1-IL2-IL2-IL2-IL1, IL1-IL2-IL2-IL2-IL2, IL2-IL1-IL1-IL1-IL1, IL2-IL1-IL1-IL1-IL2, IL2-IL1-IL1-IL2-IL1, IL2-IL1-IL1-IL2-IL2, IL2-IL1-IL2-IL1-IL1, IL2-IL1-IL2-IL1-IL2, IL2-IL1-IL2-IL2-IL1, IL2-IL1-IL2-IL2-IL2, IL2-IL2-IL1-IL1-IL1, IL2-IL2-IL1-IL1-IL2, IL2-IL2-IL1-IL2-IL1, IL2-IL2-IL1-IL2-IL2, IL2-IL2-IL2-IL1-IL1, IL2-IL2-IL2-IL1-IL2, IL2-IL2-IL2-IL2-IL1, IL2-IL2-IL2-IL2-IL2, IL1-IL1-IL1-IL1-IL1, IL1-IL1-IL1-IL1-IL3, IL1-IL1-IL1-IL3-IL1, IL1-IL1-IL1-IL3-IL3, IL1-IL1-IL3-IL1-IL1, IL1-IL1-IL3-IL1-IL3, IL1-IL1-IL3-IL3-IL1, IL1-IL1-IL3-IL3-IL3, IL1-IL3-IL1-IL1-IL1, IL1-IL3-IL1-IL1-IL3, IL1-IL3-IL1-IL3-IL1, IL1-IL3-IL1-IL3-IL3, IL1-IL3-IL3-IL1-IL1, IL1-IL3-IL3-IL1-IL3, IL1-IL3-IL3-IL3-IL1, IL1-IL3-IL3-IL3-IL3, IL3-IL1-IL1-IL1-IL1, IL3-IL1-IL1-IL1-IL3, IL3-IL1-IL1-IL3-IL1, IL3-IL1-IL1-IL3-IL3, IL3-IL1-IL3-IL1-IL1, IL3-IL1-IL3-IL1-IL3, IL3-IL1-IL3-IL3-IL1, IL3-IL1-IL3-IL3-IL3, IL3-IL3-IL1-IL1-IL1, IL3-IL3-IL1-IL1-IL3, IL3-IL3-IL1-IL3-IL1, IL3-IL3-IL1-IL3-IL3, IL3-IL3-IL3-IL1-IL1, IL3-IL3-IL3-IL1-IL3, IL3-IL3-IL3-IL3-IL1, IL3-IL3-IL3-IL3-IL3, IL1-IL1-IL1-IL1-IL4, IL1-IL1-IL1-IL4-IL1, IL1-IL1-IL1-IL4-IL4, IL1-IL1-IL4-IL1-IL1, IL1-IL1-IL4-IL1-IL4, IL1-IL1-IL4-IL4-IL1, IL1-IL1-IL4-IL4-IL4, IL1-IL4-IL1-IL1-IL1, IL1-IL4-IL1-IL1-IL4, IL1-IL4-IL1-IL4-IL1, IL1-IL4-IL1-IL4-IL4, IL1-IL4-IL4-IL1-IL1, IL1-IL4-IL4-IL1-IL4, IL1-IL4-IL4-IL4-IL1, IL1-IL4-IL4-IL4-IL4, IL4-IL1-IL1-IL1-IL1, IL4-IL1-IL1-IL1-IL4, IL4-IL1-IL1-IL4-IL1, IL4-IL1-IL1-IL4-IL4, IL4-IL1-IL4-IL1-IL1, IL4-IL1-IL4-IL1-IL4, IL4-IL1-IL4-IL4-IL1, IL4-IL1-IL4-IL4-IL4, IL4-IL4-IL1-IL1-IL1, IL4-IL4-IL1-IL1-IL4, IL4-IL4-IL1-IL4-IL1, IL4-IL4-IL1-IL4-IL4, IL4-IL4-IL4-IL1-IL1, IL4-IL4-IL4-IL1-IL4, IL4-IL4-IL4-IL4-IL1, IL4-IL4-IL4-IL4-IL4, IL1-IL1-IL1-IL2-IL3, IL1-IL1-IL1-IL3-IL1, IL1-IL1-IL1-IL3-IL2, IL1-IL1-IL1-IL3-IL3, IL1-IL1-IL2-IL1-IL1, IL1-IL1-IL2-IL1-IL2, IL1-IL1-IL2-IL1-IL3, IL1-IL1-IL2-IL2-IL1, IL1-IL1-IL2-IL2-IL2, IL1-IL1-IL2-IL2-IL3, IL1-IL1-IL2-IL3-IL1, IL1-IL1-IL2-IL3-IL2, IL1-IL1-IL2-IL3-IL3, IL1-IL1-IL3-IL1-IL1, IL1-IL1-IL3-IL1-IL2, IL1-IL1-IL3-IL1-IL3, IL1-IL1-IL3-IL2-IL1, IL1-IL1-IL3-IL2-IL2, IL1-IL1-IL3-IL2-IL3, IL1-IL1-IL3-IL3-IL1, IL1-IL1-IL3-IL3-IL2, IL1-IL1-IL3-IL3-IL3, IL1-IL2-IL1-IL1-IL1, IL1-IL2-IL1-IL1-IL2, IL1-IL2-IL1-IL1-IL3, IL1-IL2-IL1-IL2-IL1, IL1-IL2-IL1-IL2-IL2, IL1-IL2-IL1-IL2-IL3, IL1-IL2-IL1-IL3-IL1, IL1-IL2-IL1-IL3-IL2, IL1-IL2-IL1-IL3-IL3, IL1-IL2-IL2-IL1-IL1, IL1-IL2-IL2-IL1-IL2, IL1-IL2-IL2-IL1-IL3, IL1-IL2-IL2-IL2-IL1, IL1-IL2-IL2-IL2-IL2, IL1-IL2-IL2-IL2-IL3, IL1-IL2-IL2-IL3-IL1, IL1-IL2-IL2-IL3-IL2, IL1-IL2-IL2-IL3-IL3, IL1-IL2-IL3-IL1-IL1, IL1-IL2-IL3-IL1-IL2, IL1-IL2-IL3-IL1-IL3, IL1-IL2-IL3-IL2-IL1, IL1-IL2-IL3-IL2-IL2, IL1-IL2-IL3-IL2-IL3, IL1-IL2-IL3-IL3-IL1, IL1-IL2-IL3-IL3-IL2, IL1-IL2-IL3-IL3-IL3, IL1-IL3-IL1-IL1-IL1, IL1-IL3-IL1-IL1-IL2, IL1-IL3-IL1-IL1-IL3, IL1-IL3-IL1-IL2-IL1, IL1-IL3-IL1-IL2-IL2, IL1-IL3-IL1-IL2-IL3, IL1-IL3-

IL1-IL3-IL1, IL1-IL3-IL1-IL3-IL2, IL1-IL3-IL1-IL3-IL3, IL1-IL3-IL2-IL1-IL1, IL1-IL3-IL2-IL1-IL2, IL1-IL3-IL2-IL1-IL3, IL1-IL3-IL2-IL2-IL1, IL1-IL3-IL2-IL2-IL2, IL1-IL3-IL2-IL2-IL3, IL1-IL3-IL2-IL3-IL1, IL1-IL3-IL2-IL3-IL2, IL1-IL3-IL2-IL3-IL3, IL1-IL3-IL3-IL1-IL1, IL1-IL3-IL3-IL1-IL2, IL1-IL3-IL3-IL1-IL3, IL1-IL3-IL3-IL2-IL1, IL1-IL3-IL3-IL2-IL2, IL1-IL3-IL3-IL2-IL3, IL1-IL3-IL3-IL3-IL1, IL1-IL3-IL3-IL3-IL2, IL1-IL3-IL3-IL3-IL3, IL2-IL1-IL1-IL1-IL1, IL2-IL1-IL1-IL1-IL2, IL2-IL1-IL1-IL1-IL3, IL2-IL1-IL1-IL2-IL1, IL2-IL1-IL1-IL2-IL2, IL2-IL1-IL1-IL2-IL3, IL2-IL1-IL1-IL3-IL1, IL2-IL1-IL1-IL3-IL2, IL2-IL1-IL1-IL3-IL3, IL2-IL1-IL2-IL1-IL1, IL2-IL1-IL2-IL1-IL2, IL2-IL1-IL2-IL1-IL3, IL2-IL1-IL2-IL2-IL1, IL2-IL1-IL2-IL2-IL2, IL2-IL1-IL2-IL2-IL3, IL2-IL1-IL2-IL3-IL1, IL2-IL1-IL2-IL3-IL2, IL2-IL1-IL2-IL3-IL3, IL2-IL1-IL3-IL1-IL1, IL2-IL1-IL3-IL1-IL2, IL2-IL1-IL3-IL1-IL3, IL2-IL1-IL3-IL2-IL1, IL2-IL1-IL3-IL2-IL2, IL2-IL1-IL3-IL2-IL3, IL2-IL1-IL3-IL3-IL1, IL2-IL1-IL3-IL3-IL2, IL2-IL1-IL3-IL3-IL3, IL2-IL2-IL1-IL1-IL1, IL2-IL2-IL1-IL1-IL2, IL2-IL2-IL1-IL1-IL3, IL2-IL2-IL1-IL2-IL1, IL2-IL2-IL1-IL2-IL2, IL2-IL2-IL1-IL2-IL3, IL2-IL2-IL1-IL3-IL1, IL2-IL2-IL1-IL3-IL2, IL2-IL2-IL1-IL3-IL3, IL2-IL2-IL2-IL1-IL1, IL2-IL2-IL2-IL1-IL2, IL2-IL2-IL2-IL1-IL3, IL2-IL2-IL2-IL2-IL1, IL2-IL2-IL2-IL2-IL2, IL2-IL2-IL2-IL2-IL3, IL2-IL2-IL2-IL3-IL1, IL2-IL2-IL2-IL3-IL2, IL2-IL2-IL2-IL3-IL3, IL2-IL2-IL3-IL1-IL1, IL2-IL2-IL3-IL1-IL2, IL2-IL2-IL3-IL1-IL3, IL2-IL2-IL3-IL2-IL1, IL2-IL2-IL3-IL2-IL2, IL2-IL2-IL3-IL2-IL3, IL2-IL2-IL3-IL3-IL1, IL2-IL2-IL3-IL3-IL2, IL2-IL2-IL3-IL3-IL3, IL2-IL3-IL1-IL1-IL1, IL2-IL3-IL1-IL1-IL2, IL2-IL3-IL1-IL1-IL3, IL2-IL3-IL1-IL2-IL1, IL2-IL3-IL1-IL2-IL2, IL2-IL3-IL1-IL2-IL3, IL2-IL3-IL1-IL3-IL1, IL2-IL3-IL1-IL3-IL2, IL2-IL3-IL1-IL3-IL3, IL2-IL3-IL2-IL1-IL1, IL2-IL3-IL2-IL1-IL2, IL2-IL3-IL2-IL1-IL3, IL2-IL3-IL2-IL2-IL1, IL2-IL3-IL2-IL2-IL2, IL2-IL3-IL2-IL2-IL3, IL2-IL3-IL2-IL3-IL1, IL2-IL3-IL2-IL3-IL2, IL2-IL3-IL2-IL3-IL3, IL2-IL3-IL3-IL1-IL1, IL2-IL3-IL3-IL1-IL2, IL2-IL3-IL3-IL1-IL3, IL2-IL3-IL3-IL2-IL1, IL2-IL3-IL3-IL2-IL2, IL2-IL3-IL3-IL2-IL3, IL2-IL3-IL3-IL3-IL1, IL2-IL3-IL3-IL3-IL2, IL2-IL3-IL3-IL3-IL3, IL3-IL1-IL1-IL1-IL1, IL3-IL1-IL1-IL1-IL2, IL3-IL1-IL1-IL1-IL3, IL3-IL1-IL1-IL2-IL1, IL3-IL1-IL1-IL2-IL2, IL3-IL1-IL1-IL2-IL3, IL3-IL1-IL1-IL3-IL1, IL3-IL1-IL1-IL3-IL2, IL3-IL1-IL1-IL3-IL3, IL3-IL1-IL2-IL1-IL1, IL3-IL1-IL2-IL1-IL2, IL3-IL1-IL2-IL1-IL3, IL3-IL1-IL2-IL2-IL1, IL3-IL1-IL2-IL2-IL2, IL3-IL1-IL2-IL2-IL3, IL3-IL1-IL2-IL3-IL1, IL3-IL1-IL2-IL3-IL2, IL3-IL1-IL2-IL3-IL3, IL3-IL1-IL3-IL1-IL1, IL3-IL1-IL3-IL1-IL2, IL3-IL1-IL3-IL1-IL3, IL3-IL1-IL3-IL2-IL1, IL3-IL1-IL3-IL2-IL2, IL3-IL1-IL3-IL2-IL3, IL3-IL1-IL3-IL3-IL1, IL3-IL1-IL3-IL3-IL2, IL3-IL1-IL3-IL3-IL3, IL3-IL2-IL1-IL1-IL1, IL3-IL2-IL1-IL1-IL2, IL3-IL2-IL1-IL1-IL3, IL3-IL2-IL1-IL2-IL1, IL3-IL2-IL1-IL2-IL2, IL3-IL2-IL1-IL2-IL3, IL3-IL2-IL1-IL3-IL1, IL3-IL2-IL1-IL3-IL2, IL3-IL2-IL1-IL3-IL3, IL3-IL2-IL2-IL1-IL1, IL3-IL2-IL2-IL1-IL2, IL3-IL2-IL2-IL1-IL3, IL3-IL2-IL2-IL2-IL1, IL3-IL2-IL2-IL2-IL2, IL3-IL2-IL2-IL2-IL3, IL3-IL2-IL2-IL3-IL1, IL3-IL2-IL2-IL3-IL2, IL3-IL2-IL2-IL3-IL3, IL3-IL2-IL3-IL1-IL1, IL3-IL2-IL3-IL1-IL2, IL3-IL2-IL3-IL1-IL3, IL3-IL2-IL3-IL2-IL1, IL3-IL2-IL3-IL2-IL2, IL3-IL2-IL3-IL2-IL3, IL3-IL2-IL3-IL3-IL1, IL3-IL2-IL3-IL3-IL2, IL3-IL2-IL3-IL3-IL3, IL3-IL3-IL1-IL1-

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IL2-IL4-IL4-IL4, IL2-IL4-IL1-IL1-IL1, IL2-IL4-IL1-IL1-IL2, IL2-IL4-IL1-IL1-IL4, IL2-IL4-IL1-IL2-IL1, IL2-IL4-IL1-IL2-IL2, IL2-IL4-IL1-IL2-IL4, IL2-IL4-IL1-IL4-IL1, IL2-IL4-IL1-IL4-IL2, IL2-IL4-IL1-IL4-IL4, IL2-IL4-IL2-IL1-IL1, IL2-IL4-IL2-IL1-IL2, IL2-IL4-IL2-IL1-IL4, IL2-IL4-IL2-IL2-IL1, IL2-IL4-IL2-IL2-IL2, IL2-IL4-IL2-IL2-IL4, IL2-IL4-IL2-IL4-IL1, IL2-IL4-IL2-IL4-IL2, IL2-IL4-IL2-IL4-IL4, IL2-IL4-IL4-IL1-IL1, IL2-IL4-IL4-IL1-IL2, IL2-IL4-IL4-IL1-IL4, IL2-IL4-IL4-IL2-IL1, IL2-IL4-IL4-IL2-IL2, IL2-IL4-IL4-IL2-IL4, IL2-IL4-IL4-IL4-IL1, IL2-IL4-IL4-IL4-IL2, IL2-IL4-IL4-IL4-IL4, IL4-IL1-IL1-IL1-IL1, IL4-IL1-IL1-IL1-IL2, IL4-IL1-IL1-IL1-IL4, IL4-IL1-IL1-IL2-IL1, IL4-IL1-IL1-IL2-IL2, IL4-IL1-IL1-IL2-IL4, IL4-IL1-IL1-IL4-IL1, IL4-IL1-IL1-IL4-IL2, IL4-IL1-IL1-IL4-IL4, IL4-IL1-IL2-IL1-IL1, IL4-IL1-IL2-IL1-IL2, IL4-IL1-IL2-IL1-IL4, IL4-IL1-IL2-IL2-IL1, IL4-IL1-IL2-IL2-IL2, IL4-IL1-IL2-IL2-IL4, IL4-IL1-IL2-IL4-IL1, IL4-IL1-IL2-IL4-IL2, IL4-IL1-IL2-IL4-IL4, IL4-IL1-IL4-IL1-IL1, IL4-IL1-IL4-IL1-IL2, IL4-IL1-IL4-IL1-IL4, IL4-IL1-IL4-IL2-IL1, IL4-IL1-IL4-IL2-IL2, IL4-IL1-IL4-IL2-IL4, IL4-IL1-IL4-IL4-IL1, IL4-IL1-IL4-IL4-IL2, IL4-IL1-IL4-IL4-IL4, IL4-IL2-IL1-IL1-IL1, IL4-IL2-IL1-IL1-IL2, IL4-IL2-IL1-IL1-IL4, IL4-IL2-IL1-IL2-IL1, IL4-IL2-IL1-IL2-IL2, IL4-IL2-IL1-IL2-IL4, IL4-IL2-IL1-IL4-IL1, IL4-IL2-IL1-IL4-IL2, IL4-IL2-IL1-IL4-IL4, IL4-IL2-IL2-IL1-IL1, IL4-IL2-IL2-IL1-IL2, IL4-IL2-IL2-IL1-IL4, IL4-IL2-IL2-IL2-IL1, IL4-IL2-IL2-IL2-IL2, IL4-IL2-IL2-IL2-IL4, IL4-IL2-IL2-IL4-IL1, IL4-IL2-IL2-IL4-IL2, IL4-IL2-IL2-IL4-IL4, IL4-IL2-IL4-IL1-IL1, IL4-IL2-IL4-IL1-IL2, IL4-IL2-IL4-IL1-IL4, IL4-IL2-IL4-IL2-IL1, IL4-IL2-IL4-IL2-IL2, IL4-IL2-IL4-IL2-IL4, IL4-IL2-IL4-IL4-IL1, IL4-IL2-IL4-IL4-IL2, IL4-IL2-IL4-IL4-IL4, IL4-IL4-IL1-IL1-IL1, IL4-IL4-IL1-IL1-IL2, IL4-IL4-IL1-IL1-IL4, IL4-IL4-IL1-IL2-IL1, IL4-IL4-IL1-IL2-IL2, IL4-IL4-IL1-IL2-IL4, IL4-IL4-IL1-IL4-IL1, IL4-IL4-IL1-IL4-IL2, IL4-IL4-IL1-IL4-IL4, IL4-IL4-IL2-IL1-IL1, IL4-IL4-IL2-IL1-IL2, IL4-IL4-IL2-IL1-IL4, IL4-IL4-IL2-IL2-IL1, IL4-IL4-IL2-IL2-IL2, IL4-IL4-IL2-IL2-IL4, IL4-IL4-IL2-IL4-IL1, IL4-IL4-IL2-IL4-IL2, IL4-IL4-IL2-IL4-IL4, IL4-IL4-IL4-IL1-IL1, IL4-IL4-IL4-IL1-IL2, IL4-IL4-IL4-IL1-IL4, IL4-IL4-IL4-IL2-IL1, IL4-IL4-IL4-IL2-IL2, IL4-IL4-IL4-IL2-IL4, IL4-IL4-IL4-IL4-IL1, IL4-IL4-IL4-IL4-IL2, IL4-IL4-IL4-IL4-IL4, or IL4-IL4-IL4-IL4-IL4, wherein IL1, IL2, IL3 and IL4 are different types of internucleotidic linkages. In some embodiments, IL1, IL2, IL3 and IL4 are different types of internucleotidic linkages that differ in chemistry and/or stereochemistry. In some embodiments, such a pattern of internucleotidic linkages is in a first wing, a second wing, and/or a core of an oligonucleotide having an asymmetric format.

[00524] In some embodiments, a pattern of chiral centers of the backbone of an oligonucleotide (linkage phosphorus) comprises any one or more of the following patterns of stereochemistry: RRRRR, RRRRS, RRRSR, RRRSS, RRSRR, RRSRS, RRSSR, RRSSS, RSRRR, RSRRS, RSRSR, RSRSS, RSSRR, RSSRS, RSSSR, RSSSS, SRRRR, SRRRS, SRRSR, SRRSS, SRSRR, SRSRS, SRSSR, SRSSS, SSRRR, SSRRS, SSRSR, SSRSS, SSSRR, SSSRS, SSSSR, SSSSS, RRRRR, RRRRO, RRROR, RRROO, RRORR, RRORO, RROOR, RROOO, RORRR, RORRO, ROROR, ROROO, ROORR,

ROORO, ROOOR, ROOOO, ORRRR, ORRRO, ORROR, ORROO, ORORR, ORORO, OROOR, OROOO, OORRR, OORRO, OOROR, OOROO, OOORR, OOORO, OOOOR, OOOOO, OOOOO, OOOOS, OOOSO, OOOSS, OOSOO, OOSOS, OOSSO, OOSSS, OSOOO, OSOOS, OSOSO, OSOSS, OSSOO, OSSOS, OSSSO, OSSSS, SOOOO, SOOOS, SOOSO, SOOSS, SOSOO, SOSOS, SOSSO, SOSSS, SSOOO, SSOOS, SSOSO, SSOSS, SSSOO, SSSOS, SSSSO, SSSSS, RRRRR, RRRRS, RRRRO, RRRSR, RRRSS, RRRSO, RRROR, RRROS, RRROO, RRSRR, RRSRS, RRSRO, RRSSR, RRSSS, RRSSO, RRSOR, RRSOS, RRSOO, RRORR, RRORS, RRORO, RROSR, RROSS, RROSO, RROOR, RROOS, RROOO, RSRRR, RSRRS, RSRRO, RSRSR, RSRSS, RSRSO, RSROR, RSROS, RSROO, RSSRR, RSSRS, RSSRO, RSSSR, RSSSS, RSSSO, RSSOR, RSSOS, RSSOO, RSORR, RSORS, RSORO, RSOSR, RSOSS, RSOSO, RSOOR, RSOOS, RSOOO, RORRR, RORRS, RORRO, RORSR, RORSS, RORSO, ROROR, ROROS, ROROO, ROSRR, ROSRS, ROSRO, ROSSR, ROSSS, ROSSO, ROSOR, ROSOS, ROSOO, ROORR, ROORS, ROORO, ROOSR, ROOSS, ROOSO, ROOOR, ROOOS, ROOOO, SRRRR, SRRRS, SRRRO, SRRSR, SRRSS, SRRSO, SRROR, SRROS, SRROO, SRSRR, SRSRS, SRSRO, SRSSR, SRSSS, SRSSO, SRSOR, SRSOS, SRSOO, SRORR, SRORS, SRORO, SROSR, SROSS, SROSO, SROOR, SROOS, SROOO, SSRRR, SSRRS, SSRRO, SSRSR, SSRSS, SSRSO, SSROR, SSROS, SSROO, SSSRR, SSSRS, SSSRO, SSSSR, SSSSS, SSSSO, SSSOR, SSSOS, SSSOO, SSORR, SSORS, SSORO, SSOSR, SSOSS, SSOSO, SSOOR, SSOOS, SSOOO, SORRR, SORRS, SORRO, SORSR, SORSS, SORSO, SOROR, SOROS, SOROO, SOSRR, SOSRS, SOSRO, SOSSR, SOSSS, SOSSO, SOSOR, SOSOS, SOSOO, SOORR, SOORS, SOORO, SOOSR, SOOSS, SOOSO, SOOOR, SOOOS, SOOOO, ORRRR, ORRRS, ORRRO, ORRSR, ORRSS, ORRSO, ORROR, ORROS, ORROO, ORSRR, ORSRS, ORSRO, ORSSR, ORSSS, ORSSO, ORSOR, ORSOS, ORSOO, ORORR, ORORS, ORORO, OROSR, OROSS, OROSO, OROOR, OROOS, OROOO, OSRRR, OSRRS, OSRRO, OSRSR, OSRSS, OSRSO, OSROR, OSROS, OSROO, OSSRR, OSSRS, OSSRO, OSSSR, OSSSS, OSSSO, OSSOR, OSSOS, OSSOO, OSORR, OSORS, OSORO, OSOSR, OSOSS, OSOSO, OSOOR, OSOOS, OSOOO, OORRR, OORRS, OORRO, OORSR, OORSS, OORSO, OOROR, OOROS, OOROO, OOSRR, OOSRS, OOSRO, OOSSR, OOSSS, OOSSO, OOSOR, OOSOS, OOSOO, OOORR, OOORS, OOORO, OOOSR, OOOSS, OOOSO, OOOOR, OOOOS, OOOOO, OOOOO, OOOOX, OOOXO, OOOXX, OOXOO, OOXOX, OOXXO, OOXXX, OXOOO, OXOOX, OXOXO, OXOXX, OXXOO, OXXOX, OXXXO, OXXXX, XOOOO, XOOOX, XOOXO, XOOXX, XOXOO, XOXOX, XOXXO, XOXXX, XXOOO, XXOOX, XXOXO, XXOXX, XXXOO, XXXOX, XXXXO, or XXXXX, wherein R is a phosphorothioate diester in the Rp configuration, S is a phosphorothioate diester in the Sp configuration, O is a phosphodiester linkage, and X is a stereorandom phosphorothioate. In some embodiments, such a pattern of stereochemistry is in a first wing, a second wing, and/or the core.

[00525] In some embodiments, a common pattern of backbone chiral centers (*e.g.*, a pattern of backbone chiral centers in an oligonucleotide or in a core or a wing or in two wings thereof) comprises a pattern of OSOSO, OSSSO, OSSSOS, SOSO, SOSO, SOSOS, SOSOSO, SOSOSOSO, SOSSSO, SSOSSSOSS, SSSOSOSSS, SSSSOSOSSSS, SSSSS, SSSSSS, SSSSSSS, SSSSSSSS, SSSSSSSSS, or RRR, wherein S represents a phosphorothioate diester (PS) in the Sp configuration, O represents a phosphodiester, and R represents a phosphorothioate diester (PS) in the Rp configuration.

[00526] In some embodiments of an oligonucleotide, a core comprises any internucleotidic linkage described herein or known in the art, or any pattern or combination of two or more different internucleotidic linkages, wherein R = PS (phosphorothioate) in the Rp configuration, S = PS in the Sp configuration, O = PO (phosphodiester), and X is a stereorandom (not chirally controlled) PS, and nX = a non-negatively charged (e.g., neutral) internucleotidic linkage..

[00527] In some embodiments, a provided oligonucleotide or a core or a wing or both wings thereof comprises a pattern of backbone linkages. In some embodiments, a pattern of backbone linkages is or comprises a sequence of any of: OOO, OOOO, OOOOO, OOOOOOO, OOOOOOO, OOOOOOOO, OOOOOOOOO, OOOOOOOOOO, OƟOƟ, OƟOƟ, OƟƟO, ƟOOƟ, ƟƟOOOƟƟ, ƟOƟOƟOƟƟ, OƟOƟOƟOO, ƟƟƟ, ƟƟƟƟ, ƟƟƟƟƟ, ƟƟƟƟƟƟ, ƟƟƟƟƟƟƟ, ƟƟƟƟƟƟƟƟ, ƟƟƟƟƟƟƟƟƟ, ƟƟƟƟƟƟƟƟƟƟ, OOOOOOOOOOOOOOOOO, OOOOOOOOOOOOOOOOOO, OOOOOOOOOOOOOOOOOOO, OOOOOOOOOOOOOOOOOOOO, OOOOOOOOOOOOOOOOOOOOO, OOOOOOOOOOOOOOOOOOOOOO, ƟOƟOƟOOOƟOOƟƟƟƟƟO, ƟOƟOƟOƟOƟOOOOOOOOOƟƟ, ƟOƟOƟOƟOƟOOOOOOƟƟ, ƟOƟOƟOƟOƟOOOOOƟƟƟ, ƟOƟOƟOƟOƟOƟOOOOOOƟƟ, ƟOƟOƟOƟOƟOƟOOOOOƟƟ, ƟOƟOƟOƟOƟOƟƟƟƟƟƟƟ, ƟOƟOƟOƟOƟOƟƟƟƟƟƟƟO, ƟOƟOƟOƟOƟOƟƟƟƟƟƟƟƟ, ƟOƟOƟOƟOƟOƟƟƟƟƟƟƟƟƟƟƟO, ƟOƟOƟOƟOƟOƟƟƟƟƟƟƟƟƟƟƟƟ, ƟƟOƟOƟOOOƟOOƟƟƟƟƟO, ƟƟOƟOƟOƟOƟOOOOOOOOOƟƟ, ƟƟOƟOƟOƟOƟOOOOOOOƟƟ, ƟƟOƟOƟOƟOƟOOOOOOƟƟƟ, ƟƟOƟOƟOƟOƟOƟOOOOOOOƟƟ, ƟƟOƟOƟOƟOƟOƟOOOOOOƟƟ, ƟƟOƟOƟOƟOƟOƟƟƟƟƟƟƟ, ƟƟOƟOƟOƟOƟOƟƟƟƟƟƟƟO, ƟƟOƟOƟOƟOƟOƟƟƟƟƟƟƟƟ, ƟƟOƟOƟOƟOƟOƟƟƟƟƟƟƟƟƟƟƟO, ƟƟOƟOƟƟƟƟOƟOƟƟƟƟƟƟƟƟƟƟ, ƟƟOƟOƟƟƟOOOƟOOƟƟƟƟƟO, ƟƟOƟOƟƟƟOƟOOOOOOOOƟƟ, ƟƟOƟOƟƟƟOƟOOOOOOOƟƟ, ƟƟOƟƟƟOƟOƟOOOOOOOƟƟ, ƟƟOƟOƟƟƟOƟOOOOOOƟƟƟ, ƟƟOƟƟƟOƟOƟOOOOOOƟƟ, ƟƟOƟƟƟOƟOƟƟƟƟƟƟƟO, ƟƟOƟƟƟOƟOƟƟƟƟƟƟƟƟO,

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ΘΘΘΘΘΘOΘOOOΘOOΘΘΘΘΘO, ΘΘΘΘΘΘOΘOOOΘOOΘΘΘΘΘO,
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ΘΘΘΘΘΘOΘOΘOΘOΘΘΘΘΘΘΘΘΘΘO, ΘΘΘΘΘΘOΘOΘOΘΘΘΘΘΘΘΘΘΘΘΘΘ,
ΘΘΘΘΘΘOΘOΘΘΘOOOOOOOOΘΘ, ΘΘΘΘΘΘOΘOΘΘΘOOOOOOΘΘ,
ΘΘΘΘΘΘOΘOΘΘΘOOOOOΘΘΘ, ΘΘΘΘΘΘOΘOΘΘΘOOOOOOOOΘΘ,
ΘΘΘΘΘΘOΘOΘΘΘOΘOOOOΘΘ, ΘΘΘΘΘΘOΘOΘΘΘOΘΘΘΘΘΘ,
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ΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘ, ΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘ,
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ΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘ, ΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘ,
ΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘ, or ΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘΘ, or any span of at least 5 consecutive internucleotidic linkages thereof, wherein O indicates a phosphodiester, and Θ indicates an internucleotidic linkage or modified internucleotidic linkage which is not phosphodiester; in some embodiments, a modified internucleotidic linkage is a phosphorothioate; in some embodiments, a modified internucleotidic linkage is chirally controlled; in some embodiments, a modified internucleotidic linkage is a chirally controlled phosphorothioate.

[00528] In some embodiments, an oligonucleotide having an asymmetric format comprises a wing-core-wing structure, wherein the first wing and the second differ in their internucleotidic linkages or combinations or patterns thereof, and wherein the first and/or the second wing differ from the core in their internucleotidic linkages or combinations or patterns thereof.

[00529] Figure 1C provides non-limiting examples of an oligonucleotide having an asymmetric format comprises a wing-core-wing structure, wherein the first wing and the second differ in their internucleotidic linkages or combinations or patterns thereof, and wherein the first and/or the second wing differ from the core in their internucleotidic linkages or combinations or patterns thereof. Figure 1D provides a legend to Figure 1C.

[00530] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-10406, WV-10407, WV-10408, WV-10409, WV-10410, WV-10411, WV-10412, WV-10413, WV-10414, WV-10415, WV-10416, WV-10417, WV-10418, WV-10419, WV-10420, WV-10421, WV-10422.

[00531] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-10406, WV-10407, WV-10408, WV-10409, WV-10410, WV-10411, WV-10412, WV-10413, WV-10414, WV-10415, WV-10416, WV-10417, WV-10418, WV-10419, WV-10420, WV-10421, WV-10422.

[00532] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-10406, WV-10407, WV-10408, WV-10409, WV-10410, WV-10411, WV-10412, WV-10413, WV-10414, WV-10415, WV-10416, WV-10417, WV-10418, WV-10419, WV-10420, WV-10421, WV-10422.

[00533] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXX. Non-limiting example(s) of such an oligonucleotide include: WV-10406, WV-10407, WV-10408, WV-10409, WV-10410, WV-10411, WV-10412, WV-10413, WV-10414, WV-10415, WV-10416, WV-10417, WV-10418, WV-10419, WV-10420, WV-10421, WV-10422.

[00534] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXX. Non-limiting example(s) of such an oligonucleotide include: WV-10406, WV-10407, WV-10408, WV-10409, WV-10410, WV-10411, WV-10412, WV-10413, WV-10414, WV-10415, WV-10416, WV-10417, WV-10418, WV-10419, WV-10420, WV-10421, WV-10422.

[00535] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XX. Non-limiting example(s) of such an oligonucleotide include: WV-10406, WV-10407, WV-10408, WV-10409, WV-10410, WV-10411, WV-10412, WV-10413, WV-10414, WV-10415, WV-10416, WV-10417, WV-10418, WV-10419, WV-10420, WV-10421, WV-10422.

[00536] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: X. Non-limiting example(s) of such an oligonucleotide include: WV-10406, WV-10407, WV-10408, WV-10409, WV-10410, WV-10411, WV-10412, WV-10413, WV-

10414, WV-10415, WV-10416, WV-10417, WV-10418, WV-10419, WV-10420, WV-10421, WV-10422.

[00537] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OORSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00538] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OORSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00539] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OORSSSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00540] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OORSSSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00541] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OORSSSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00542] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OORSSSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00543] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OORSSSSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00544] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OORSSSSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00545] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OORSSSSRSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00546] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OORSSSSRSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00547] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OORSSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00548] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OORSSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00549] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[00550] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00551] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[00552] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00553] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[00554] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00555] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[00556] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00557] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSSSSR. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[00558] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSSSSRO. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[00559] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00560] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00561] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00562] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00563] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSSSRSSSSRO. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[00564] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00565] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00566] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00567] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00568] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00569] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSSSRO. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[00570] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00571] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSSSRO. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[00572] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSSSRO. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[00573] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00574] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00575] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00576] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00577] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSSSRO. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[00578] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSSSRO. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[00579] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00580] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00581] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00582] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00583] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00584] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00585] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: O and X. Non-limiting example(s) of such an oligonucleotide include: WV-10252, WV-8600, WV-8613, WV-8628, WV-8632, WV-8640, WV-8648.

[00586] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more O and two or more X. Non-limiting example(s) of such an oligonucleotide include: WV-10252, WV-8600, WV-8613, WV-8628, WV-8632, WV-8640, WV-8648.

[00587] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: nXnX . Non-limiting example(s) of such an oligonucleotide include: WV-15355.

[00588] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: nXS. Non-limiting example(s) of such an oligonucleotide include: WV-15354.

[00589] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: nXSSnX . Non-limiting example(s) of such an oligonucleotide include: WV-15351.

[00590] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: nXSSnXSSnXS. Non-limiting example(s) of such an oligonucleotide include: WV-15351.

[00591] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: nXSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-15352.

[00592] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RnXnX . Non-limiting example(s) of such an oligonucleotide include: WV-15357.

[00593] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RnXnXRnXnXRnX. Non-limiting example(s) of such an oligonucleotide include: WV-15355.

[00594] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RnXnXRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-15356.

[00595] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSnX. Non-limiting example(s) of such an oligonucleotide include: WV-15361.

[00596] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSnXSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-15353.

[00597] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSRnXnXRS. Non-limiting example(s) of such an oligonucleotide include: WV-15357.

[00598] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSRSSnXS. Non-limiting example(s) of such an oligonucleotide include: WV-15354.

[00599] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSRSSRnX. Non-limiting example(s) of such an oligonucleotide include: WV-15358.

[00600] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SHORTENED:. Non-limiting example(s) of such an oligonucleotide include: .

[00601] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SnX . Non-limiting example(s) of such an oligonucleotide include: WV-15353.

[00602] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SnXnX. Non-limiting example(s) of such an oligonucleotide include: WV-15359.

[00603] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SnXS . Non-limiting example(s) of such an oligonucleotide include: WV-15352.

[00604] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SnXSSnXSSnX. Non-limiting example(s) of such an oligonucleotide include: WV-15351.

[00605] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SnXSSnXSSnXS. Non-limiting example(s) of such an oligonucleotide include: WV-15351.

[00606] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SnXSSRSSR. Non-limiting example(s) of such an oligonucleotide include: WV-15352.

[00607] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SnXSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-15352.

[00608] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRnX. Non-limiting example(s) of such an oligonucleotide include: WV-15358.

[00609] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRnXnXRnXnXR. Non-limiting example(s) of such an oligonucleotide include: WV-15355.

[00610] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRnXnXRnXnXRnX. Non-limiting example(s) of such an oligonucleotide include: WV-15355.

[00611] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRnXnXRSSR. Non-limiting example(s) of such an oligonucleotide include: WV-15356.

[00612] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRnXnXRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-15356.

[00613] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSnXSSR. Non-limiting example(s) of such an oligonucleotide include: WV-15353.

[00614] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSnXSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-15353.

[00615] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRnXnXR. Non-limiting example(s) of such an oligonucleotide include: WV-15357.

[00616] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRnXnXRS. Non-limiting example(s) of such an oligonucleotide include: WV-15357.

[00617] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRSSnX. Non-limiting example(s) of such an oligonucleotide include: WV-15354.

[00618] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRSSnXS. Non-limiting example(s) of such an oligonucleotide include: WV-15354.

[00619] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRSSRnX. Non-limiting example(s) of such an oligonucleotide include: WV-15358.

[00620] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSnXS. Non-limiting example(s) of such an oligonucleotide include: WV-15360.

[00621] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRnX. Non-limiting example(s) of such an oligonucleotide include: WV-15362.

[00622] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRnX. Non-limiting example(s) of such an oligonucleotide include: WV-15364.

[00623] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRnX. Non-limiting example(s) of such an oligonucleotide include: WV-15365.

[00624] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSnXnX. Non-limiting example(s) of such an oligonucleotide include: WV-15359.

[00625] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSnXS. Non-limiting example(s) of such an oligonucleotide include: WV-15360.

[00626] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSRnX. Non-limiting example(s) of such an oligonucleotide include: WV-15362.

[00627] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSRnX. Non-limiting example(s) of such an oligonucleotide include: WV-15364.

[00628] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSRnX. Non-limiting example(s) of such an oligonucleotide include: WV-15365.

[00629] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-15363.

[00630] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSRSnX. Non-limiting example(s) of such an oligonucleotide include: WV-15361.

[00631] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSnX. Non-limiting example(s) of such an oligonucleotide include: WV-15359.

[00632] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSnX. Non-limiting example(s) of such an oligonucleotide include: WV-15360.

[00633] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSnXnX. Non-limiting example(s) of such an oligonucleotide include: WV-15359.

[00634] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSnXS. Non-limiting example(s) of such an oligonucleotide include: WV-15360.

[00635] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSRnX. Non-limiting example(s) of such an oligonucleotide include: WV-15362.

[00636] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSRnX. Non-limiting example(s) of such an oligonucleotide include: WV-15364.

[00637] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSRnX. Non-limiting example(s) of such an oligonucleotide include: WV-15365.

[00638] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-15363.

[00639] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSRSnX. Non-limiting example(s) of such an oligonucleotide include: WV-15361.

[00640] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XnXR . Non-limiting example(s) of such an oligonucleotide include: WV-15356.

[00641] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: 5MSd. Non-limiting example(s) of such an oligonucleotide include: WV-9396, WV-9397.

[00642] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: 5MRd. Non-limiting example(s) of such an oligonucleotide include: WV-9398, WV-9399.

[00643] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRS. Non-limiting example(s) of such an oligonucleotide include: WV-10244, WV-10246, WV-9872.

[00644] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSS. Non-limiting example(s) of such an oligonucleotide include: WV-10244, WV-10246, WV-9872.

[00645] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSR. Non-limiting example(s) of such an oligonucleotide include: WV-10244, WV-10246, WV-9872.

[00646] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-10244, WV-10246, WV-9872.

[00647] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-10243, WV-10245, WV-10249, WV-10252, WV-11963, WV-11964, WV-12445, WV-12446, WV-12447, WV-12448, WV-12449, WV-12450, WV-12451, WV-12480, WV-12481, WV-12482, WV-12483, WV-12484, WV-12486.

[00648] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-10243.

[00649] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-10244, WV-10246, WV-8610, WV-8629, WV-9526.

[00650] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSSRSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-10244, WV-10246, WV-9872.

[00651] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-10245, WV-10249, WV-10252, WV-11963, WV-11964, WV-12445, WV-12446, WV-12447, WV-12448, WV-12449, WV-12450, WV-12451, WV-12480, WV-12481, WV-12482, WV-12483.

[00652] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSR. Non-limiting example(s) of such an oligonucleotide include: WV-10250, WV-10253, WV-8560, WV-8562, WV-8564, WV-8566, WV-8620, WV-8637, WV-8645, WV-8665, WV-8673, WV-8677, WV-9859, WV-9861.

[00653] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-10250, WV-10253, WV-8560, WV-9859, WV-9861.

[00654] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSSSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-10251, WV-10254, WV-11958, WV-11962, WV-12100, WV-9670, WV-9862.

[00655] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-10251, WV-10254, WV-11958, WV-11962, WV-8597, WV-8599, WV-8625, WV-8638, WV-8646, WV-8666, WV-8674, WV-8678, WV-9670, WV-9862.

[00656] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-10406, WV-10407, WV-10408, WV-10409, WV-10410, WV-10411, WV-10412, WV-10413, WV-10414, WV-10415, WV-10416, WV-10417, WV-10418, WV-10419, WV-10420, WV-10421, WV-10422.

[00657] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-10406, WV-10407, WV-10408, WV-10409, WV-10410, WV-10411, WV-10412, WV-10413, WV-10414, WV-10415, WV-10416, WV-10417.

[00658] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-10418, WV-10419, WV-10420, WV-10421, WV-10422, WV-10423, WV-10424, WV-10425, WV-10426.

[00659] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-10423.

[00660] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-10424, WV-10425, WV-10426, WV-10427, WV-11966, WV-12113, WV-12114, WV-12439, WV-12440, WV-12441, WV-12442, WV-12443, WV-12444, WV-12485, WV-12582, WV-12583, WV-12947, WV-12948, WV-12949, WV-12950, WV-12951, WV-12952.

[00661] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-10427.

[00662] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRSSRS. Non-limiting example(s) of such an oligonucleotide

include: WV-11114, WV-12503, WV-12504, WV-12505, WV-13809, WV-14349, WV-8043, WV-8044, WV-8045, WV-8046, WV-8047, WV-8048, WV-8257, WV-9696, WV-9697.

[00663] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRSSR. Non-limiting example(s) of such an oligonucleotide include: WV-11114, WV-12503, WV-12504, WV-12505, WV-13809, WV-14349, WV-8043, WV-8044, WV-8045, WV-8046, WV-8047, WV-8048, WV-8257.

[00664] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more R and two or more S. Non-limiting example(s) of such an oligonucleotide include: WV-11532, WV-11965, WV-11967, WV-13305, WV-13306, WV-13307, WV-14552, WV-7124, WV-7130, WV-7601, WV-7604, WV-7606, WV-7658, WV-8006, WV-8008, WV-8010, WV-8012, WV-8101, WV-8107, WV-8321, WV-8453, WV-8455, WV-8580, WV-8586, WV-8592, WV-9508, WV-11114, WV-12503, WV-12504, WV-12505, WV-13809, WV-14349, WV-8043, WV-8044, WV-8045, WV-8046, WV-8047, WV-8048, WV-8257, WV-9696, WV-9697, WV-9698, WV-11533, WV-12110, WV-12112, WV-13303, WV-13304, WV-8083, WV-8102, WV-8108, WV-8575, WV-8581, WV-8587, WV-8593

[00665] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-11532, WV-11965, WV-11967, WV-13305, WV-13306, WV-13307, WV-14552, WV-7124, WV-7130, WV-7601, WV-7604, WV-7606, WV-7658, WV-8006, WV-8008, WV-8010, WV-8012, WV-8101, WV-8107, WV-8321, WV-8453, WV-8455, WV-8580, WV-8586, WV-8592.

[00666] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: R and S. Non-limiting example(s) of such an oligonucleotide include: WV-11532, WV-11965, WV-11967, WV-13305, WV-13306, WV-13307, WV-14552, WV-7124, WV-7130, WV-7601, WV-7604, WV-7606, WV-7658, WV-8006, WV-8008, WV-8010, WV-8012, WV-8101, WV-8107, WV-8321, WV-8453, WV-8455, WV-8580, WV-8586, WV-8592, WV-9508, WV-11114, WV-12503, WV-12504, WV-12505, WV-13809, WV-14349, WV-8043, WV-8044, WV-8045, WV-8046, WV-8047, WV-8048, WV-8257, WV-9696, WV-9697, WV-9698, WV-11533, WV-12110, WV-12112, WV-13303, WV-13304, WV-8083, WV-8102, WV-8108, WV-8575, WV-8581, WV-8587, WV-8593.

[00667] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-11532.

[00668] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRSSRS. Non-limiting example(s) of such an oligonucleotide

include: WV-11533, WV-12110, WV-12112, WV-13303, WV-13304, WV-8083, WV-8102, WV-8108, WV-8575, WV-8581, WV-8587, WV-8593.

[00669] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSRSSR. Non-limiting example(s) of such an oligonucleotide include: WV-11533, WV-12110, WV-12112, WV-13303, WV-13304, WV-8083, WV-8102, WV-8108, WV-8575, WV-8581, WV-8587, WV-8593, WV-9058.

[00670] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-11960, WV-8606, WV-8608, WV-8654, WV-8662, WV-8670, WV-8682, WV-8686, WV-9890, WV-9893, WV-9896, WV-8611, WV-9527.

[00671] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-11960, WV-8606, WV-8608, WV-8654, WV-8662, WV-8670, WV-8682, WV-8686, WV-9890, WV-9893.

[00672] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-11965.

[00673] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-11966, WV-12113, WV-12114, WV-12439, WV-12440, WV-12441, WV-12442, WV-12443, WV-12444, WV-12582, WV-12583, WV-12947, WV-12948, WV-12949.

[00674] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-11967.

[00675] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00676] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OORSSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00677] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSSSSRO. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[00678] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSSSRSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00679] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00680] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: ORSSSSRSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00681] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OORSSSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00682] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OXXXXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-12105.

[00683] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OOXXXXXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-12105.

[00684] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-12107, WV-12485, WV-8132.

[00685] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OXXXXXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-12107.

[00686] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OXXXXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-12109.

[00687] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OOXXXXXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-12109.

[00688] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12111.

[00689] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12111.

[00690] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-12484, WV-12486, WV-12977, WV-12978, WV-12979, WV-12980, WV-12981, WV-12982, WV-12983, WV-12984, WV-12985, WV-12986, WV-12987, WV-12988, WV-12989, WV-12990.

[00691] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12893, WV-13312, WV-13313, WV-14087, WV-7603, WV-7605, WV-7659, WV-8005, WV-8007, WV-8009, WV-8011.

[00692] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-12893.

[00693] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-12950.

[00694] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-12953.

[00695] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-12977, WV-12978, WV-12979, WV-12980, WV-12981, WV-12982, WV-12983, WV-12984, WV-12985, WV-12986, WV-12987, WV-12988, WV-12989, WV-12990, WV-12991, WV-12992, WV-12993, WV-12994, WV-12995, WV-12996, WV-12997.

[00696] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-12991.

[00697] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-12998.

[00698] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-12999, WV-13000, WV-13001, WV-13002, WV-13003, WV-13004, WV-13005, WV-13006, WV-13007, WV-13008, WV-13804, WV-13805, WV-3421, WV-3662, WV-3688, WV-3690, WV-6408, WV-6474.

[00699] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-13005, WV-13006, WV-13007, WV-13008, WV-13804, WV-13805, WV-3421, WV-3662, WV-3688, WV-3690, WV-6408, WV-6474, WV-6936.

[00700] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-13305, WV-13306, WV-13307, WV-14552, WV-7124, WV-7130, WV-7601, WV-7604, WV-7606, WV-7658, WV-8006, WV-8008, WV-8010, WV-8012, WV-8101, WV-8107, WV-8321, WV-8453, WV-8455, WV-8580, WV-8586, WV-8592.

[00701] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-13308, WV-13309, WV-13310, WV-13311, WV-9505.

[00702] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-13312, WV-13313, WV-14087, WV-7603, WV-7605, WV-7659, WV-8005, WV-8007, WV-8009, WV-8011, WV-8452, WV-8454.

[00703] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-13803, WV-3174, WV-3536, WV-3542, WV-8132, WV-8548, WV-8550, WV-8552, WV-8553, WV-8556, WV-8594, WV-8595, WV-8609, WV-8617, WV-8656, WV-8664, WV-8672, WV-8684, WV-8688.

[00704] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-6936.

[00705] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-6951.

[00706] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSS. Non-limiting example(s) of such an oligonucleotide

include: WV-7657, WV-8099, WV-8105, WV-8322, WV-8329, WV-8572, WV-8578, WV-8584, WV-8590.

[00707] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-7657.

[00708] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8097, WV-8103, WV-8248, WV-8250, WV-8570, WV-8576, WV-8582, WV-8588.

[00709] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSR. Non-limiting example(s) of such an oligonucleotide include: WV-8097, WV-8103, WV-8248, WV-8250, WV-8570, WV-8576, WV-8582, WV-8588, WV-8602, WV-8605, WV-8616, WV-8655, WV-8663, WV-8671.

[00710] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-8098, WV-8104, WV-8571, WV-8577, WV-8583, WV-8589, WV-8619, WV-9506.

[00711] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8098, WV-8104, WV-8571, WV-8577, WV-8583, WV-8589, WV-8619, WV-9506.

[00712] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-8099, WV-8105, WV-8322, WV-8329, WV-8572, WV-8578, WV-8584, WV-8590.

[00713] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8100, WV-8106, WV-8114, WV-8115, WV-8116, WV-8117, WV-8118, WV-8119, WV-8120, WV-8121.

[00714] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSR. Non-limiting example(s) of such an oligonucleotide include: WV-8100, WV-8106, WV-8114, WV-8115, WV-8116, WV-8117, WV-8118, WV-8119, WV-8120, WV-8121, WV-8246, WV-8311, WV-8312, WV-8313, WV-8314, WV-8466, WV-8468, WV-8470, WV-8472, WV-8474, WV-8476.

[00715] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-8122, WV-8123, WV-8124, WV-8125, WV-8126, WV-8127, WV-8128, WV-8129, WV-

8315, WV-8316, WV-8317, WV-8318, WV-8467, WV-8469, WV-8471, WV-8473, WV-8475, WV-8569, WV-8614, WV-8692, WV-8695, WV-9530, WV-9886.

[00716] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8122.

[00717] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8123.

[00718] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8124, WV-8125, WV-8126, WV-8127, WV-8128, WV-8129, WV-8315, WV-8316, WV-8317, WV-8318, WV-8467, WV-8469.

[00719] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8246, WV-8311, WV-8312, WV-8313, WV-8314, WV-8466, WV-8468.

[00720] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8259.

[00721] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSSSSR. Non-limiting example(s) of such an oligonucleotide include: WV-8259.

[00722] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-8452.

[00723] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-8454.

[00724] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-8456.

[00725] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-8456.

[00726] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8470.

[00727] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8471.

[00728] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8472, WV-8474, WV-8476, WV-8568, WV-8573, WV-8579, WV-8585, WV-8591, WV-8601, WV-8603, WV-8653, WV-8661, WV-8669, WV-8681, WV-8685, WV-8691, WV-8694, WV-9889, WV-9892.

[00729] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8473.

[00730] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8475.

[00731] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8562, WV-8564, WV-8566, WV-8620, WV-8637, WV-8645, WV-8665, WV-8673.

[00732] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8563, WV-8565, WV-8567, WV-8596, WV-8612, WV-8621, WV-8624, WV-8639, WV-8647, WV-8667, WV-8675.

[00733] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSR. Non-limiting example(s) of such an oligonucleotide include: WV-8563, WV-8565, WV-8567, WV-8596, WV-8612, WV-8621, WV-8624, WV-8639, WV-8647, WV-8667, WV-8675.

[00734] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSR. Non-limiting example(s) of such an oligonucleotide include: WV-8568.

[00735] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-8597.

[00736] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-8599, WV-8625, WV-8638, WV-8646, WV-8666, WV-8674.

[00737] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8602.

[00738] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8605, WV-8616, WV-8655, WV-8663, WV-8671, WV-8683.

[00739] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-8610.

[00740] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-8611.

[00741] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-8615.

[00742] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-8615.

[00743] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-8618.

[00744] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8618.

[00745] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-8629.

[00746] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-8676, WV-8680, WV-8689, WV-8693, WV-8696, WV-8697, WV-8809, WV-8844, WV-8846, WV-8847, WV-8849, WV-8851, WV-8853, WV-8855, WV-8857, WV-8858, WV-8860.

[00747] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8677.

[00748] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-8678.

[00749] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8679.

[00750] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSR. Non-limiting example(s) of such an oligonucleotide include: WV-8679.

[00751] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSR. Non-limiting example(s) of such an oligonucleotide include: WV-8683.

[00752] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-8687.

[00753] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSR. Non-limiting example(s) of such an oligonucleotide include: WV-8687.

[00754] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-8690, WV-8845, WV-8848, WV-8850, WV-8852, WV-8854, WV-8856, WV-8859, WV-9431, WV-9432, WV-9433, WV-9434, WV-9435, WV-9441, WV-9442, WV-9443, WV-9444, WV-9445, WV-9486.

[00755] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-8810.

[00756] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-9058.

[00757] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-9059.

[00758] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSRSSR. Non-limiting example(s) of such an oligonucleotide include: WV-9059.

[00759] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-9060.

[00760] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9062.

[00761] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9062.

[00762] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9063.

[00763] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9063.

[00764] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9285, WV-9286, WV-9380, WV-9381.

[00765] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-9285, WV-9286, WV-9380, WV-9381.

[00766] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSOSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9394.

[00767] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SOSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9394.

[00768] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SOSSOSS. Non-limiting example(s) of such an oligonucleotide include: WV-9395, WV-9397.

[00769] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSOSSOSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9395.

[00770] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSOSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9396.

[00771] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SOSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9396.

[00772] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSOSSOSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9397.

[00773] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSOSSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9398.

[00774] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SOSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9398.

[00775] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSOSSOSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9399.

[00776] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SOSSOSS. Non-limiting example(s) of such an oligonucleotide include: WV-9399.

[00777] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9421.

[00778] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-9421.

[00779] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-9487.

[00780] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9507.

[00781] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-9507.

[00782] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9508, WV-13308, WV-13309, WV-13310, WV-13311, WV-9505.

[00783] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-9508.

[00784] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-9509.

[00785] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-9509.

[00786] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-9526.

[00787] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9527.

[00788] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-9528.

[00789] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-9528.

[00790] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9531.

[00791] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9531.

[00792] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-9532.

[00793] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-9532.

[00794] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-9533, WV-9885, WV-9887, WV-9891, WV-9894.

[00795] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-9590.

[00796] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-9590.

[00797] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9591.

[00798] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9591.

[00799] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-9592.

[00800] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-9592.

[00801] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRSSR. Non-limiting example(s) of such an oligonucleotide include: WV-9696.

[00802] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRSSR. Non-limiting example(s) of such an oligonucleotide include: WV-9697.

[00803] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSRSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-9698.

[00804] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SRSSRSSR. Non-limiting example(s) of such an oligonucleotide include: WV-9698.

[00805] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: XXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-980.

[00806] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSR. Non-limiting example(s) of such an oligonucleotide include: WV-9869.

[00807] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-9869.

[00808] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9870.

[00809] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSSSRSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9870.

[00810] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-9872.

[00811] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-9874.

[00812] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: RSSSRSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-9874.

[00813] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSRSS. Non-limiting example(s) of such an oligonucleotide include: WV-9888.

[00814] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSSRSSRS. Non-limiting example(s) of such an oligonucleotide include: WV-9895.

[00815] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SSSRSSS. Non-limiting example(s) of such an oligonucleotide include: WV-9896.

[00816] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: 4 or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10424, WV-10425, WV-10426, WV-10427, WV-11966, WV-12113, WV-12114, WV-12439, WV-12440, WV-12441, WV-12442, WV-12443, WV-12444, WV-12485, WV-12582, WV-12583, WV-12947, WV-12948, WV-12949, WV-12950, WV-12951, WV-12952.

[00817] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive O, and two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12105.

[00818] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive O, and two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12109.

[00819] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive O, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00820] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive O, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00821] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and O, and two or more consecutive S, and O, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9395.

[00822] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and O, and two or more consecutive S, and O, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9397.

[00823] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and O, and two or more consecutive S, and O, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9399.

[00824] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and O, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9394.

[00825] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and O, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9396.

[00826] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and O, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9398.

[00827] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8097, WV-8103, WV-8248, WV-8250, WV-8570, WV-8576, WV-8582, WV-8588, WV-8602, WV-8605, WV-8616, WV-8655, WV-8663, WV-8671.

[00828] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8683.

[00829] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8687.

[00830] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8122.

[00831] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8123.

[00832] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8124, WV-8125, WV-8126, WV-8127, WV-8128, WV-8129, WV-8315, WV-8316, WV-8317, WV-8318, WV-8467, WV-8469.

[00833] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8471.

[00834] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8473.

[00835] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8475.

[00836] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9285, WV-9286, WV-9380, WV-9381.

[00837] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9421.

[00838] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide

include: WV-11114, WV-12503, WV-12504, WV-12505, WV-13809, WV-14349, WV-8043, WV-8044, WV-8045, WV-8046, WV-8047, WV-8048, WV-8257, WV-9696, WV-9697.

[00839] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-9698.

[00840] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-11532.

[00841] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-11965.

[00842] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-11967.

[00843] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-13305, WV-13306, WV-13307, WV-14552, WV-7124, WV-7130, WV-7601, WV-7604, WV-7606, WV-7658, WV-8006, WV-8008, WV-8010, WV-8012, WV-8101, WV-8107, WV-8321, WV-8453, WV-8455, WV-8580, WV-8586, WV-8592.

[00844] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9508, WV-13308, WV-13309, WV-13310, WV-13311, WV-9505.

[00845] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9509.

[00846] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8615.

[00847] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9531.

[00848] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9062.

[00849] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9063.

[00850] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8259.

[00851] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12893, WV-13312, WV-13313, WV-14087, WV-7603, WV-7605, WV-7659, WV-8005, WV-8007, WV-8009, WV-8011.

[00852] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8452.

[00853] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8454.

[00854] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8456.

[00855] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8100, WV-8106, WV-8114, WV-8115, WV-8116, WV-8117, WV-8118, WV-8119, WV-8120, WV-8121, WV-8246, WV-8311, WV-8312, WV-8313, WV-8314, WV-8466, WV-8468, WV-8470, WV-8472, WV-8474, WV-8476.

[00856] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8568.

[00857] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-10244, WV-10246, WV-8610, WV-8629, WV-9526.

[00858] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-9590.

[00859] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-9872.

[00860] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-9874.

[00861] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8122, WV-8123, WV-8124, WV-8125, WV-8126, WV-8127, WV-8128, WV-8129, WV-8315, WV-8316, WV-8317, WV-8318, WV-8467, WV-8469, WV-8471, WV-8473, WV-8475, WV-8569, WV-8614, WV-8692, WV-8695, WV-9530, WV-9886.

[00862] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9888.

[00863] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9285, WV-9286, WV-9380, WV-9381.

[00864] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9421.

[00865] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-11960, WV-8606, WV-8608, WV-8654, WV-8662, WV-8670, WV-8682, WV-8686, WV-9890, WV-9893.

[00866] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9896.

[00867] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8611.

[00868] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9527.

[00869] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9591.

[00870] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8615.

[00871] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9531.

[00872] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9062.

[00873] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9063.

[00874] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-7657, WV-8099, WV-8105, WV-8322, WV-8329, WV-8572, WV-8578, WV-8584, WV-8590.

[00875] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9507.

[00876] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R. Non-limiting example(s) of such an oligonucleotide include: WV-10250, WV-10253, WV-8560, WV-8562, WV-8564, WV-8566, WV-8620, WV-8637, WV-8645, WV-8665, WV-8673, WV-8677, WV-9859, WV-9861.

[00877] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R. Non-limiting example(s) of such an oligonucleotide include: WV-9869.

[00878] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8100, WV-8106, WV-8114, WV-8115, WV-8116, WV-8117, WV-8118, WV-8119, WV-8120, WV-8121.

[00879] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8246, WV-8311, WV-8312, WV-8313, WV-8314, WV-8466, WV-8468.

[00880] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8470.

[00881] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8472, WV-8474, WV-8476, WV-8568, WV-8573, WV-8579, WV-8585, WV-8591, WV-8601, WV-8603, WV-8653, WV-8661, WV-8669, WV-8681, WV-8685, WV-8691, WV-8694, WV-9889, WV-9892.

[00882] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-9895.

[00883] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8610.

[00884] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8629.

[00885] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9526.

[00886] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9590.

[00887] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-10251, WV-10254, WV-11958, WV-11962, WV-8597, WV-8599, WV-8625, WV-8638, WV-8646, WV-8666, WV-8674, WV-8678, WV-9670, WV-9862.

[00888] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9870.

[00889] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-11960, WV-8606, WV-8608, WV-8654, WV-8662, WV-8670, WV-8682, WV-8686, WV-9890, WV-9893, WV-9896, WV-8611, WV-9527.

[00890] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9591.

[00891] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8562, WV-8564, WV-8566, WV-8620, WV-8637, WV-8645, WV-8665, WV-8673.

[00892] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8677.

[00893] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-7657.

[00894] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8099, WV-8105, WV-8322, WV-8329, WV-8572, WV-8578, WV-8584, WV-8590.

[00895] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9507.

[00896] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8597.

[00897] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8599, WV-8625, WV-8638, WV-8646, WV-8666, WV-8674.

[00898] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8678.

[00899] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8098, WV-8104, WV-8571, WV-8577, WV-8583, WV-8589, WV-8619, WV-9506.

[00900] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9532.

[00901] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and RS. Non-limiting example(s) of

such an oligonucleotide include: WV-8098, WV-8104, WV-8571, WV-8577, WV-8583, WV-8589, WV-8619, WV-9506.

[00902] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-9532.

[00903] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8618.

[00904] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-9528.

[00905] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-9592.

[00906] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: 5 or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10406, WV-10407, WV-10408, WV-10409, WV-10410, WV-10411, WV-10412, WV-10413, WV-10414, WV-10415, WV-10416, WV-10417, WV-10418, WV-10419, WV-10420, WV-10421, WV-10422.

[00907] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: 6 or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10243, WV-10245, WV-10249, WV-10252, WV-11963, WV-11964, WV-12445, WV-12446, WV-12447, WV-12448, WV-12449, WV-12450, WV-12451, WV-12480, WV-12481, WV-12482, WV-12483, WV-12484, WV-12486.

[00908] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: 7 or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12977, WV-12978, WV-12979, WV-12980, WV-12981, WV-12982, WV-12983, WV-12984, WV-12985, WV-12986, WV-12987, WV-12988, WV-12989, WV-12990, WV-12991, WV-12992, WV-12993, WV-12994, WV-12995, WV-12996, WV-12997.

[00909] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: 8 or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12999, WV-13000, WV-13001, WV-13002, WV-13003, WV-13004, WV-13005, WV-13006, WV-13007, WV-13008, WV-13804, WV-13805, WV-3421, WV-3662, WV-3688, WV-3690, WV-6408, WV-6474.

[00910] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: 9 or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-8676, WV-8680, WV-8689, WV-8693, WV-8696, WV-8697, WV-8809, WV-8844, WV-8846, WV-8847, WV-8849, WV-8851, WV-8853, WV-8855, WV-8857, WV-8858, WV-8860.

[00911] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: and two or more consecutive S and R. Non-limiting example(s) of such an oligonucleotide include: WV-8563, WV-8565, WV-8567, WV-8596, WV-8612, WV-8621, WV-8624, WV-8639, WV-8647, WV-8667, WV-8675.

[00912] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: and two or more consecutive S and R. Non-limiting example(s) of such an oligonucleotide include: WV-8679.

[00913] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: and two or more consecutive S and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8618.

[00914] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: and two or more consecutive S and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9528.

[00915] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: and two or more consecutive S and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9592.

[00916] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: and two or more consecutive S and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8097, WV-8103, WV-8248, WV-8250, WV-8570, WV-8576, WV-8582, WV-8588.

[00917] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: and two or more consecutive S and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8602.

[00918] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: and two or more consecutive S and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8605, WV-8616, WV-8655, WV-8663, WV-8671, WV-8683.

[00919] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: and two or more consecutive S and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8687.

[00920] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: and two or more consecutive S and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8563, WV-8565, WV-8567, WV-8596, WV-8612, WV-8621, WV-8624, WV-8639, WV-8647, WV-8667, WV-8675.

[00921] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: and two or more consecutive S and RS. Non-limiting example(s) of such an oligonucleotide include: WV-8679.

[00922] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: O, and 4 or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12101, WV-9394, WV-9396, WV-9398.

[00923] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: O, and 5 or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12101, WV-9394, WV-9396, WV-9398.

[00924] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: O, and 6 or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12101, WV-9394, WV-9396, WV-9398.

[00925] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: O, and two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12105.

[00926] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: O, and two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12109.

[00927] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: O, and two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12107.

[00928] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: O, R and S. Non-limiting example(s) of such an oligonucleotide include: WV-12100, WV-12099, WV-12103, WV-12101.

[00929] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: O, R, and 4 or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12099, WV-12103.

[00930] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OR, and two or more consecutive S, and R, and two or more consecutive S, and RO. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[00931] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OR, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[00932] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OR, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[00933] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: OR, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00934] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: R, and two or more consecutive S, and R, and two or more consecutive S, and R. Non-limiting example(s) of such an oligonucleotide include: WV-11533, WV-12110, WV-12112, WV-13303, WV-13304, WV-8083, WV-8102, WV-8108, WV-8575, WV-8581, WV-8587, WV-8593, WV-9058.

[00935] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: R, and two or more consecutive S, and R, and two or more consecutive S, and R. Non-limiting example(s) of such an oligonucleotide include: WV-9059.

[00936] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12111.

[00937] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: R, and two or more consecutive S, and R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-10244, WV-10246, WV-9872.

[00938] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: R, and two or more consecutive S, and R, and two or more

consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9874.

[00939] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: R, and two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-10250, WV-10253, WV-8560, WV-9859, WV-9861.

[00940] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: R, and two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-9869.

[00941] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-10251, WV-10254, WV-11958, WV-11962, WV-12100, WV-9670, WV-9862.

[00942] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9870.

[00943] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: R, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[00944] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SO, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9394.

[00945] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SO, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9396.

[00946] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SO, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9398.

[00947] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SO, and two or more consecutive S, and O, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9395, WV-9397.

[00948] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SO, and two or more consecutive S, and O, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9399.

[00949] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12893.

[00950] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-13312, WV-13313, WV-14087, WV-7603, WV-7605, WV-7659, WV-8005, WV-8007, WV-8009, WV-8011, WV-8452, WV-8454.

[00951] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8456.

[00952] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8259.

[00953] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-11532, WV-11965, WV-11967, WV-13305, WV-13306, WV-13307, WV-14552, WV-7124, WV-7130, WV-7601, WV-7604, WV-7606, WV-7658, WV-8006, WV-8008, WV-8010, WV-8012, WV-8101, WV-8107, WV-8321, WV-8453, WV-8455, WV-8580, WV-8586, WV-8592.

[00954] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9508.

[00955] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S, and R, and two or more consecutive S, and R. Non-limiting example(s) of such an oligonucleotide include: WV-11114, WV-12503, WV-12504, WV-12505, WV-13809, WV-14349, WV-8043, WV-8044, WV-8045, WV-8046, WV-8047, WV-8048, WV-8257.

[00956] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S, and R, and two or more consecutive S, and R. Non-limiting example(s) of such an oligonucleotide include: WV-9696.

[00957] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S, and R, and two or more consecutive S, and R. Non-limiting example(s) of such an oligonucleotide include: WV-9697.

[00958] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S, and R, and two or more consecutive S, and R. Non-limiting example(s) of such an oligonucleotide include: WV-9698.

[00959] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-11533, WV-12110, WV-12112, WV-13303, WV-13304, WV-8083, WV-8102, WV-8108, WV-8575, WV-8581, WV-8587, WV-8593.

[00960] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-9058.

[00961] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S, and R, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-9059.

[00962] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S, and R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12111.

[00963] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-13308, WV-13309, WV-13310, WV-13311, WV-9505.

[00964] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: SR, and two or more consecutive S, and RS. Non-limiting example(s) of such an oligonucleotide include: WV-9509.

[00965] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-8810.

[00966] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-980.

[00967] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10406, WV-10407, WV-10408, WV-10409, WV-10410, WV-10411, WV-10412, WV-10413, WV-10414, WV-10415, WV-10416, WV-10417.

[00968] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10418, WV-10419, WV-10420, WV-10421, WV-10422, WV-10423, WV-10424, WV-10425, WV-10426.

[00969] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10427.

[00970] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12484, WV-12486, WV-12977, WV-12978, WV-12979, WV-12980, WV-12981, WV-12982, WV-12983, WV-12984, WV-12985, WV-12986, WV-12987, WV-12988, WV-12989, WV-12990.

[00971] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12991.

[00972] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-13005, WV-13006, WV-13007, WV-13008, WV-13804, WV-13805, WV-3421, WV-3662, WV-3688, WV-3690, WV-6408, WV-6474, WV-6936.

[00973] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-6951.

[00974] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10406, WV-10407, WV-10408, WV-10409, WV-10410, WV-10411, WV-10412, WV-10413, WV-10414, WV-10415, WV-10416, WV-10417, WV-10418, WV-10419, WV-10420, WV-10421, WV-10422.

[00975] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10423.

[00976] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10424, WV-10425, WV-10426, WV-10427, WV-11966, WV-12113, WV-12114, WV-12439, WV-12440, WV-12441, WV-12442, WV-12443, WV-12444, WV-12485, WV-12582, WV-12583, WV-12947, WV-12948, WV-12949, WV-12950, WV-12951, WV-12952.

[00977] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12953.

[00978] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a core comprises: two or more O, two or more R, and two or more S. Non-limiting example(s) of such an oligonucleotide include: WV-12100, WV-12099, WV-12103, WV-12101.

[00979] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format, a first and/or a second wing can comprise any internucleotidic linkage described herein or known in the art, or any pattern or combination of two or more different internucleotidic linkages, wherein R = PS (phosphorothioate) in the Rp configuration, S = PS in the Sp configuration, O = PO (phosphodiester), and X is a stereorandom (not chirally controlled) PS, and nX = a non-negatively charged (e.g., neutral) internucleotidic linkage.

[00980] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S and nX; and a second wing comprises: S and no nX. Non-limiting example(s) of such an oligonucleotide include: WV-15361.

[00981] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S and nX; and a second wing comprises: S and O. Non-limiting example(s) of such an oligonucleotide include: WV-15361.

[00982] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S and nX; and a second wing comprises: S and O and no nX. Non-limiting example(s) of such an oligonucleotide include: WV-15361.

[00983] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: nX; and a second wing comprises: no nX. Non-limiting example(s) of such an oligonucleotide include: WV-11533, WV-14556, WV-14557, WV-14558, WV-14559, WV-14560, WV-14561, WV-14562, WV-14563, WV-14564.

[00984] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: nX and O; and a second wing comprises: S. Non-limiting example(s) of such an oligonucleotide include: WV-14556, WV-14557, WV-14558, WV-14559, WV-14560, WV-14561, WV-14562, WV-14563, WV-14564.

[00985] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: nX and O; and a second wing comprises: two or more S. Non-limiting example(s) of such an oligonucleotide include: WV-14556, WV-14557, WV-14558, WV-14559, WV-14560, WV-14561, WV-14562, WV-14563, WV-14564.

[00986] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X and 2 or more consecutive O; and a second wing comprises: 2 or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10249, and WV-10252.

[00987] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: XOOOOO; and a second wing comprises: XXXXXX. Non-limiting example(s) of such an oligonucleotide include: WV-12109.

[00988] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: XOOO; and a second wing comprises: XXXX. Non-limiting example(s) of such an oligonucleotide include: WV-10249, and WV-10252.

[00989] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S and 2 or more consecutive O; and a second wing comprises: 2 or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-10250, and WV-10251.

[00990] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SOOO; and a second wing comprises: SSSS. Non-limiting example(s) of such an oligonucleotide include: WV-10250, and WV-10251.

[00991] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SOOOOO; and a second wing comprises: SSSSSS. Non-limiting example(s) of such an oligonucleotide include: WV-11962.

[00992] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive S; and a second wing comprises: 2 or more consecutive R. Non-limiting example(s) of such an oligonucleotide include: WV-8044.

[00993] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SSSS; and a second wing comprises: RRRR. Non-limiting example(s) of such an oligonucleotide include: WV-8044.

[00994] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive S; and a second wing comprises: 2 or more consecutive O and S. Non-limiting example(s) of such an oligonucleotide include: WV-8045.

[00995] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SSSS; and a second wing comprises: OOOS. Non-limiting example(s) of such an oligonucleotide include: WV-8045.

[00996] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: 2 or more consecutive S; and a second wing comprises: 2 or more consecutive O R. Non-limiting example(s) of such an oligonucleotide include: WV-8047.

[00997] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SSSS; and a second wing comprises: OOOR. Non-limiting example(s) of such an oligonucleotide include: WV-8047.

[00998] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10426, WV-10427, WV-3174, WV-3536, WV-3542, WV-9431, WV-9432, WV-9433, WV-9434, WV-9435.

[00999] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive X; and/or a second wing comprises: XX, and two or more consecutive O, and X. Non-limiting example(s) of such an oligonucleotide include: WV-12445, WV-12446, WV-12447, WV-12448, WV-12449, WV-12450, WV-12451, WV-12977, WV-12978, WV-12979, WV-12980, WV-12981, WV-12982, WV-12983, WV-12984, WV-12985, WV-12986, WV-12987, WV-12988, WV-12989, WV-12990, WV-12991, WV-12992, WV-12993, WV-12994, WV-12995, WV-12996, WV-12997, WV-12998, WV-12999, WV-13000, WV-13001, WV-13002, WV-13003, WV-13004, WV-13005, WV-13006, WV-13007, WV-13008, WV-8844, WV-8846, WV-8847, WV-8849, WV-8851, WV-8853, WV-8855, WV-8857, WV-8858, WV-8860.

[001000] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: XO, and two or more consecutive X; and/or a second wing comprises: XX, and two or more consecutive O, and XX. Non-limiting example(s) of such an oligonucleotide include: WV-8110.

[001001] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and XXX; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-8553.

[001002] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and XXX; and/or a second wing comprises: XX, and two or more consecutive O, and XX. Non-limiting example(s) of such an oligonucleotide include: WV-8555.

[001003] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and XX; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10406, WV-10407, WV-10408, WV-10409, WV-10410, WV-10411, WV-10412, WV-10413, WV-10414, WV-10415, WV-10416, WV-10417, WV-10418, WV-10419, WV-10420, WV-10421, WV-10422.

[001004] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and XX; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10423, WV-10424, WV-10425, WV-11966, WV-12113, WV-12439, WV-12440, WV-12441, WV-12442, WV-12443, WV-12444, WV-12582, WV-12583, WV-12947, WV-12948, WV-12949, WV-12950, WV-12951, WV-12952, WV-12953.

[001005] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and XX; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12954, WV-12955, WV-12956, WV-12957, WV-12958, WV-12959, WV-12960, WV-12961, WV-12962, WV-12963, WV-12964, WV-12965, WV-12966, WV-12967, WV-12968, WV-12969, WV-12970, WV-12971, WV-12972, WV-12973, WV-12974, WV-12975, WV-12976, WV-8548, WV-8550, WV-8552, WV-8556, WV-8594, WV-8595, WV-8609, WV-8617, WV-8656, WV-8664, WV-8672, WV-8684, WV-8688.

[001006] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and XX; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-8690, WV-8845, WV-8848, WV-8850, WV-8852, WV-8854, WV-8856, WV-8859, WV-9441, WV-9442, WV-9443, WV-9444, WV-9445, WV-9486, WV-9487, WV-9488, WV-9489, WV-9490, WV-9491, WV-9492, WV-9494, WV-9510, WV-9533, WV-9885, WV-9887, WV-9891, WV-9894.

[001007] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and XX; and/or a second wing comprises: XXXOXX. Non-limiting example(s) of such an oligonucleotide include: WV-8551, WV-8693, WV-9061.

[001008] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and XX; and/or a second wing comprises: XXOXXX. Non-limiting example(s) of such an oligonucleotide include: WV-9060, WV-8547, WV-8549, WV-8554, WV-8557, WV-8696.

[001009] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and XX; and/or a second wing comprises: XX, and two or more consecutive O, and X. Non-limiting example(s) of such an oligonucleotide include: WV-11963, WV-11964, WV-12480, WV-12481, WV-12482, WV-12483, WV-12484, WV-12486, WV-3421, WV-3662, WV-3688, WV-3690, WV-6408, WV-6474, WV-6936, WV-6951, WV-6952, WV-6969, WV-6976, WV-6981, WV-6982, WV-6989, WV-7002, WV-7027, WV-7118, WV-7805, WV-8109, WV-9436, WV-9437, WV-9438, WV-9439, WV-9440, WV-9493, WV-9694, WV-9695, WV-12485.

[001010] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and XX; and/or a second wing comprises: XX, and two or more consecutive Xn, and X. Non-limiting example(s) of such an oligonucleotide include: WV-13804.

[001011] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12114.

[001012] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12107.

[001013] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive Xn, and XX; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-13803.

[001014] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive Xn, and XX; and/or a second wing comprises: XX, and two or more consecutive Xn, and X. Non-limiting example(s) of such an oligonucleotide include: WV-13805.

[001015] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8315, WV-8311.

[001016] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S; and/or a second wing comprises:

SR, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8318.

[001017] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S O, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8122.

[001018] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S O, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8114.

[001019] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S O, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8125.

[001020] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S O, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8117.

[001021] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S O, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8314.

[001022] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S, and, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8124, WV-8116.

[001023] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S, and, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8128, WV-8129, WV-8120, WV-8121.

[001024] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SO, and two or more consecutive S; and/or a second wing

comprises: two or more consecutive S, and, and two or more consecutive O, and, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8108, WV-8107, WV-8106, WV-8105, WV-8104, WV-8103.

[001025] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SOSO, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8123.

[001026] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SOSO, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8115.

[001027] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SOSO, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8127.

[001028] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SOSO, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8119.

[001029] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8476.

[001030] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S; and/or a second wing comprises: two or more consecutive S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8475.

[001031] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S; and/or a second wing comprises: two or more consecutive S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8474.

[001032] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more

consecutive S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8473.

[001033] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8472.

[001034] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8587, WV-9395, WV-9397, WV-9399, WV-9394, WV-9396, WV-9398, WV-11967, WV-7606, WV-8012, WV-8586, WV-9508, WV-9505, WV-9509, WV-12893, WV-14087, WV-7605, WV-8011, WV-8569, WV-8614, WV-9530, WV-8615, WV-9531, WV-8568, WV-8585, WV-8601, WV-8653, WV-8661, WV-8669, WV-8681, WV-8685, WV-8606.

[001035] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8654, WV-8662, WV-8670, WV-8682, WV-8686, WV-8584, WV-9507, WV-8583, WV-8619, WV-9506, WV-9532, WV-8582, WV-8602, WV-8605, WV-8616, WV-8655, WV-8663, WV-8671, WV-8683.

[001036] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8687.

[001037] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S O, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9059, WV-8455, WV-8454, WV-8692, WV-8691.

[001038] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8126.

[001039] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more

consecutive S, and; and/or a second wing comprises: two or more consecutive S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8118.

[001040] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and O, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9058.

[001041] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8593, WV-7604, WV-8010, WV-8592, WV-7603, WV-8009, WV-8695, WV-8591, WV-8694, WV-8590, WV-8589.

[001042] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8588, WV-8083, WV-8102, WV-11965, WV-7124, WV-7130, WV-8101, WV-8453, WV-8452, WV-8100, WV-8246, WV-8603, WV-8608, WV-8099, WV-8098, WV-8097, WV-8248.

[001043] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8250.

[001044] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive Xn, and S. Non-limiting example(s) of such an oligonucleotide include: WV-13303.

[001045] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and RS; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12110, WV-12111, WV-13306, WV-13310, WV-9886, WV-9892, WV-11960.

[001046] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and RS; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9893.

[001047] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and RS; and/or a second wing comprises: SR, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9888, WV-9895, WV-9896.

[001048] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and RS; and/or a second wing comprises: SR, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-9889.

[001049] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and RS; and/or a second wing comprises: SR, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-9890.

[001050] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12112.

[001051] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[001052] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O; and/or a second wing comprises: R, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[001053] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive Xn, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-11533.

[001054] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive Xn, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-11532.

[001055] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive Xn, and, and two or more

consecutive S, and; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-13312.

[001056] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive Xn, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive Xn, and S. Non-limiting example(s) of such an oligonucleotide include: WV-13304.

[001057] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive Xn, and RS; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-13307.

[001058] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive Xn, and RS; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-13311.

[001059] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive R, and S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive R. Non-limiting example(s) of such an oligonucleotide include: WV-8313.

[001060] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive R, and S; and/or a second wing comprises: S, and two or more consecutive R. Non-limiting example(s) of such an oligonucleotide include: WV-7601, WV-8317.

[001061] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive R, and S; and/or a second wing comprises: S, and two or more consecutive R. Non-limiting example(s) of such an oligonucleotide include: WV-7657.

[001062] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive R, and ORS; and/or a second wing comprises: SR, and two or more consecutive O, and, and two or more consecutive R. Non-limiting example(s) of such an oligonucleotide include: WV-8322.

[001063] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive R, and, and two or more consecutive O, and RS; and/or a second wing comprises: SR, and two or more consecutive O, and, and two or more consecutive R. Non-limiting example(s) of such an oligonucleotide include: WV-8321.

[001064] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive R, and, and two or more consecutive O, and RS; and/or a second wing comprises: SR, and two or more consecutive O, and, and two or more consecutive R. Non-limiting example(s) of such an oligonucleotide include: WV-8329.

[001065] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and RS; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8575, WV-8008, WV-13308, WV-8007, WV-8471, WV-8470, WV-8573.

[001066] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and RS; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8572, WV-8571.

[001067] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and RS; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8570.

[001068] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and RS; and/or a second wing comprises: two or more consecutive S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8469.

[001069] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and RS; and/or a second wing comprises: two or more consecutive S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8468.

[001070] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and RS; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8581, WV-8006, WV-8580, WV-8005, WV-8579, WV-8578, WV-8577.

[001071] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and RS; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8576.

[001072] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and RS; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8456, WV-8467, WV-8466.

[001073] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and RS; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8312.

[001074] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and RS; and/or a second wing comprises: SR, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-14552.

[001075] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and RS; and/or a second wing comprises: SR, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-7658.

[001076] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and RS; and/or a second wing comprises: SR, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-7659.

[001077] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and RS; and/or a second wing comprises: SR, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8316.

[001078] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive Xn, and RS; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-13305.

[001079] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive Xn, and RS; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-13309.

[001080] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive Xn, and RS; and/or a second

wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-13313.

[001081] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-8448.

[001082] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-8809.

[001083] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OX, and two or more consecutive O, and X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10243, WV-10245, WV-10249, WV-10252, WV-8600, WV-8613, WV-8628, WV-8632, WV-8640, WV-8648, WV-8668, WV-8676, WV-8680, WV-8689, WV-8697, WV-9529, WV-9593, WV-9860, WV-9868, WV-9871.

[001084] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OX, and two or more consecutive O, and X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-9873.

[001085] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OX, and two or more consecutive O, and X; and/or a second wing comprises: XX, and two or more consecutive O, and X. Non-limiting example(s) of such an oligonucleotide include: WV-8132.

[001086] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OX, and two or more consecutive O; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12105.

[001087] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OX, and two or more consecutive O; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12109.

[001088] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing

comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8043.

[001089] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive R. Non-limiting example(s) of such an oligonucleotide include: WV-8044.

[001090] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive R. Non-limiting example(s) of such an oligonucleotide include: WV-8257.

[001091] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive R. Non-limiting example(s) of such an oligonucleotide include: WV-8259.

[001092] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8045.

[001093] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8046.

[001094] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8047.

[001095] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8048.

[001096] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-11114, WV-12503, WV-13809, WV-14349, WV-9696, WV-9697, WV-9698, WV-9380, WV-9381,

WV-9421, WV-9062, WV-9063, WV-8610, WV-8629, WV-9526, WV-9590, WV-8611, WV-9527, WV-9591, WV-8562, WV-8564, WV-8620, WV-8637, WV-8645, WV-8665, WV-8673, WV-8677, WV-8597, WV-8625, WV-8638, WV-8646, WV-8666, WV-8674, WV-8678, WV-8618, WV-9528, WV-9592, WV-8563.

[001097] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8565, WV-8596, WV-8612, WV-8621, WV-8624, WV-8639, WV-8647, WV-8667, WV-8675.

[001098] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8679.

[001099] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S O, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9285.

[001100] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S O, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9286.

[001101] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8566.

[001102] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8599.

[001103] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8567.

[001104] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and R; and/or a second

wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-10244, WV-9872, WV-10250, WV-9869, WV-10251, WV-11958.

[001105] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and R; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-11962.

[001106] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and R; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9870.

[001107] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and R; and/or a second wing comprises: SR, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-10246, WV-9874, WV-10253, WV-9861, WV-10254.

[001108] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and R; and/or a second wing comprises: SR, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9862.

[001109] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and R; and/or a second wing comprises: SR, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-9859.

[001110] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and R; and/or a second wing comprises: SR, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-9670.

[001111] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12099.

[001112] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12103.

[001113] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive Xn, and S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12504.

[001114] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive Xn, and S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12505.

[001115] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OR, and two or more consecutive O, and R; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8560.

[001116] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive O, and XX; and/or a second wing comprises: XXX, and two or more consecutive O. Non-limiting example(s) of such an oligonucleotide include: WV-980.

[001117] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10426, WV-10427, WV-3174, WV-3536, WV-3542, WV-9431, WV-9432, WV-9433, WV-9434.

[001118] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-9435.

[001119] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive X; and/or a second wing comprises: X, and two or more consecutive O, and X. Non-limiting example(s) of such an oligonucleotide include: WV-12445, WV-12446, WV-12447, WV-12448, WV-12449, WV-12450, WV-12451, WV-12977, WV-12978, WV-12979, WV-12980, WV-12981.

[001120] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive X; and/or a second wing comprises: X, and two or more consecutive O, and X. Non-limiting example(s) of such an oligonucleotide include: WV-12982, WV-12983, WV-12984, WV-12985, WV-12986, WV-12987, WV-12988, WV-12989, WV-12990, WV-12991, WV-12992, WV-12993, WV-12994, WV-12995, WV-12996, WV-12997, WV-12998, WV-12999, WV-13000.

[001121] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive X; and/or a second wing comprises: X, and two or more consecutive O, and X. Non-limiting example(s) of such an oligonucleotide include: WV-13001, WV-13002, WV-13003, WV-13004, WV-13005, WV-13006, WV-13007, WV-13008, WV-8844, WV-8846, WV-8847, WV-8849, WV-8851, WV-8853, WV-8855, WV-8857, WV-8858.

[001122] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive X; and/or a second wing comprises: X, and two or more consecutive O, and X. Non-limiting example(s) of such an oligonucleotide include: WV-8860.

[001123] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: XOXXX; and/or a second wing comprises: X, and two or more consecutive O, and XX. Non-limiting example(s) of such an oligonucleotide include: WV-8110.

[001124] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and XX; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-8553.

[001125] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and XX; and/or a second wing comprises: X, and two or more consecutive O, and XX. Non-limiting example(s) of such an oligonucleotide include: WV-8555.

[001126] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10406, WV-10407, WV-10408.

[001127] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10409, WV-10410, WV-10411, WV-10412, WV-10413, WV-10414, WV-10415, WV-10416, WV-10417, WV-10418, WV-10419.

[001128] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-10420, WV-10421, WV-10422, WV-10423, WV-10424, WV-10425, WV-11966, WV-12113, WV-

12439, WV-12440, WV-12441, WV-12442, WV-12443, WV-12444, WV-12582, WV-12583, WV-12947, WV-12948, WV-12949, WV-12950, WV-12951, WV-12952, WV-12953.

[001129] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12954, WV-12955, WV-12956, WV-12957, WV-12958, WV-12959, WV-12960, WV-12961, WV-12962, WV-12963, WV-12964, WV-12965, WV-12966, WV-12967, WV-12968, WV-12969, WV-12970, WV-12971, WV-12972, WV-12973, WV-12974, WV-12975, WV-12976, WV-8548.

[001130] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-8550, WV-8552, WV-8556, WV-8594, WV-8595, WV-8609, WV-8617, WV-8656, WV-8664, WV-8672, WV-8684, WV-8688, WV-8690, WV-8845, WV-8848, WV-8850, WV-8852, WV-8854, WV-8856, WV-8859, WV-9441, WV-9442, WV-9443, WV-9444.

[001131] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-9445, WV-9486, WV-9487, WV-9488, WV-9489, WV-9490, WV-9491, WV-9492, WV-9494, WV-9510, WV-9533, WV-9885, WV-9887, WV-9891.

[001132] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-9894.

[001133] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: XXOXX. Non-limiting example(s) of such an oligonucleotide include: WV-8551, WV-8693.

[001134] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: XXOXX. Non-limiting example(s) of such an oligonucleotide include: WV-9061.

[001135] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: XOXXX. Non-limiting example(s) of such an oligonucleotide include: WV-9060.

[001136] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: X, and two or more consecutive O, and XX. Non-limiting example(s) of such an oligonucleotide include: WV-8547, WV-8549, WV-8554, WV-8557.

[001137] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: X, and two or more consecutive O, and XX. Non-limiting example(s) of such an oligonucleotide include: WV-8696.

[001138] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: X, and two or more consecutive O, and X. Non-limiting example(s) of such an oligonucleotide include: WV-11963, WV-11964, WV-12480, WV-12481, WV-12482, WV-12483, WV-12484, WV-12486, WV-3421, WV-3662, WV-3688, WV-3690, WV-6408, WV-6474, WV-6936, WV-6951, WV-6952, WV-6969, WV-6976, WV-6981, WV-6982, WV-6989, WV-7002, WV-7027, WV-7118, WV-7805, WV-8109, WV-9436, WV-9437, WV-9438, WV-9439, WV-9440, WV-9493, WV-9694.

[001139] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: X, and two or more consecutive O, and X. Non-limiting example(s) of such an oligonucleotide include: WV-9695.

[001140] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: X, and two or more consecutive O, and X. Non-limiting example(s) of such an oligonucleotide include: WV-12485.

[001141] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O, and X; and/or a second wing comprises: X, and two or more consecutive Xn, and X. Non-limiting example(s) of such an oligonucleotide include: WV-13804.

[001142] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12107.

[001143] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive O; and/or a second wing

comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12114.

[001144] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: XnXnXnXX; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-13803.

[001145] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: X, and two or more consecutive Xn, and X; and/or a second wing comprises: X, and two or more consecutive Xn, and X. Non-limiting example(s) of such an oligonucleotide include: WV-13805.

[001146] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8315.

[001147] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8311.

[001148] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S; and/or a second wing comprises: R, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8318.

[001149] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S OS; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8122.

[001150] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S OS; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8114.

[001151] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S OS; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8125.

[001152] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S OS; and/or a second wing

comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8117.

[001153] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S OS; and/or a second wing comprises: S, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8314.

[001154] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S, and, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8124.

[001155] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S, and, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8116.

[001156] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S, and, and two or more consecutive O, and S; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8128, WV-8129, WV-8120.

[001157] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive S, and, and two or more consecutive O, and S; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8121.

[001158] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SO, and two or more consecutive S; and/or a second wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and. Non-limiting example(s) of such an oligonucleotide include: WV-8108, WV-8107, WV-8106, WV-8105, WV-8104.

[001159] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SO, and two or more consecutive S; and/or a second wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and. Non-limiting example(s) of such an oligonucleotide include: WV-8103.

[001160] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SOSOS; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8123.

[001161] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SOSOS; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8115.

[001162] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SOSOS; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8127.

[001163] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: SOSOS; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8119.

[001164] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8476.

[001165] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8475.

[001166] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8474.

[001167] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8473.

[001168] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8472.

[001169] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8587, WV-9395, WV-9397, WV-9399, WV-9394, WV-9396, WV-9398, WV-11967, WV-7606.

[001170] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8012, WV-8586, WV-9508, WV-9505, WV-9509, WV-12893, WV-14087, WV-7605, WV-8011, WV-8569, WV-8614, WV-9530, WV-8615, WV-9531, WV-8568, WV-8585, WV-8601, WV-8653, WV-8661.

[001171] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8669, WV-8681, WV-8685, WV-8606, WV-8654, WV-8662, WV-8670, WV-8682, WV-8686, WV-8584, WV-9507, WV-8583, WV-8619, WV-9506, WV-9532, WV-8582, WV-8602, WV-8605, WV-8616, WV-8655, WV-8663, WV-8671, WV-8683.

[001172] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8687.

[001173] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S, and O, and two or more consecutive S, and. Non-limiting example(s) of such an oligonucleotide include: WV-9059, WV-8455, WV-8454, WV-8692.

[001174] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S, and O, and two or more consecutive S, and. Non-limiting example(s) of such an oligonucleotide include: WV-8691.

[001175] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8126.

[001176] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8118.

[001177] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second

wing comprises: SO, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9058.

[001178] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and. Non-limiting example(s) of such an oligonucleotide include: WV-8593, WV-7604.

[001179] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and. Non-limiting example(s) of such an oligonucleotide include: WV-8010.

[001180] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and. Non-limiting example(s) of such an oligonucleotide include: WV-8592, WV-7603, WV-8009, WV-8695, WV-8591, WV-8694, WV-8590, WV-8589.

[001181] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and. Non-limiting example(s) of such an oligonucleotide include: WV-8588.

[001182] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8083, WV-8102, WV-11965, WV-7124, WV-7130, WV-8101, WV-8453, WV-8452, WV-8100, WV-8246, WV-8603, WV-8608, WV-8099, WV-8098, WV-8097, WV-8248.

[001183] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8250.

[001184] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and S; and/or a second wing comprises: S, and two or more consecutive Xn, and S. Non-limiting example(s) of such an oligonucleotide include: WV-13303.

[001185] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and R; and/or a second

wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12110, WV-12111, WV-13306, WV-13310, WV-9886, WV-9892, WV-11960.

[001186] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and R; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9893.

[001187] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and R; and/or a second wing comprises: R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9888.

[001188] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and R; and/or a second wing comprises: R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9895.

[001189] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and R; and/or a second wing comprises: R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9896.

[001190] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and R; and/or a second wing comprises: R, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-9889.

[001191] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O, and R; and/or a second wing comprises: R, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-9890.

[001192] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12101.

[001193] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12112.

[001194] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive O; and/or a second wing comprises: two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-12100.

[001195] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive Xn, and S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-11533.

[001196] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive Xn, and S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-11532.

[001197] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive Xn, and S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-13312.

[001198] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive Xn, and S; and/or a second wing comprises: S, and two or more consecutive Xn, and S. Non-limiting example(s) of such an oligonucleotide include: WV-13304.

[001199] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive Xn, and R; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-13307.

[001200] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: S, and two or more consecutive Xn, and R; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-13311.

[001201] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive R, and; and/or a second wing comprises: S, and two or more consecutive R, and. Non-limiting example(s) of such an oligonucleotide include: WV-8313.

[001202] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive R, and; and/or a second wing

comprises: two or more consecutive R, and. Non-limiting example(s) of such an oligonucleotide include: WV-7601.

[001203] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive R, and; and/or a second wing comprises: two or more consecutive R, and. Non-limiting example(s) of such an oligonucleotide include: WV-8317.

[001204] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive R, and; and/or a second wing comprises: two or more consecutive R, and. Non-limiting example(s) of such an oligonucleotide include: WV-7657.

[001205] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive R, and OR; and/or a second wing comprises: R, and two or more consecutive O, and, and two or more consecutive R, and. Non-limiting example(s) of such an oligonucleotide include: WV-8322.

[001206] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive R, and, and two or more consecutive O, and R; and/or a second wing comprises: R, and two or more consecutive O, and, and two or more consecutive R, and. Non-limiting example(s) of such an oligonucleotide include: WV-8321.

[001207] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive R, and, and two or more consecutive O, and R; and/or a second wing comprises: R, and two or more consecutive O, and, and two or more consecutive R, and. Non-limiting example(s) of such an oligonucleotide include: WV-8329.

[001208] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and R; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8575, WV-8008, WV-13308, WV-8007, WV-8471, WV-8470, WV-8573, WV-8572, WV-8571.

[001209] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and R; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8570.

[001210] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and R; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8469.

[001211] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and R; and/or a second wing comprises: two or more consecutive S, and, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8468.

[001212] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and R; and/or a second wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and. Non-limiting example(s) of such an oligonucleotide include: WV-8581, WV-8006, WV-8580, WV-8005, WV-8579, WV-8578, WV-8577.

[001213] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and R; and/or a second wing comprises: S, and two or more consecutive O, and, and two or more consecutive S, and. Non-limiting example(s) of such an oligonucleotide include: WV-8576.

[001214] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and R; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8456, WV-8467.

[001215] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and R; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8466.

[001216] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and R; and/or a second wing comprises: S, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8312.

[001217] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and R; and/or a second wing comprises: R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-14552.

[001218] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and R; and/or a second wing comprises: R, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-7658, WV-7659.

[001219] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive O, and R; and/or a second wing comprises: R, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8316.

[001220] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive Xn, and R; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-13305.

[001221] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive Xn, and R; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-13309.

[001222] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: R, and two or more consecutive Xn, and R; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-13313.

[001223] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive X; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-8810, WV-8448, WV-8809.

[001224] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OX, and two or more consecutive O, and; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-12105, WV-12109, WV-10243, WV-10245, WV-10249, WV-10252, WV-8600, WV-8613.

[001225] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OX, and two or more consecutive O, and; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-8628, WV-8632, WV-8640, WV-8648, WV-8668, WV-8676, WV-8680, WV-8689, WV-8697, WV-9529, WV-9593, WV-9860, WV-9868, WV-9871.

[001226] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OX, and two or more consecutive O, and; and/or a second wing comprises: two or more consecutive X. Non-limiting example(s) of such an oligonucleotide include: WV-9873.

[001227] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OX, and two or more consecutive O, and; and/or a second wing comprises: X, and two or more consecutive O, and X. Non-limiting example(s) of such an oligonucleotide include: WV-8132.

[001228] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8043.

[001229] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing comprises: S, and two or more consecutive R, and. Non-limiting example(s) of such an oligonucleotide include: WV-8044, WV-8257.

[001230] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing comprises: S, and two or more consecutive R, and. Non-limiting example(s) of such an oligonucleotide include: WV-8259.

[001231] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8045.

[001232] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8046.

[001233] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing comprises: S, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8047.

[001234] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: O, and two or more consecutive S; and/or a second wing comprises: S, and two or more consecutive O, and R. Non-limiting example(s) of such an oligonucleotide include: WV-8048.

[001235] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and; and/or a second

wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12099, WV-12103, WV-10244, WV-9872, WV-10250, WV-9869, WV-10251, WV-11958.

[001236] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-11962, WV-9870, WV-11114, WV-12503, WV-13809, WV-14349, WV-9696, WV-9697, WV-9698, WV-9380, WV-9381, WV-9421, WV-9062, WV-9063, WV-8610, WV-8629, WV-9526, WV-9590.

[001237] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8611, WV-9527, WV-9591, WV-8562, WV-8564, WV-8620, WV-8637, WV-8645, WV-8665, WV-8673, WV-8677, WV-8597, WV-8625, WV-8638, WV-8646.

[001238] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8666, WV-8674, WV-8678, WV-8618, WV-9528, WV-9592, WV-8563, WV-8565, WV-8596, WV-8612, WV-8621, WV-8624, WV-8639, WV-8647, WV-8667, WV-8675.

[001239] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8679.

[001240] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and; and/or a second wing comprises: two or more consecutive S, and O, and two or more consecutive S, and. Non-limiting example(s) of such an oligonucleotide include: WV-9285.

[001241] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and; and/or a second wing comprises: two or more consecutive S, and O, and two or more consecutive S, and. Non-limiting example(s) of such an oligonucleotide include: WV-9286.

[001242] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8566.

[001243] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8599.

[001244] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and; and/or a second wing comprises: S, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-8567.

[001245] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and; and/or a second wing comprises: R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-10246, WV-9874, WV-10253, WV-9861, WV-10254.

[001246] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and; and/or a second wing comprises: R, and two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-9862.

[001247] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and; and/or a second wing comprises: R, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-9859.

[001248] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive O, and; and/or a second wing comprises: R, and two or more consecutive O, and S. Non-limiting example(s) of such an oligonucleotide include: WV-9670.

[001249] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive Xn, and; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12504.

[001250] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OS, and two or more consecutive Xn, and; and/or a second wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-12505.

[001251] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: OR, and two or more consecutive O, and; and/or a second

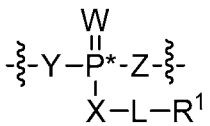
wing comprises: two or more consecutive S. Non-limiting example(s) of such an oligonucleotide include: WV-8560.

[001252] In some embodiments of an oligonucleotide, e.g., an oligonucleotide having an asymmetric format: a first wing comprises: two or more consecutive O, and X; and/or a second wing comprises: XX, and two or more consecutive O, and. Non-limiting example(s) of such an oligonucleotide include: WV-980.

[001253] In some embodiments, an oligonucleotide, e.g., an oligonucleotide having an asymmetric format can comprise any internucleotidic linkage described herein or known in the art.

[001254] A non-limiting example of an internucleotidic linkage or unmodified internucleotidic linkage is a phosphodiester; non-limiting examples of modified internucleotidic linkages include those in which one or more oxygen of a phosphodiester has been replaced by, as non-limiting examples, sulfur (as in a phosphorothioate), H, alkyl, or another moiety or element which is not oxygen. A non-limiting example of an internucleotidic linkage is a moiety which does not a comprise a phosphorus but serves to link two sugars. A non-limiting example of an internucleotidic linkage is a moiety which does not a comprise a phosphorus but serves to link two sugars in the backbone of an oligonucleotide. Disclosed herein are additional non-limiting examples of nucleotides, modified nucleotides, nucleotide analogs, internucleotidic linkages, modified internucleotidic linkages, bases, modified bases, and base analogs, sugars, modified sugars, and sugar analogs, and nucleosides, modified nucleosides, and nucleoside analogs.

[001255] In some embodiments, an internucleotidic linkage which has the structure of Formula **I**:



(I)

wherein:

P* is a symmetric phosphorus atom, or asymmetric phosphorus atom that 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 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–, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)-$, $-N(R')C(O)O-$, $-OC(O)N(R')-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-N(R')S(O)_2-$ –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 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)–, $-S(O)_2-$, $-S(O)_2N(R')-$, $-N(R')S(O)_2-$ –SC(O)–, –C(O)S–, –OC(O)–, and –C(O)O–

each R′ is independently –R, -C(O)R, $-CO_2R$, or $-SO_2R$, 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 $-\!\!\lesssim$ independently represents a connection to a nucleoside.

[001256] 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)–, $-S(O)_2-$, $-S(O)_2N(R')-$, $-N(R')S(O)_2-$, –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)–, $-S(O)_2-$, $-S(O)_2N(R')-$, $-N(R')S(O)_2-$, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–;

each R′ is independently –R, -C(O)R, $-CO_2R$, or $-SO_2R$, 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, and heterocyclylene;

each R is independently hydrogen, or an optionally substituted group selected from C_1–C_6 aliphatic,

phenyl, carbocyclyl, aryl, heteroaryl, and heterocyclyl; and

each $-\xi-$ independently represents a connection to a nucleoside.

[001257] 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. In some embodiments, a chirally controlled oligonucleotide comprises at least four phosphorothioate triester linkages. In some embodiments, a chirally controlled oligonucleotide comprises at least five phosphorothioate triester linkages. Examples of such modified internucleotidic phosphorus linkages are described further herein.

[001258] In some embodiments, a linkage of Formula **I** is chiral. 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. In some embodiments, a chirally controlled oligonucleotide is an oligonucleotide in a chirally controlled composition that is of the 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 non-random or controlled level of a plurality of oligonucleotides that share a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers, and the chirally controlled oligonucleotide shares the common base sequence, the common pattern of backbone linkages, and the common pattern of backbone chiral centers.

[001259] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide having an asymmetric format, wherein at least two of the individual internucleotidic linkages within the oligonucleotide have different stereochemistry and/or different P-modifications relative to one another. 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 relative to one another, and wherein at least a portion of the structure of the chirally controlled oligonucleotide is characterized by a repeating pattern of alternating stereochemisty.

[001260] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide having an asymmetric format, wherein at least two of the individual 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, wherein XLR^1 is equivalent to X-L-R^1 and X, L, and R^1 are as defined in Formula **I.**

[001261] 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. In some embodiments, a chirally controlled oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least four phosphorothioate triester linkages. In some embodiments, a chirally controlled oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least five phosphorothioate triester linkages. Examples of such modified internucleotidic phosphorus linkages are described further herein.

[001262] 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. In some embodiments, a phosphorothioate triester linkage is intentionally maintained until and/or during the administration to a

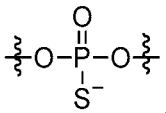
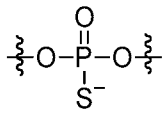
subject.

[001263] In some embodiments, a chirally controlled oligonucleotide is linked to a solid support. In some embodiments, a chirally controlled oligonucleotide is cleaved from a solid support.

[001264] In some embodiments, a chirally controlled oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least two consecutive modified internucleotidic linkages. In some embodiments, a chirally controlled oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least two consecutive phosphorothioate triester internucleotidic linkages.

[001265] In some embodiments, an oligonucleotide can comprise any internucleotidic linkage described herein or known in the art.

[001266] In some embodiments, the present disclosure provides oligonucleotides comprising one or more modified internucleotidic linkages independently having the structure of Formula **I**, disclosed herein. In some embodiments, a modified internucleotidic linkage is phosphorothioate. Examples of internucleotidic linkages having the structure of Formula **I** are widely known in the art.

[001267] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein at least one internucleotidic linkage has a chiral linkage phosphorus. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein at least one internucleotidic linkage has the structure of Formula **I**. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein each internucleotidic linkage has the structure of Formula **I**. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein at least one internucleotidic linkage has the structure of Formula **I-c**. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein each internucleotidic linkage has the structure of Formula **I-c**. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein at least one internucleotidic linkage is  . In some embodiments, the present disclosure provides a chirally controlled oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein each internucleotidic linkage is  .

[001268] 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. In some embodiments, a modified internucleotidic linkage has a structure of Formula **I**. In some embodiments, a modified internucleotidic linkage has a structure of Formula **I**-a.

[001269] In some embodiments, a modified internucleotidic linkage has a structure of Formula **I**. In some embodiments, a modified internucleotidic linkage has a structure of Formula **I-a**.

[001270] In some embodiments, a chirally controlled oligonucleotide is designed such that one or more nucleotides 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 described in the present disclosure. In some embodiments, an autorelease group comprises a morpholino group. In some embodiments, an autorelease group is characterized by the ability to deliver an agent to the internucleotidic phosphorus linker, which agent facilitates further modification of the phosphorus atom such as, *e.g.*, desulfurization. In some embodiments, the agent is water and the further modification is hydrolysis to form a phosphate diester as is found in naturally occurring DNA and RNA.

[001271] In some embodiments, a chiral internucleotidic linkage has the structure of Formula **I**, disclosed herein. In some embodiments, a chiral internucleotidic linkage is phosphorothioate. In some embodiments, each chiral internucleotidic linkage in a single oligonucleotide of a provided composition independently has the structure of Formula **I**, disclosed herein. In some embodiments, each chiral internucleotidic linkage in a single oligonucleotide of a provided composition is a phosphorothioate.

[001272] In some embodiments, a chirally controlled oligonucleotide is designed such that the resulting pharmaceutical properties are improved through one or more particular modifications at phosphorus. It is well documented in the art that certain oligonucleotides are rapidly degraded by nucleases and exhibit poor cellular uptake through the cytoplasmic cell membrane (Poijarvi-Virta *et al.*, Curr. Med. Chem. (2006), 13(28);3441-65; Wagner *et al.*, Med. Res. Rev. (2000), 20(6):417-51; Peyrottes *et al.*, Mini Rev. Med. Chem. (2004), 4(4):395-408; Gosselin *et al.*, (1996), 43(1):196-208; Bologna *et al.*, (2002), Antisense & Nucleic Acid Drug Development 12:33-41). For instance, Vives *et al.*, (Nucleic Acids Research (1999), 27(20):4071-76) found that tert-butyl SATE pro-oligonucleotides displayed markedly increased cellular penetration compared to the parent oligonucleotide.

[001273] 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. In certain embodiments, the present disclosure provides a chirally controlled oligonucleotide, wherein at least two individual internucleotidic linkages within the oligonucleotide have different P-modifications relative to one another. In certain embodiments, the present disclosure provides a chirally controlled oligonucleotide, wherein at least two of the individual internucleotidic linkages within the oligonucleotide have different P-modifications relative to one another, and wherein the chirally controlled oligonucleotide comprises at least one phosphate diester internucleotidic linkage. In certain embodiments, the present disclosure provides a chirally controlled oligonucleotide, wherein at least two of the individual internucleotidic linkages within the oligonucleotide have different P-modifications relative to one another, and wherein the chirally controlled oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least one phosphorothioate diester internucleotidic linkage. In certain embodiments, the present disclosure provides a chirally controlled oligonucleotide, wherein at least two of the individual internucleotidic linkages within the oligonucleotide have different P-modifications relative to one another, and wherein the chirally controlled oligonucleotide comprises at least one phosphorothioate triester internucleotidic linkage. In certain embodiments, the present disclosure provides a chirally controlled oligonucleotide, wherein at least two of the individual internucleotidic linkages within the oligonucleotide have different P-modifications relative to one another, and wherein the chirally controlled oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least one phosphorothioate triester internucleotidic linkage.

[001274] In some embodiments, provided oligonucleotides are capable of directing a decrease in the expression, level and/or activity of a target gene or its gene product. In some embodiments, a target gene comprises a repeat expansion. In some embodiments, provided oligonucleotides comprise any internucleotidic linkage described herein or known in the art.

[001275] In some embodiments, an oligonucleotide can comprise any internucleotidic linkage described herein or known in the art.

[001276] A non-limiting example of an internucleotidic linkage or unmodified internucleotidic linkage is a phosphodiester; non-limiting examples of modified internucleotidic linkages include those in which one or more oxygen of a phosphodiester has been replaced by, as non-limiting examples, sulfur (as in a phosphorothioate), H, alkyl, or another moiety or element which is not oxygen. A non-limiting example of an internucleotidic linkage is a moiety which does not a comprise a phosphorus but serves to link two sugars. A non-limiting example of an internucleotidic linkage is a moiety which does not a comprise a phosphorus but serves to link two sugars in the backbone of an oligonucleotide. Disclosed

herein are additional non-limiting examples of nucleotides, modified nucleotides, nucleotide analogs, internucleotidic linkages, modified internucleotidic linkages, bases, modified bases, and base analogs, sugars, modified sugars, and sugar analogs, and nucleosides, modified nucleosides, and nucleoside analogs.

[001277] 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. 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 relative to one another, and wherein at least a portion of the structure of the chirally controlled oligonucleotide is characterized by a repeating pattern of alternating stereochemisty.

[001278] In some embodiments, a chirally controlled oligonucleotide comprises one or more modified internucleotidic phosphorus linkages. Examples of such modified internucleotidic phosphorus linkages are described further herein.

[001279] 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. Examples of such modified internucleotidic phosphorus linkages are described further herein.

[001280] 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. In some embodiments, a phosphorothioate triester linkage is intentionally maintained until and/or during the administration to a subject.

[001281] In some embodiments, a chirally controlled oligonucleotide is linked to a solid support. In some embodiments, a chirally controlled oligonucleotide is cleaved from a solid support.

[001282] In some embodiments, a chirally controlled oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least two consecutive modified internucleotidic linkages. In some embodiments, a chirally controlled oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least two consecutive phosphorothioate triester internucleotidic linkages.

[001283] 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 such provided oligonucleotides are of the same type, *i.e.*, all have the same base sequence, pattern of backbone linkages (*i.e.*, pattern of internucleotidic linkage types,

for example, phosphate, phosphorothioate, etc), pattern of backbone chiral centers (*i.e.* pattern of linkage phosphorus stereochemistry (*R*p/*S*p)), and pattern of backbone phosphorus modifications (*e.g.*, pattern of "-XLR^1" groups in Formula **I**, disclosed herein). In some embodiments, all oligonucleotides of the same type are identical. In many embodiments, however, provided compositions comprise a plurality of oligonucleotides types, typically in pre-determined relative amounts.

[001284] In some embodiments, an oligonucleotide can comprise any internucleotidic linkage described herein or known in the art. In some embodiments, an oligonucleotide can comprise any internucleotidic linkage described herein or known in the art in combination with any other structural element or modification described herein, including but not limited to, base sequence or portion thereof, sugar, base (nucleobase); stereochemistry or combination or pattern thereof; additional chemical moiety, including but not limited to, a targeting moiety, a carbohydrate moiety, etc.; additional chemical moiety, including but not limited to, a targeting moiety, etc.; format or any structural element thereof, and/or any other structural element or modification described herein; and in some embodiments, the present disclosure pertains to multimers of any such oligonucleotides.

[001285] In some embodiments, the present disclosure provides oligonucleotides comprising one or more modified internucleotidic linkages independently having the structure of Formula **I**, disclosed herein.

[001286] In some embodiments of Formula **I**, P in T^{LD} is P^*. 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.

[001287] In some embodiments of Formula **I**, 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.

[001288] In some embodiments of Formula **I**, 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.

[001289] In some embodiments, each R is independently hydrogen, or an optionally substituted group selected from C_1–C_6 aliphatic, phenyl, carbocyclyl, aryl, heteroaryl, and heterocyclyl.

[001290] In some embodiments, R is hydrogen. In some embodiments, R is an optionally substituted group selected from C_1–C_6 aliphatic, phenyl, carbocyclyl, aryl, heteroaryl, and heterocyclyl.

[001291] In some embodiments, R is an optionally substituted C_1–C_6 aliphatic. In some embodiments, R is an optionally substituted C_1–C_6 alkyl. In some embodiments, R is optionally substituted, linear or branched hexyl. In some embodiments, R is optionally substituted, linear or branched pentyl. In some embodiments, R is optionally substituted, linear or branched butyl. In some embodiments, R is optionally substituted, linear or branched propyl. In some embodiments, R is optionally substituted ethyl. In some embodiments, R is optionally substituted methyl.

[001292] In some embodiments, R is optionally substituted phenyl. In some embodiments, R is substituted phenyl. In some embodiments, R is phenyl.

[001293] In some embodiments, R is optionally substituted carbocyclyl. In some embodiments, R is optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R is optionally substituted monocyclic carbocyclyl. In some embodiments, R is optionally substituted cycloheptyl. In some embodiments, R is optionally substituted cyclohexyl. In some embodiments, R is optionally substituted cyclopentyl. In some embodiments, R is optionally substituted cyclobutyl. In some embodiments, R is an optionally substituted cyclopropyl. In some embodiments, R is optionally substituted bicyclic carbocyclyl.

[001294] In some embodiments, R is an optionally substituted aryl. In some embodiments, R is an optionally substituted bicyclic aryl ring.

[001295] In some embodiments, R is an optionally substituted heteroaryl. 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.

[001296] In some embodiments, R is an optionally substituted 5-membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, sulfur, and oxygen. In some embodiments, R is an optionally substituted 6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001297] In some embodiments, R is an optionally substituted 5-membered monocyclic heteroaryl ring having 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R is selected from pyrrolyl, furanyl, and thienyl.

[001298] In some embodiments, R is an optionally substituted 5-membered heteroaryl ring having 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 5-membered heteroaryl ring having 1 nitrogen atom, and an additional heteroatom selected from sulfur and oxygen. Example R groups include optionally substituted pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl or isoxazolyl.

[001299] In some embodiments, R is a 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 2 nitrogen atoms. In certain embodiments, R is an optionally substituted 6-membered heteroaryl ring having 1 nitrogen. Example R groups include optionally substituted pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, or tetrazinyl.

[001300] 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.

[001301] 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. According to one aspect, 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 a quinazoline or a quinoxaline.

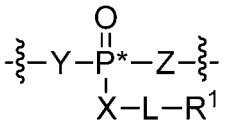
[001302] In some embodiments, R is an optionally substituted heterocyclyl. In some embodiments, R is an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is a substituted 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 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 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001303] In some embodiments, R is an optionally substituted heterocyclyl. 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 2 oxygen atom.

[001304] 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 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 is an optionally substituted 5-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[001305] In some embodiments, a structure of Formula I is a structure of Formula I as described in

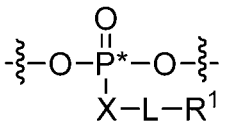
WO2017/210647.–In some embodiments, the internucleotidic linkage of Formula **I** has the structure of Formula **I-a**:



(I-a)

wherein each variable is independently described in the present disclosure, as in Formula **I**.

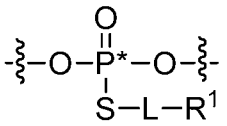
[001306] In some embodiments, the internucleotidic linkage of Formula **I** has the structure of Formula **I-b**:



(I-b)

wherein each variable is independently described in the present disclosure, as in Formula **I**.

[001307] In some embodiments, the internucleotidic linkage of Formula **I** is an phosphorothioate triester linkage having the structure of Formula **I-c**:



(I-c)

wherein:

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

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_2R, or –SO_2R, 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;

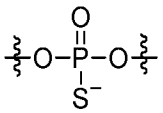
–Cy– is an optionally substituted bivalent ring selected from phenylene, carbocyclylene, arylene, heteroarylene, and heterocyclylene;

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

each $-\!\!\lesssim\!\!-$ independently represents a connection to a nucleoside; and

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

[001308] In some embodiments, the internucleotidic linkage having the structure of Formula **I** is



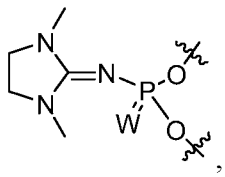
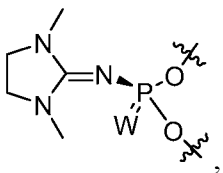
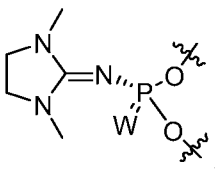
or an internucleotidic linkage as shown in the art, e.g., WO2017/210647.

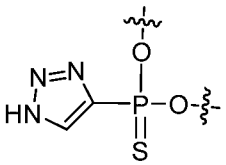
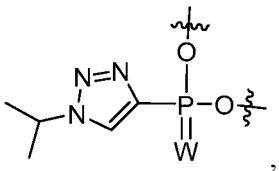
[001309] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising one or more phosphate diester linkages, and one or more modified internucleotide linkages having the formula of **I-a**, **I-b**, or **I-c**.

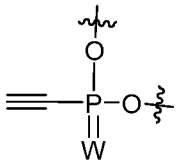
[001310] In some embodiments, a modified internucleotidic linkage has the structure of **I**. In some embodiments, a modified internucleotidic linkage has the structure of **I-a**. In some embodiments, a modified internucleotidic linkage has the structure of **I-b**. In some embodiments, a modified internucleotidic linkage has the structure of **I-c.**

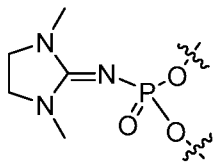
[001311] In some embodiments, a modified internucleotidic linkage is phosphorothioate. Examples of internucleotidic linkages having the structure of Formula **I** are widely known in the art, including but not limited to those described in US 20110294124, US 20120316224, US 20140194610, US 20150211006, US 20150197540, WO 2015107425, PCT/US2016/043542, and PCT/US2016/043598, each of which is incorporated herein by reference. In some embodiments, a modified internucleotidic linkage is a vinylphosphonate. Whittaker et al. 2008 Tetrahedron Letters 49: 6984–6987.

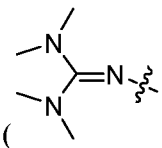
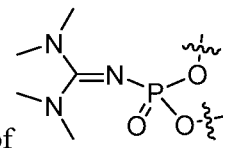
[001312] Non-limiting examples of internucleotidic linkages also include those described in the art, including, but not limited to, those described in any of: Gryaznov, S.; Chen, J.-K. J. Am. Chem. Soc. 1994, 116, 3143, Jones et al. J. Org. Chem. 1993, 58, 2983, Koshkin et al. 1998 Tetrahedron 54: 3607-3630, 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.

[001313] In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a neutral internucleotidic linkage. 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 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.

[001314] In some embodiments, an internucleotidic linkage comprising a triazole moiety (e.g., an optionally substituted triazolyl group) in a provided oligonucleotide, e.g., a C9orf72 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

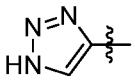
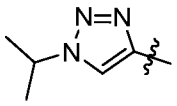


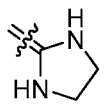
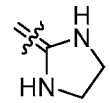
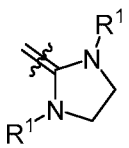
the formula of: , wherein W is O or S. In some embodiments, an internucleotidic linkage comprises a cyclic guanidine moiety. In some embodiments, an internucleotidic linkage comprising a cyclic guanidine moiety has the structure of:  . In some embodiments, a neutral internucleotidic linkage or internucleotidic linkage comprising a cyclic guanidine moiety is stereochemically controlled.

[001315] In some embodiments, a C9orf72 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.

[001316] 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**, **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.

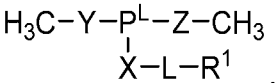
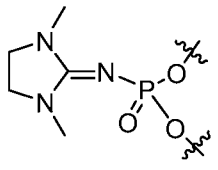
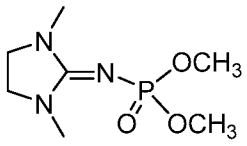
[001317] In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heteroaryl group having 1-10 heteroatoms. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heteroaryl 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.,  .

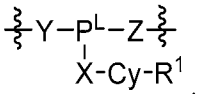
[001318] In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heterocyclyl group having 1-10 heteroatoms. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heterocyclyl 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 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_{1-6} alkyl. In some embodiments, each R^1 is independently methyl.

[001319] 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.

[001320] 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 leat 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.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.

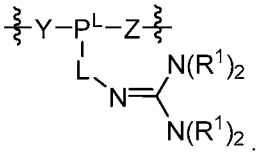
[001321] In some embodiments, a non-negatively charged internucleotidic linkage has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **II**, **II-a-1**, **II-a-2, II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof (not 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

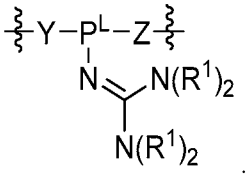
[001322] In some embodiments, X is a covalent bond and –X–Cy–R^1 is –Cy–R^1. In some embodiments, –Cy– is an optionally substituted bivalent group selected from a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms. In some embodiments, –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.

[001323] 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

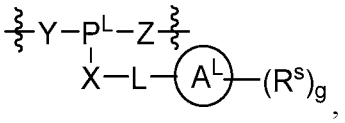
[001324] In some embodiments, R^1 is R'. In some embodiments, L is a covalent bond. In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, has the structure of formula **I-n-3** or a salt form thereof:



I-n-3

[001325] 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 $-CH_3$.

[001326] In some embodiments, a 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;

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)−, $-S(O)_2-$, $-S(O)_2N(R')-$, −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 $-S(O)_2R$;

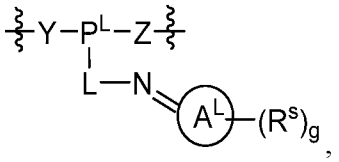
each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered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

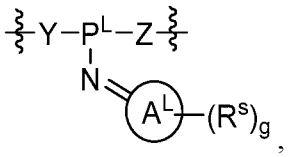
[001327] In some embodiments, a internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II**, has the structure of formula **II-a-1** or a salt form thereof:



II-a-1

or a salt form thereof.

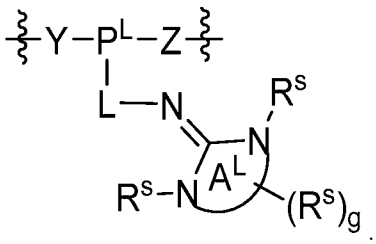
[001328] In some embodiments, a internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II**, has the structure of formula **II-a-2** or a salt form thereof:



II-a-2

or a salt form thereof.

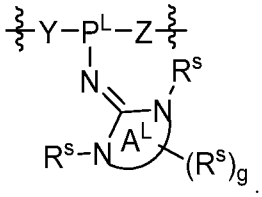
[001329] In some embodiments, A^L is bonded to –N= or L through a carbon atom. In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II** or **II-a-1**, **II-a-2**, has the structure of formula **II-b-1** or a salt form thereof:



II-b-1

[001330] 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**.

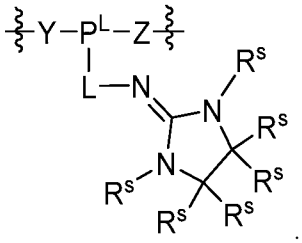
[001331] In some embodiments, A^L is bonded to –N= or L through a carbon atom. In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II** or **II-a-1**, **II-a-2**, has the structure of formula **II-b-2** or a salt form thereof:



II-b-2

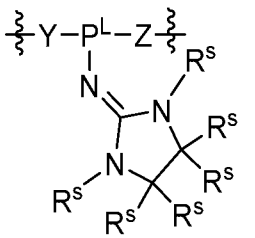
[001332] In some embodiments, Ring A^L is an optionally substituted 3-20 membered monocyclic ring having 0-10 heteroatoms (in addition to the two nitrogen atoms for formula **II-b)**. In some embodiments, Ring A^L is an optionally substituted 5- membered monocyclic saturated ring.

[001333] 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:



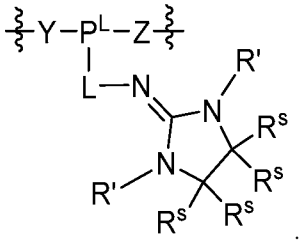
II-c-1

[001334] 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:



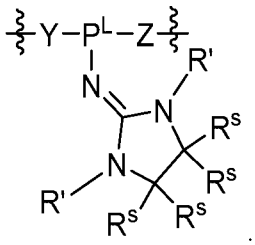
II-c-2

[001335] 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:



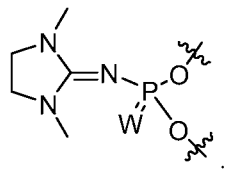
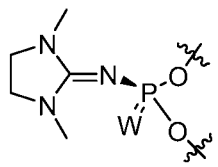
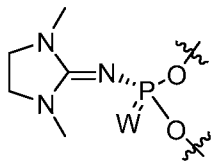
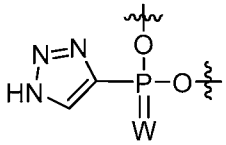
II-d-1

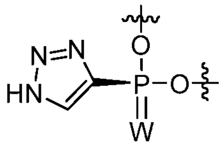
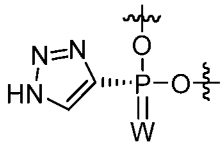
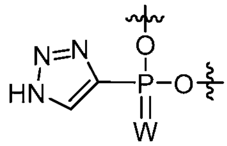
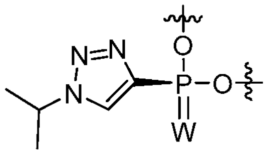
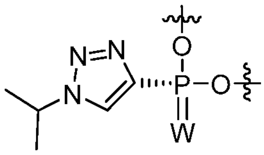
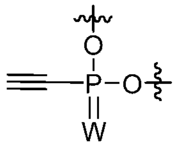
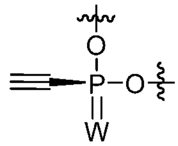
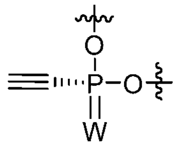
[001336] In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II**, **II-a**, **II-b**, or **II-c** has the structure of formula **II-d-2** or a salt form thereof:



II-d-2

[001337] 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 $-H$.

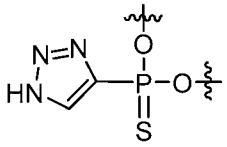
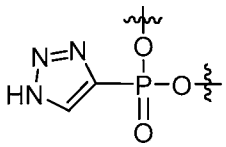
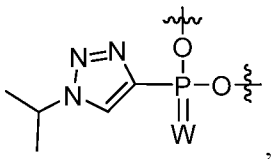
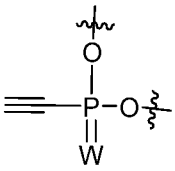
[001338] In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged

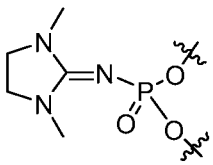
internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic 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.

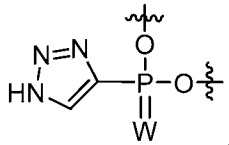
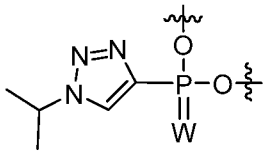
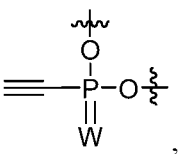
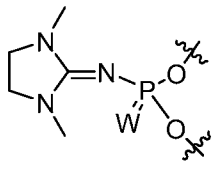
[001339] In some embodiments, each L^P independently has the structure of formula I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1, II-d-2, or a salt form thereof.

[001340] 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**, **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.

[001341] 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.

[001342] 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.

[001343] 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.

[001344] 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.

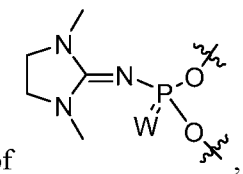
[001345] Without wishing to be bound by any particular theory, the present disclosure notes that a neutral internucleotidic linkage can be more hydrophobic than a phosphorothioate internucleotidic linkage (PS), which is more hydrophobic than a phosphodiester linkage (natural phosphate linkage, PO). Typically, 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.

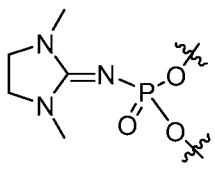
[001346] Without wishing to be bound by any particular theory, the present disclosure notes that incorporation of one or more non-negatively charged internucleotidic linkages, e.g., neutral internucleotidic linkages, into an oligonucleotide may be able to increase the oligonucleotide's ability to mediate a function such as exon skipping or gene knockdown. In some embodiments, an oligonucleotide capable of 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.

[001347] 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 *R*p. In some embodiments, a non-negatively charged internucleotidic linkage is chirally controlled and its linkage phosphorus is *S*p.

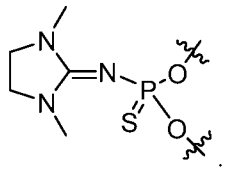
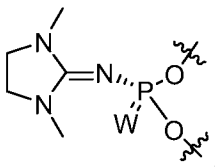
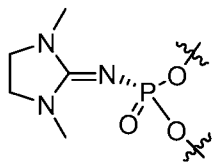
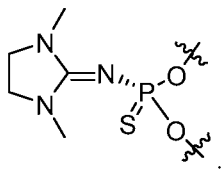
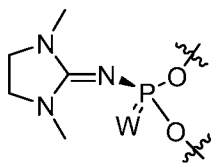
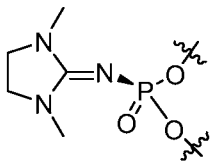
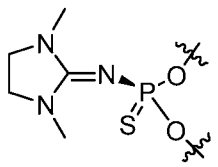
[001348] In some embodiments, a provided oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more non-negatively charged internucleotidic linkages. In some embodiments, a provided oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more neutral internucleotidic linkages. In some embodiments, 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 *R*p configuration, and at least one non-negatively charged internucleotidic linkage wherein its linkage phosphorus is in *S*p configuration.

[001349] 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 *R*p 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 *R*p 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 *R*p 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.

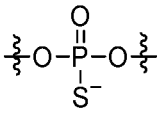
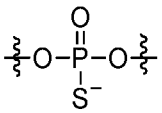
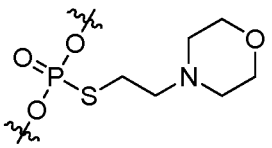
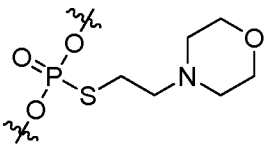
[001350] Oligonucleotides of the provided technologies can be of various lengths. In some embodiments, provided oligonucleotides comprise 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 50 or more bases. In some embodiments, provided oligonucleotides comprise 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 50 or more bases. In some embodiments, provided oligonucleotides comprise 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 50 or more bases.

[001351] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising at least one phosphate diester internucleotidic linkage and at least one phosphorothioate triester linkage having the structure of Formula **I-c**. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising at least one phosphate diester internucleotidic linkage and at least two phosphorothioate triester linkages having the structure of Formula **I-c**. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising at least one phosphate diester internucleotidic linkage and at least three phosphorothioate triester linkages having the structure of Formula **I-c**. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising at least one phosphate diester internucleotidic linkage and at least four phosphorothioate triester linkages having the structure of Formula **I-c**. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising at least one phosphate diester internucleotidic linkage and at least five phosphorothioate triester linkages having the structure of Formula **I-c**. In some embodiments, the present disclosure provides a chirally controlled

oligonucleotide comprising a non-negatively charged internucleotidic linkage having the structure of formula **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.

[001352] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence found in any oligonucleotide disclosed herein. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence found in any oligonucleotide disclosed herein, wherein one or more U is replaced with T or vice versa. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence found in any oligonucleotide disclosed herein, wherein the said sequence has over 50% identity with the sequence of any oligonucleotide disclosed herein. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence found in any oligonucleotide disclosed herein, wherein the said sequence has over 60% identity with the sequence of any oligonucleotide disclosed herein. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence found in any oligonucleotide disclosed herein, wherein the said sequence has over 70% identity with the sequence of any oligonucleotide disclosed herein. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence found in any oligonucleotide disclosed herein, wherein the said sequence has over 80% identity with the sequence of any oligonucleotide disclosed herein. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence found in any oligonucleotide disclosed herein, wherein the said sequence has over 90% identity with the sequence of any oligonucleotide disclosed herein. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence found in any oligonucleotide disclosed herein, wherein the said sequence has over 95% identity with the sequence of any oligonucleotide disclosed herein. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising the sequence of any oligonucleotide disclosed herein. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide having the sequence of any oligonucleotide disclosed herein. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence found in any oligonucleotide disclosed herein, wherein the oligonucleotides have a pattern of backbone linkages, pattern of backbone chiral centers, and/or pattern of backbone phosphorus modifications described herein.

[001353] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence (or a portion of at least 10 contiguous bases thereof) found in any oligonucleotide disclosed herein, wherein at least one internucleotidic linkage has a chiral linkage phosphorus. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide

comprising a sequence found in any oligonucleotide disclosed herein, wherein at least one internucleotidic linkage has the structure of Formula **I**. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence (or a portion of at least 10 contiguous bases thereof) found in any oligonucleotide disclosed herein, wherein each internucleotidic linkage has the structure of Formula **I**. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence (or a portion of at least 10 contiguous bases thereof) found in any oligonucleotide disclosed herein, wherein at least one internucleotidic linkage has the structure of Formula **I-c**. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence (or a portion of at least 10 contiguous bases thereof) found in any oligonucleotide disclosed herein, wherein each internucleotidic linkage has the structure of Formula **I-c**. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence (or a portion of at least 10 contiguous bases thereof) found in any oligonucleotide disclosed herein, wherein at least one internucleotidic linkage is  . In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence (or a portion of at least 10 contiguous bases thereof) found in any oligonucleotide disclosed herein, wherein each internucleotidic linkage is  . In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence (or a portion of at least 10 contiguous bases thereof) found in any oligonucleotide disclosed herein, wherein at least one internucleotidic linkage is  .
In some embodiments, the present disclosure provides a chirally controlled oligonucleotide comprising a sequence (or a portion of at least 10 contiguous bases thereof) found in any oligonucleotide disclosed herein, wherein each internucleotidic linkage is  .

[001354] In some embodiments, a modification at a linkage phosphorus is characterized by its ability to be transformed to a phosphate diester, such as those present in naturally occurring DNA and RNA, by one or more esterases, nucleases, and/or cytochrome P450 enzymes, including but not limited to: CYP1A1, CYP1A2, CYP1B1 (Family: CYP1); CYP2A6, CYP2A7, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2F1, CYP2J2, CYP2R1, CYP2S1, CYP2U1,

CYP2W1 (CYP2); CYP3A4, CYP3A5, CYP3A7, CYP3A43 (CYP3); CYP4A11, CYP4A22, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4F22, CYP4V2, CYP4X1, CYP4Z1 (CYP4); CYP5A1 (CYP5); CYP7A1, CYP7B1 (CYP7); CYP8A1 (prostacyclin synthase), CYP8B1 (bile acid biosynthesis) (CYP8); CYP11A1, CYP11B1, CYP11B2 (CYP11); CYP17A1 (CYP17); CYP19A1 (CYP19); CYP20A1 (CYP20); CYP21A2 (CYP21); CYP24A1 (CYP24); CYP26A1, CYP2XXX1, CYP26C1 (CYP26); CYP27A1 (bile acid biosynthesis), CYP27B1 (vitamin D3 1-alpha hydroxylase, activates vitamin D3), CYP27C1 (unknown function) (CYP27); CYP39A1 (CYP39); CYP46A1 (CYP46); or CYP51A1 (lanosterol 14-alpha demethylase) (CYP51).

[001355] In some embodiments, a modification at phosphorus results in a P-modification moiety characterized in that it acts as a pro-drug, *e.g.*, the 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.

[001356] 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.

[001357] 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.

[001358] In some embodiments, a P-modification moiety is characterized in that it acts as an agent which promotes cell entry and/or endosomal escape, such as a membrane-disruptive lipid or peptide.

[001359] In some embodiments, a P-modification moiety is characterized in that it acts as a targeting agent. In some embodiments, a P-modification moiety is or comprises a targeting agent. The phrase "targeting agent," as used herein, 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 agent to a

materially greater extent than is observed under otherwise comparable conditions when the payload of interest is not associated with the targeting agent. A targeting agent may be, or comprise, any of a variety of chemical moieties, including, for example, small molecule moieties, nucleic acids, polypeptides, carbohydrates, etc. Targeting agents are described further by Adarsh *et al.*, "Organelle Specific Targeted Drug Delivery – A Review," International Journal of Research in Pharmaceutical and Biomedical Sciences, 2011, p. 895.

[001360] Examples of such targeting agents include, but are not limited to, proteins (*e.g.* Transferrin), oligopeptides (*e.g.*, cyclic and acylic RGD-containing oligopedptides), 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.

[001361] In some embodiments, a P-modification moiety is a targeting agent of formula –-X-L-R^1 wherein each of X, L, and R^1 are as defined in Formula **I**, disclosed herein.

[001362] In some embodiments, a P-modification moiety is characterized in that it facilitates cell specific delivery.

[001363] In some embodiments, a P-modification moiety is characterized in that it falls into one or more of the above-described categories. 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. One of skill in the relevant arts would recognize that numerous other such combinations are possible and are contemplated by the present disclosure.

[001364] In some embodiments, a carbocyclyl, aryl, heteroaryl, or heterocyclyl group, or a bivalent or polyvalent group thereof, is a C_3-C_{30} carbocyclyl, aryl, heteroaryl, or heterocyclyl group, or a bivalent and/or polyvalent group thereof.

[001365] In some embodiments, a pattern of backbone chiral centers of a provided oligonucleotide or a region thereof (*e.g.*, a core) comprises or is (*S*p)m(*R*p)n, (*R*p)n(*S*p)m, (*O*p)n(*S*p)m, (*N*p)t[(*O*p)n(*S*p)m]y, (*S*p)t[(*O*p)n(*S*p)m]y, (*N*p)t[(*R*p)n(*S*p)m]y, or (*S*p)t[(*R*p)n(*S*p)m]y, wherein each variable is as described in the present disclosure. In some embodiments, y is 1. In some embodiments, a

pattern of backbone chiral centers comprises or is (*S*p)m(*R*p)n, (*R*p)n(*S*p)m, (*N*p)t(*R*p)n(*S*p)m, (*S*p)t(*R*p)n(*S*p)m, (*N*p)t[(*R*p)n(*S*p)m]2, (*S*p)t[(*R*p)n(*S*p)m]2, (*N*p)t(*O*p)n(*S*p)m, (*S*p)t(*O*p)n(*S*p)m, (*N*p)t[(*O*p)n(*S*p)m]2, or (*S*p)t[(*O*p)n(*S*p)m]2. In some embodiments, y is 2. In some embodiments, a pattern is (*N*p)t(*O*p/*R*p)n(*S*p)m(*O*p/*R*p)n(*S*p)m. In some embodiments, a pattern is (*N*p)t(*O*p/*R*p)n(*S*p)1-5(*O*p/*R*p)n(*S*p)m. In some embodiments, a pattern is (*N*p)t(*O*p/*R*p)n(*S*p)2-5(*O*p/*R*p)n(*S*p)m. In some embodiments, a pattern is (*N*p)t(*O*p/*R*p)n(*S*p)2(*O*p/*R*p)n(*S*p)m. In some embodiments, a pattern is (*N*p)t(*O*p/*R*p)n(*S*p)3(*O*p/*R*p)n(*S*p)m. In some embodiments, a pattern is (*N*p)t(*O*p/*R*p)n(*S*p)4(*O*p/*R*p)n(*S*p)m. In some embodiments, a pattern is (*N*p)t(*O*p/*R*p)n(*S*p)5(*O*p/*R*p)n(*S*p)m. In some embodiments, *N*p is *S*p. In some embodiments, (*O*p/*R*p) is *O*p. In some embodiments, (*O*p/*R*p) is *R*p. In some embodiments, *N*p is *S*p and (*O*p/*R*p) is *R*p. In some embodiments, *N*p is *S*p and (*O*p/*R*p) is *O*p. In some embodiments, *N*p is *S*p and at least one (*O*p/*R*p) is *R*p, and at least one (*O*p/*R*p) is *O*p. In some embodiments, a pattern of backbone chiral centers comprises or is (*R*p)n(*S*p)m, (*N*p)t(*R*p)n(*S*p)m, or (*S*p)t(*R*p)n(*S*p)m, wherein m > 2. In some embodiments, a pattern of backbone chiral centers comprises or is (*R*p)n(*S*p)m, (*N*p)t(*R*p)n(*S*p)m, or (*S*p)t(*R*p)n(*S*p)m, wherein n is 1, at least one t >1, and at least one m > 2. In some embodiments, at one n is 1, at least one t is no less than 1, and at least one m is no less than 2. In some embodiments, at one n is 1, at least one t is no less than 2, and at least one m is no less than 3. In some embodiments, each n is 1. In some embodiments, at least one t > 1. In some embodiments, at least one t > 2. In some embodiments, at least one t > 3. In some embodiments, at least one t > 4. In some embodiments, at least one m > 1. In some embodiments, at least one m > 2. In some embodiments, at least one m > 3. In some embodiments, at least one m > 4. In some embodiments, a pattern of backbone chiral centers comprises one or more achiral natural phosphate linkages. In some embodiments, the sum of m, t, and n (or m and n if no t in a pattern) is no less than 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20. In some embodiments, the sum is 5. In some embodiments, the sum is 6. In some embodiments, the sum is 7. In some embodiments, the sum is 8. In some embodiments, the sum is 9 In some embodiments, the sum is 10. In some embodiments, the sum is 11. In some embodiments, the sum is 12. In some embodiments, the sum is 13. In some embodiments, the sum is 14. In some embodiments, the sum is 15.

[001366] In some embodiments, a nucleotidic unit comprising *O*p is Nu^O as described in the present disclosure. For example, in some embodiments, Nu^O comprises a 5'-substitution/modification as described in the present disclosure, *e.g.*, $-C(R^{5s})_2-$ as described in the present disclosure. In some embodiments, $-C(R^{5s})_2-$ is 5MRd as described in the present disclosure. In some embodiments, $-C(R^{5s})_2-$ is 5MSd as described in the present disclosure.

[001367] In some embodiments, a pattern of backbone chiral centers comprises or is (*R*p)n(*S*p)m. In some embodiments, a pattern of backbone chiral centers comprises or is (*S*p)t(*R*p)n. In some

embodiments, a pattern of backbone chiral centers comprises or is (*N*p)t(*R*p)n(*S*p)m. In some embodiments, a pattern of backbone chiral centers comprises or is (*S*p)t(*S*p)m, optionally with n achiral phosphate diester internucleotidic linkages and/or stereorandom (non-chirally controlled) chiral internucleotidic linkages between the section having (*S*p)t and the section having (*S*p)m. In some embodiments, there are n achiral phosphate diester internucleotidic linkages in between. In some embodiments, there are n stereorandom chiral internucleotidic linkages in between. In some embodiments, a pattern of backbone chiral centers comprises or is (*S*p)t(*R*p)n(*S*p)m. In some embodiments, each of t and m is independently equal to or greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

[001368] In some embodiments, a common pattern of backbone chiral centers in a provided oligonucleotide comprises a pattern of i^{o}-i^{s}-i^{o}-i^{s}-i^{o}, i^{o}-i^{s}-i^{s}-i^{s}-i^{o}, i^{o}-i^{s}-i^{s}-i^{s}-i^{o}-i^{s}, i^{s}-i^{o}-i^{s}-i^{o}, i^{s}-i^{o}-i^{s}-i^{o}, i^{s}-i^{o}-i^{s}-i^{o}-i^{s}, i^{s}-i^{o}-i^{s}-i^{o}-i^{s}-i^{o}, i^{s}-i^{o}-i^{s}-i^{o}-i^{s}-i^{o}-i^{s}, i^{s}-i^{o}-i^{s}-i^{s}-i^{s}-i^{o}, i^{s}-i^{s}-i^{o}-i^{s}-i^{s}-i^{s}-i^{o}-i^{s}-i^{s}, i^{s}-i^{s}-i^{s}-i^{o}-i^{s}-i^{o}-i^{s}-i^{s}-i^{s}, i^{s}-i^{s}-i^{s}-i^{s}-i^{o}-i^{s}-i^{o}-i^{s}-i^{s}-i^{s}, i^{s}-i^{s}-i^{s}-i^{s}-i^{s}, i^{s}-i^{s}-i^{s}-i^{s}-i^{s}-i^{s}-i^{s}, i^{s}-i^{s}-i^{s}-i^{s}-i^{s}-i^{s}-i^{s}-i^{s}, i^{s}-i^{s}-i^{s}-i^{s}-i^{s}-i^{s}-i^{s}-i^{s}-i^{s}, i^{s}-i^{s}-i^{s}-i^{s}-i^{s}-i^{s}-i^{s}-i^{s}-i^{s}-i^{s}, or i^{r}-i^{r}-i^{r}, wherein i^{s} represents an internucleotidic linkage in the Sp configuration; i^{o} represents an achiral internucleotidic linkage; and i^{r} represents an internucleotidic linkage in the Rp configuration.

[001369] In some embodiments, a common pattern of backbone chiral centers comprises a pattern of OSOSO, OSSSO, OSSSOS, SOSO, SOSO, SOSOS, SOSOSO, SOSOSOSO, SOSSSO, SSOSSSOSS, SSSOSOSSS, SSSSOSOSSSS, SSSSS, SSSSSS, SSSSSSS, SSSSSSSS, SSSSSSSSS, or RRR, wherein S represents a phosphorothioate of the Sp configuration, O represents a phosphodiester, and R represents a phosphorothioate of the Rp configuration.

[001370] In some embodiments, the non-chiral center is a linkage phosphorus of a phosphodiester linkage. In some embodiments, the chiral center in a *S*p configuration is a linkage phosphorus of a phosphorothioate linkage. In some embodiments, the chiral center in a *R*p configuration is a linkage phosphorus of a phosphorothioate linkage.

[001371] As defined herein, m is 1-50. In some embodiments, m is 1. In some embodiments, m is 2-50. 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 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 greater than 25.

[001372] In some embodiments, a pattern of backbone chiral centers of a provided oligonucleotide or a region thereof comprises a repeating pattern. In some embodiments, a repeating pattern is (*S*p)m(*R*p)n, wherein n is 1-10, and m is independently described in the present disclosure. In some embodiments, a repeating pattern is (*R*p)n(*S*p)m, wherein n is 1-10, and m is independently described in the present disclosure. In some embodiments, a repeating pattern is (*O*p)n(*S*p)m, wherein n is 1-10, and m is independently described in the present disclosure. In some embodiments, (*R*p)n(*S*p)m is (*R*p)(*S*p)$_2$. In some embodiments, (*S*p)n(*R*p)m is (*S*p)$_2$(*R*p). In some embodiments, (*O*p)n(*S*p)m is (*O*p)(*S*p)$_2$.

[001373] In some embodiments, a repeating pattern is (*N*p)t(*R*p)n(*S*p)m, wherein n is 1-10, t is 1-50, *N*p is independently *R*p or *S*p, and m is as described in the present disclosure. In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises (*N*p)t(*R*p)n(*S*p)m. In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises (*N*p)t(*R*p)n(*S*p)m. In some embodiments, a repeating pattern is (*N*p)m(*R*p)n(*S*p)t, wherein n is 1-10, t is 1-50, *N*p is independently *R*p or *S*p, and m is as described in the present disclosure. In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises (*N*p)m(*R*p)n(*S*p)t. In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises (*N*p)m(*R*p)n(*S*p)t. In some embodiments, *N*p is *R*p. In some embodiments, *N*p is *S*p. In some embodiments, all *N*p are the same. In some embodiments, all *N*p are *S*p. In some embodiments, at least one *N*p is different from the other *N*p. In some embodiments, t is 2.

[001374] As defined herein, 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.

[001375] As defined herein, t is 1-50. In some embodiments, t is 1. In some embodiments, t is 2-50. In some embodiments, t is 2, 3, 4, 5, 6, 7 or 8. In some embodiments, t is 3, 4, 5, 6, 7 or 8. In some embodiments, t is 4, 5, 6, 7 or 8. In some embodiments, t is 5, 6, 7 or 8. In some embodiments, t is 6, 7 or 8. In some embodiments, t is 7 or 8. 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. In some embodiments, t is 21. In some embodiments, t is 22. In some embodiments, t is 23. In some embodiments, t is 24. In some embodiments, t is 25. In some embodiments, t is greater than 25.

[001376] In some embodiments, at least one of m and t is greater than 2. In some embodiments, at least one of m and t is greater than 3. In some embodiments, at least one of m and t is greater than 4. In some embodiments, at least one of m and t is greater than 5. In some embodiments, at least one of m and t is greater than 6. In some embodiments, at least one of m and t is greater than 7. In some embodiments, at least one of m and t is greater than 8. In some embodiments, at least one of m and t is greater than 9. In some embodiments, at least one of m and t is greater than 10. In some embodiments, at least one of m and t is greater than 11. In some embodiments, at least one of m and t is greater than 12. In some embodiments, at least one of m and t is greater than 13. In some embodiments, at least one of m and t is greater than 14. In some embodiments, at least one of m and t is greater than 15. In some embodiments, at least one of m and t is greater than 16. In some embodiments, at least one of m and t is greater than 17. In some embodiments, at least one of m and t is greater than 18. In some embodiments, at least one of m and t is greater than 19. In some embodiments, at least one of m and t is greater than 20. In some embodiments, at least one of m and t is greater than 21. In some embodiments, at least one of m and t is greater than 22. In some embodiments, at least one of m and t is greater than 23. In some embodiments, at least one of m and t is greater than 24. In some embodiments, at least one of m and t is greater than 25.

[001377] In some embodiments, each one of m and t is greater than 2. In some embodiments, each one of m and t is greater than 3. In some embodiments, each one of m and t is greater than 4. In some embodiments, each one of m and t is greater than 5. In some embodiments, each one of m and t is greater than 6. In some embodiments, each one of m and t is greater than 7. In some embodiments, each one of m and t is greater than 8. In some embodiments, each one of m and t is greater than 9. In some embodiments, each one of m and t is greater than 10. In some embodiments, each one of m and t is greater than 11. In some embodiments, each one of m and t is greater than 12. In some embodiments, each one of m and t is greater than 13. In some embodiments, each one of m and t is greater than 14. In some embodiments, each one of m and t is greater than 15. In some embodiments, each one of m and t is greater than 16. In some embodiments, each one of m and t is greater than 17. In some embodiments, each one of m and t is greater than 18. In some embodiments, each one of m and t is greater than 19. In some embodiments, each one of m and t is greater than 20.

[001378] In some embodiments, the sum of m and t is greater than 3. In some embodiments, the sum of m and t is greater than 4. In some embodiments, the sum of m and t is greater than 5. In some embodiments, the sum of m and t is greater than 6. In some embodiments, the sum of m and t is greater than 7. In some embodiments, the sum of m and t is greater than 8. In some embodiments, the sum of m and t is greater than 9. In some embodiments, the sum of m and t is greater than 10. In some embodiments, the sum of m and t is greater than 11. In some embodiments, the sum of m and t is greater than 12. In some embodiments, the sum of m and t is greater than 13. In some embodiments, the sum of m and t is greater than 14. In some embodiments, the sum of m and t is greater than 15. In some embodiments, the sum of m and t is greater than 16. In some embodiments, the sum of m and t is greater than 17. In some embodiments, the sum of m and t is greater than 18. In some embodiments, the sum of m and t is greater than 19. In some embodiments, the sum of m and t is greater than 20. In some embodiments, the sum of m and t is greater than 21. In some embodiments, the sum of m and t is greater than 22. In some embodiments, the sum of m and t is greater than 23. In some embodiments, the sum of m and t is greater than 24. In some embodiments, the sum of m and t is greater than 25.

[001379] In some embodiments, n is 1, and at least one of m and t is greater than 1. In some embodiments, n is 1 and each of m and t is independently greater than 1. In some embodiments, m>n and t>n. In some embodiments, (*S*p)m(*R*p)n(*S*p)t is $(Sp)_2Rp(Sp)_2$. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is $(Sp)_2Rp(Sp)_2$. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is $SpRp(Sp)_2$. In some embodiments, (*N*p)t(*R*p)n(*S*p)m is (*N*p)t*R*p(*S*p)m. In some embodiments, (*N*p)t(*R*p)n(*S*p)m is $(Np)_2Rp(Sp)m$. In some embodiments, (*N*p)t(*R*p)n(*S*p)m is $(Rp)_2Rp(Sp)m$. In some embodiments, (*N*p)t(*R*p)n(*S*p)m is $(Sp)_2Rp(Sp)m$. In some embodiments, (*N*p)t(*R*p)n(*S*p)m is *R*p*S*p*R*p(*S*p)m. In some embodiments, (*N*p)t(*R*p)n(*S*p)m is *S*p*R*p*R*p(*S*p)m.

[001380] In some embodiments, n is 1, and at least one of m and t is greater than 1. In some embodiments, n is 1 and each of m and t is independently greater than 1. In some embodiments, m>n and t>n. In some embodiments, (*S*p)m(*O*p)n(*S*p)t is $(Sp)_2Op(Sp)_2$. In some embodiments, (*S*p)t(*O*p)n(*S*p)m is $(Sp)_2Op(Sp)_2$. In some embodiments, (*S*p)t(*O*p)n(*S*p)m is $SpOp(Sp)_2$. In some embodiments, (*N*p)t(*O*p)n(*S*p)m is (*N*p)t*O*p(*S*p)m. In some embodiments, (*N*p)t(*O*p)n(*S*p)m is $(Np)_2Op(Sp)m$. In some embodiments, (*N*p)t(*O*p)n(*S*p)m is $(Op)_2Op(Sp)m$. In some embodiments, (*N*p)t(*O*p)n(*S*p)m is $(Sp)_2Op(Sp)m$. In some embodiments, (*N*p)t(*O*p)n(*S*p)m is *R*p*S*p*O*p(*S*p)m. In some embodiments, (*N*p)t(*O*p)n(*S*p)m is *S*p*R*p*O*p(*S*p)m.

[001381] In some embodiments, (*S*p)t(*R*p)n(*S*p)m is *S*p*R*p*S*p*S*p. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is $(Sp)_2Rp(Sp)_2$. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is $(Sp)_3Rp(Sp)_3$. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is $(Sp)_4Rp(Sp)_4$. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is $(Sp)tRp(Sp)_5$. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is $SpRp(Sp)_5$. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is

$(Sp)_2Rp(Sp)_5$. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is $(Sp)_3Rp(Sp)_5$. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is $(Sp)_4Rp(Sp)_5$. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is $(Sp)_5Rp(Sp)_5$.

[001382] In some embodiments, (*S*p)t(*O*p)n(*S*p)m is *S*p*O*p*S*p*S*p. In some embodiments, (*S*p)t(*O*p)n(*S*p)m is $(Sp)_2Op(Sp)_2$. In some embodiments, (*S*p)t(*O*p)n(*S*p)m is $(Sp)_3Op(Sp)_3$. In some embodiments, (*S*p)t(*O*p)n(*S*p)m is $(Sp)_4Op(Sp)_4$. In some embodiments, (*S*p)t(*O*p)n(*S*p)m is (*S*p)t$Op(Sp)_5$. In some embodiments, (*S*p)t(*O*p)n(*S*p)m is *S*p$Op(Sp)_5$. In some embodiments, (*S*p)t(*O*p)n(*S*p)m is $(Sp)_2Op(Sp)_5$. In some embodiments, (*S*p)t(*O*p)n(*S*p)m is $(Sp)_3Op(Sp)_5$. In some embodiments, (*S*p)t(*O*p)n(*S*p)m is $(Sp)_4Op(Sp)_5$. In some embodiments, (*S*p)t(*O*p)n(*S*p)m is $(Sp)_5Op(Sp)_5$.

[001383] The present invention demonstrates, among other things, that individual stereoisomers of a particular oligonucleotide can show different stability and/or activity from each other. In some embodiments, inclusion of particular pattern of backbone chiral centers, e.g., those described in the present disclosure comprising *O*p*S*p*S*p, within an oligonucleotide can surprisingly change the cleavage pattern of a nucleic acid polymer when such an oligonucleotide is utilized for cleaving said nucleic acid polymer. In some embodiments, a pattern of backbone chiral centers provides unexpectedly high cleavage efficiency of a target nucleic acid polymer. In some embodiments, a pattern of backbone chiral centers provides new cleavage sites. In some embodiments, a pattern of backbone chiral centers increase cleavage (e.g., percentage, rate, absolute amount, etc.) at a cleavage site. In some embodiments, a pattern of backbone chiral centers decrease cleavage (e.g., percentage, rate, absolute amount, etc.) at a cleavage site. In some embodiments, a pattern of backbone chiral centers provides fewer cleavage sites, for example, by blocking certain existing cleavage sites. Even more unexpectedly, in some embodiments, a pattern of backbone chiral centers provides cleavage predominantly at only one site of a target nucleic acid polymer within the sequence that is complementary to an oligonucleotide utilized for cleavage. In some embodiments, higher cleavage efficiency is achieved by selecting a pattern of backbone chiral centers to minimize the number of cleavage sites. In some embodiments, a pattern of backbone chiral centers of the oligonucleotide improves cleavage of a target nucleic acid polymer. In some embodiments, a pattern of backbone chiral centers increases selectivity. In some embodiments, a pattern of backbone chiral centers minimizes off-target effect. In some embodiments, a pattern of backbone chiral centers increase selectivity, *e.g.*, cleavage selectivity among target sequences differing by point mutations or single nucleotide polymorphisms (SNPs). In some embodiments, a pattern of backbone chiral centers increase selectivity, *e.g.*, cleavage selectivity among target sequences differing by only one point mutation or single nucleotide polymorphism (SNP). In some embodiments, the present disclosure provides oligonucleotides whose pattern of backbone chiral centers comprising (*O*p)n(*S*p)m, (*N*p)t[(*O*p)n(*S*p)m]y, or (*S*p)t[(*O*p)n(*S*p)m]y, wherein n is 1 and m is 2 or greater. In some embodiments, the present disclosure provides oligonucleotides whose pattern of backbone chiral centers comprising

(*O*p)n(*S*p)m, wherein n is 1 and m is 2. In some embodiments, the present disclosure provides chirally controlled oligonucleotide compositions of oligonucleotides wherein the oligonucleotides have the same base sequence, the same pattern of backbone linkages, and the same pattern of backbone chiral centers of the oligonucleotides which comprises (*O*p)n(*S*p)m, (*N*p)t[(*O*p)n(*S*p)m]y, or (*S*p)t[(*O*p)n(*S*p)m]y, wherein n is 1 and m is 2 or greater. In some embodiments, the present disclosure provides chirally controlled oligonucleotide compositions of a plurality of oligonucleotides wherein the oligonucleotides have the same base sequence, the same pattern of backbone linkages, and the same pattern of backbone chiral centers of the oligonucleotides which comprises (*O*p)n(*S*p)m, wherein n is 1 and m is 2. In some embodiments, oligonucleotides of the plurality have the same constitution. In some embodiments, oligonucleotides of the plurality are structurally identical. In some embodiments, at least 0.1%, 0.5%, 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% of all oligonucleotides in the composition that have the same base sequence are oligonucleotides of the plurality. In some embodiments, the percentage is at least 5%. In some embodiments, the percentage is at least 10%. In some embodiments, the percentage is at least 20%. In some embodiments, the percentage is at least 30%. In some embodiments, the percentage is at least 40%. In some embodiments, the percentage is at least 50%. In some embodiments, the percentage is at least 60%. In some embodiments, the percentage is at least 70%. In some embodiments, the percentage is at least 80%. In some embodiments, the percentage is at least 90%.

[001384] In some embodiments, the present invention provides a method for controlled cleavage of a nucleic acid polymer, comprising providing a chirally controlled oligonucleotide composition of the present disclosure, wherein the nucleic acid polymer is cleaved in a cleavage pattern that is different than a reference cleavage pattern. In some embodiments, a provided chirally controlled oligonucleotide composition is of a plurality of oligonucleotides whose common pattern of backbone chiral centers comprises (*O*p)n(*S*p)m, (*N*p)t[(*O*p)n(*S*p)m]y, or (*S*p)t[(*O*p)n(*S*p)m]y, wherein n is 1 and m is 2 or greater.

[001385] In some embodiments, a reference cleavage pattern is a cleavage pattern of a reference composition (e.g., non-chirally controlled oligonucleotide composition, a chirally controlled oligonucleotide composition of oligonucleotides having a different pattern of backbone chiral centers (e.g., not containing (*O*p/*R*p)(*S*p)m), etc.). As appreciated by those skilled in the art, a cleavage pattern of a nucleic acid polymer includes the number of cleavage sites, the locations of the cleavage sites, and the percentage of cleavage at each sites.

[001386] In some embodiments, the present invention provides a method for changing a first cleavage pattern of a nucleic acid polymer resulted from using a first oligonucleotide composition, comprising providing a second composition which is a chirally controlled oligonucleotide composition of the present disclosure, wherein the second composition provides a second cleavage pattern that is

different than the first cleavage pattern. In some embodiments, a provided chirally controlled oligonucleotide composition is of a plurality of oligonucleotides whose common pattern of backbone chiral centers comprises (*O*p)n(*S*p)m, (*N*p)t[(*O*p)n(*S*p)m]y, or (*S*p)t[(*O*p)n(*S*p)m]y, wherein n is 1 and m is 2 or greater. In some embodiments, a second cleavage pattern has a different cleavage site. In some embodiments, a second cleavage pattern has fewer cleavage sites. In some embodiments, a second cleavage pattern has a predominant cleavage site (e.g., at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% cleavage) that is different than and/or absent from the first cleavage pattern.

[001387] In some embodiments, the present disclosure provides a method for altering a cleavage pattern observed when a nucleic acid polymer whose nucleotide sequence includes a target sequence is contacted with a reference oligonucleotide composition that comprises oligonucleotides having a particular base sequence and length, which particular base sequence is or comprises a sequence that is complementary to the target sequence, the method comprising providing a chirally controlled oligonucleotide composition of the present disclosure, which chirally controlled oligonucleotide composition comprises a plurality of oligonucleotides whose base sequence is or comprises the particular base sequence, and whose common pattern of backbone chiral centers comprises (*O*p)n(*S*p)m, (*N*p)t[(*O*p)n(*S*p)m]y, or (*S*p)t[(*O*p)n(*S*p)m]y, wherein n is 1 and m is 2 or greater.

[001388] In some embodiments, a nucleic acid polymer is RNA. In some embodiments, a nucleic acid polymer is an oligonucleotide. In some embodiments, a nucleic acid polymer is an RNA oligonucleotide. In some embodiments, a nucleic acid polymer is a transcript. In some embodiments, oligonucleotides of a provided chirally controlled oligonucleotide composition form duplexes with a nucleic acid polymer to be cleaved.

[001389] In some embodiments, a provided chirally controlled oligonucleotide composition comprising oligonucleotides with a common pattern of backbone chiral centers provides unexpectedly high selectivity so that nucleic acid polymers that have only small sequence variations within a target region can be selectively targeted. In some embodiments, a nucleic acid polymer is a transcript from an allele. In some embodiments, transcripts from different alleles can be selectively targeted by provided chirally controlled oligonucleotide compositions.

[001390] In some embodiments, provided chirally controlled oligonucleotide compositions and methods thereof enables precise control of cleavage sites within a target sequence. In some embodiments, a cleavage site is around a sequence of *O*p*S*p*S*p backbone chiral centers. In some embodiments, a cleavage site is upstream of and near a sequence of *O*p*S*p*S*p backbone chiral centers. In some embodiments, a cleavage site is within 5 base pairs upstream of a sequence of *O*p*S*p*S*p backbone chiral centers. In some embodiments, a cleavage site is within 4 base pairs upstream of a sequence of *O*p*S*p*S*p backbone chiral centers. In some embodiments, a cleavage site is within 3 base pairs upstream of a

sequence of *O*p*S*p*S*p backbone chiral centers. In some embodiments, a cleavage site is within 2 base pairs upstream of a sequence of *O*p*S*p*S*p backbone chiral centers. In some embodiments, a cleavage site is within 1 base pair upstream of a sequence of *O*p*S*p*S*p backbone chiral centers. In some embodiments, a cleavage site is downstream of and near a sequence of *O*p*S*p*S*p backbone chiral centers. In some embodiments, a cleavage site is within 5 base pairs downstream of a sequence of *O*p*S*p*S*p backbone chiral centers. In some embodiments, a cleavage site is within 4 base pairs downstream of a sequence of *O*p*S*p*S*p backbone chiral centers. In some embodiments, a cleavage site is within 3 base pairs downstream of a sequence of *O*p*S*p*S*p backbone chiral centers. In some embodiments, a cleavage site is within 2 base pairs downstream of a sequence of *O*p*S*p*S*p backbone chiral centers. In some embodiments, a cleavage site is within 1 base pair downstream of a sequence of *O*p*S*p*S*p backbone chiral centers. Among other things, the present invention therefore provides control of cleavage sites with in a target sequence. As extensively described in the present disclosure, a sequence of *O*p*S*p*S*p backbone chiral centers can be found in a single or repeating units of (*N*p)m(*O*p)n(*S*p)t, (*N*p)t(*O*p)n(*S*p)m, (*S*p)m(*O*p)n(*S*p)t, (*S*p)t(*O*p)n(*S*p)m, (*O*p)n(*S*p)m, (*O*p)m(*S*p)n, (*S*p)m*O*p and/or *O*p(*S*p)m, each of which is independently as defined above and described herein. In some embodiments, a provided chirally controlled oligonucleotide composition creates a new cleavage site 2 base pairs downstream of *O*p*S*p*S*p backbone chiral centers in a target molecule wherein said new cleavage site does not exist if a reference (*e.g.*, chirally uncontrolled) oligonucleotide composition is used (cannot be detected). In some embodiments, a provided chirally controlled oligonucleotide composition enhances cleavage at a cleavage site 2 base pairs downstream of *O*p*S*p*S*p backbone chiral centers in a target molecule (*e.g.*, see Figure 2), wherein cleavage at such a site occurs at a higher percentage than when a reference (*e.g.*, chirally uncontrolled) oligonucleotide composition is used. In some embodiments, cleavage at such a site by a provided chirally controlled oligonucleotide composition is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 500 or 1000 fold of that by a reference oligonucleotide composition (for example, when measured by percentage of cleavage at a site). In some embodiments, a provided chirally controlled oligonucleotide composition provides accelerated cleavage at a cleavage site 2 base pairs downstream of *O*p*S*p*S*p backbone chiral centers in a target molecule (*e.g.*, see Figure 2), compared to when a reference (*e.g.*, chirally uncontrolled) oligonucleotide composition is used. In some embodiments, cleavage by a provided chirally controlled oligonucleotide composition is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 500 or 1000 fold faster than that by a reference oligonucleotide composition. In some embodiments, a cleavage site of a provided chirally controlled oligonucleotide composition 2 base pairs downstream of *O*p*S*p*S*p backbone chiral centers in a target molecule (*e.g.*, see Figure 2) is a cleavage site when a reference (*e.g.*, chirally uncontrolled) oligonucleotide composition is used. In some embodiments, a cleavage site of a provided chirally controlled oligonucleotide

composition 2 base pairs downstream of *O*p*S*p*S*p backbone chiral centers in a target molecule (*e.g.*, see Figure 2) is within one base pair of a cleavage site when a reference (*e.g.*, chirally uncontrolled) oligonucleotide composition is used. In some embodiments, a cleavage site of a provided chirally controlled oligonucleotide composition 2 base pairs downstream of *O*p*S*p*S*p backbone chiral centers in a target molecule (*e.g.*, see Figure 2) is within 2 base pairs of a cleavage site when a reference (*e.g.*, chirally uncontrolled) oligonucleotide composition is used. In some embodiments, it is within 3 base pairs. In some embodiments, it is within 4 base pairs. In some embodiments, it is within 5 base pairs. In some embodiments, a cleavage site of a provided chirally controlled oligonucleotide composition 2 base pairs downstream of *O*p*S*p*S*p backbone chiral centers in a target molecule is one of the major cleavage sites when a reference (*e.g.*, chirally uncontrolled) oligonucleotide composition is used. In some embodiments, such a site is the cleavage site with the highest cleavage percentage when a reference (*e.g.*, chirally uncontrolled) oligonucleotide composition is used. In some embodiments, a cleavage site of a provided chirally controlled oligonucleotide composition 2 base pairs downstream of *O*p*S*p*S*p backbone chiral centers in a target molecule is one of the cleavage sites with higher cleavage rate when a reference (*e.g.*, chirally uncontrolled) oligonucleotide composition is used. In some embodiments, such a site is the cleavage site with the highest cleavage rate when a reference (*e.g.*, chirally uncontrolled) oligonucleotide composition is used.

[001391] In some embodiments, a provided chirally controlled oligonucleotide composition enhances cleavage at one or more sites, *e.g.*, relative to a reference (*e.g.*, chirally uncontrolled/stereorandom) oligonucleotide composition. In some embodiments, a provided chirally controlled oligonucleotide composition selectively enhances cleavage at a single site relative to a reference (*e.g.*, chirally uncontrolled/stereorandom) composition. In some embodiments, a chirally controlled oligonucleotide composition enhances cleavage at a site by providing a higher cleavage rate. In some embodiments, a chirally controlled oligonucleotide composition enhances cleavage at a site by providing a higher percentage of cleavage at said site. Percentage of cleavage at a site can be determined by various methods widely known and practiced in the art. In some embodiments, percentage of cleavage at a site is determined by analysis of cleavage products, for example, as by HPLC-MS. In some embodiments, enhancement is relative to a reference oligonucleotide composition. In some embodiments, enhancement is relative to another cleavage site. In some embodiments, a provided chirally controlled oligonucleotide composition enhances cleavage at a site that is a preferred cleavage site of a reference oligonucleotide composition. In some embodiments, a preferred cleavage site, or a group of preferred cleavage sites, is a site or sites that have relatively higher percentage of cleavage compared to one or more other cleavage sites. In some embodiments, preferred cleavage sites can indicate preference of an enzyme. For example, for RNase H, when a DNA oligonucleotide is used, resulting cleavage sites may

indicate preference of RNase H. In some embodiments, a provided chirally controlled oligonucleotide composition enhances cleavage at a site that is a preferred cleavage site of an enzyme. In some embodiments, a provided chirally controlled oligonucleotide composition enhances cleavage at a site that is not a preferred cleavage site of a reference oligonucleotide composition. In some embodiments, a provided chirally controlled oligonucleotide composition enhances cleavage at a site that is not a cleavage site of a reference oligonucleotide composition, effectively creating a new cleavage site which does not exist when a reference oligonucleotide composition is used. In some embodiments, a provided chirally controlled oligonucleotide composition enhances cleavage at a site within 5 base pairs from a targeted mutation or SNP, thereby increasing selective cleavage of the undesired target oligonucleotide. In some embodiments, a provided chirally controlled oligonucleotide composition enhances cleavage at a site within 4 base pairs from a targeted mutation or SNP, thereby increasing selective cleavage of the undesired target oligonucleotide. In some embodiments, a provided chirally controlled oligonucleotide composition enhances cleavage at a site within 3 base pairs from a targeted mutation or SNP, thereby increasing selective cleavage of the undesired target oligonucleotide. In some embodiments, a provided chirally controlled oligonucleotide composition enhances cleavage at a site within 2 base pairs from a targeted mutation or SNP, thereby increasing selective cleavage of the undesired target oligonucleotide. In some embodiments, a provided chirally controlled oligonucleotide composition enhances cleavage at a site immediately upstream or downstream targeted characteristic sequence elements (e.g., a mutation, a SNP, etc.) thereby increasing selective cleavage of the undesired target oligonucleotide.

[001392] In some embodiments, a provided chirally controlled oligonucleotide composition suppresses cleavage at one or more sites, *e.g.*, relative to a reference (*e.g.*, chirally uncontrolled/stereorandom) oligonucleotide composition. In some embodiments, a chirally controlled oligonucleotide composition suppresses cleavage at a site by providing a lower cleavage rate. In some embodiments, a chirally controlled oligonucleotide composition suppresses cleavage at a site by providing a lower percentage of cleavage at said site. In some embodiments, suppression is relative to a reference oligonucleotide composition. In some embodiments, suppression is relative to another cleavage site. In some embodiments, a provided chirally controlled oligonucleotide composition suppresses cleavage at a site that is a preferred cleavage site of a reference oligonucleotide composition. In some embodiments, a preferred cleavage site, or a group of preferred cleavage sites, is a site or sites that have relatively higher percentage of cleavage compared to one or more other cleavage sites. In some embodiments, preferred cleavage sites can indicate preference of an enzyme. For example, for RNase H, when a DNA oligonucleotide is used, resulting cleavage sites may indicate preference of RNase H. In some embodiments, a provided chirally controlled oligonucleotide composition suppresses cleavage at a site that is a preferred cleavage site of an enzyme. In some embodiments, a provided chirally controlled

oligonucleotide composition suppresses cleavage at a site that is not a preferred cleavage site of a reference oligonucleotide composition. In some embodiments, a provided chirally controlled oligonucleotide composition suppresses all cleavage sites of a reference oligonucleotide composition. In some embodiments, a provided chirally controlled oligonucleotide composition generally enhances cleavage of target oligonucleotides. In some embodiments, a provided chirally controlled oligonucleotide composition generally suppresses cleavage of non-target oligonucleotides. In some embodiments, a provided chirally controlled oligonucleotide composition enhances cleavage of target oligonucleotides and suppresses cleavage of non-target oligonucleotides. In a subject comprising a diseased tissue comprising a mutation or SNP, a target oligonucleotide for cleavage can be transcripts with a mutation or SNP, while a non-target oligonucleotide can be normal transcripts without a mutation or SNP, such as those expressed in healthy tissues.

[001393] In some embodiments, the present invention provides a method for allele-specific suppression of a transcript from a target nucleic acid sequence for which a plurality of alleles exist within a population, each of which contains a specific nucleotide characteristic sequence element that defines the allele relative to other alleles of the same target nucleic acid sequence, the method comprising steps of:

contacting a sample comprising transcripts of the target nucleic acid sequence with a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides that have

1) a common base sequence;

2) a common pattern of backbone linkages;

3) a common pattern of backbone chiral centers;

wherein the common base sequence for the oligonucleotides of the particular oligonucleotide type is or comprises a sequence that is complementary to the characteristic sequence element that defines a particular allele. In some embodiments, the present disclosure provides a method for selective suppression of a transcript from a target nucleic acid sequence for which one or more similar sequences exist within a population, each of which contains a specific nucleotide characteristic sequence element that defines the target nucleic acid sequence relative to the similar sequences, the method comprising steps of:

contacting a sample comprising transcripts of the target nucleic acid sequence with a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides that have

1) a common base sequence;

2) a common pattern of backbone linkages;

3) a common pattern of backbone chiral centers;

wherein the common base sequence for the oligonucleotides of the particular oligonucleotide type is or comprises a sequence that is complementary to the characteristic sequence element that defines the target

nucleic acid sequence. In some embodiments, a similar sequence shares at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% but less than 100% homology with the target nucleic acid sequence within the portion of the sequence that is complementary to the common base sequence. In some embodiments, a similar sequence differs at no more than 5, 4, 3, 2, or 1 nucleobases from (but not identical with) the target nucleic acid sequence within the portion of the sequence that is complementary to the common base sequence. In some embodiments, a similar sequence differs at only 1 nucleobases from the target nucleic acid sequence within the portion of the sequence that is complementary to the common base sequence. In some embodiments, the common pattern of backbone chiral centers comprises (*O*p)n(*S*p)m, (*N*p)t[(*O*p)n(*S*p)m]y, or (*S*p)t[(*O*p)n(*S*p)m]y, wherein each variable is as described in the present disclosure, and n is 1 and m is 2 or greater. In some embodiments, oligonucleotides of the plurality comprise an asymmetric format. In some embodiments, when the composition is contacted with a system comprising transcripts of both the target allele and another allele of the same nucleic acid sequence, transcripts of the particular allele are suppressed at a greater level (e.g., at least 1.5, 2, 3, 4, or 5 fold) than a level of suppression observed for another allele of the same nucleic acid sequence. In some embodiments, when the composition is contacted with a system comprising transcripts of the same target nucleic acid sequence, it shows suppression of transcripts of the particular allele at a level that is:

a) greater than when the composition is absent;

b) greater than a level of suppression observed for another allele of the same nucleic acid sequence; or

c) both greater than when the composition is absent, and greater than a level of suppression observed for another allele of the same nucleic acid sequence.

In some embodiments, the contacting is performed under conditions determined to permit the composition to suppress transcripts of the particular allele.

[001394] In some embodiments, a transcript is suppressed by cleavage of said transcript. In some embodiments, a specific nucleotide characteristic sequence element is in an intron. In some embodiments, a specific nucleotide characteristic sequence element is in an exon. In some embodiments, a specific nucleotide characteristic sequence element is partially in an exon and partially in an intron. In some embodiments, a specific nucleotide characteristic sequence element is or comprises a mutation that differentiates an allele from other alleles. In some embodiments, a mutation is or comprises a deletion. In some embodiments, a mutation is or comprises an insertion. In some embodiments, a mutation is or comprises a point mutation. In some embodiments, a specific nucleotide characteristic sequence element is or comprises a single nucleotide polymorphism (SNP) that differentiates an allele from other alleles. In some embodiments, a specific nucleotide characteristic sequence element is or comprises one or more nucleobases that differentiate a target nucleic acid sequence from similar sequence(s) in a genome and/or products encoded thereby.

[001395] In some embodiments, suppression of transcripts of a particular allele is at a level that is greater than when the composition is absent. In some embodiments, suppression of transcripts of a particular allele is at a level that is at least 1.1 fold relative to when the composition is absent, in that transcripts from the particular allele are detected in amounts that are at least 1.1 fold lower when the composition is present relative to when it is absent. In some embodiments, a level is at least 1.2 fold. In some embodiments, a level is at least 1.3 fold. In some embodiments, a level is at least 1.4 fold. In some embodiments, a level is at least 1.5 fold. In some embodiments, a level is at least 1.6 fold. In some embodiments, a level is at least 1.7 fold. In some embodiments, a level is at least 1.8 fold. In some embodiments, a level is at least 1.9 fold. In some embodiments, a level is at least 2 fold. In some embodiments, a level is at least 3 fold. In some embodiments, a level is at least 4 fold. In some embodiments, a level is at least 5 fold. In some embodiments, a level is at least 6 fold. In some embodiments, a level is at least 7 fold. In some embodiments, a level is at least 8 fold. In some embodiments, a level is at least 9 fold. In some embodiments, a level is at least 10 fold. In some embodiments, a level is at least 11 fold. In some embodiments, a level is at least 12 fold. In some embodiments, a level is at least 13 fold. In some embodiments, a level is at least 14 fold. In some embodiments, a level is at least 15 fold. In some embodiments, a level is at least 20 fold. In some embodiments, a level is at least 30 fold. In some embodiments, a level is at least 40 fold. In some embodiments, a level is at least 50 fold. In some embodiments, a level is at least 75 fold. In some embodiments, a level is at least 100 fold. In some embodiments, a level is at least 150 fold. In some embodiments, a level is at least 200 fold. In some embodiments, a level is at least 300 fold. In some embodiments, a level is at least 400 fold. In some embodiments, a level is at least 500 fold. In some embodiments, a level is at least 750 fold. In some embodiments, a level is at least 1000 fold. In some embodiments, a level is at least 5000 fold.

[001396] In some embodiments, suppression of transcripts of a particular allele is at a level that is greater than a level of suppression observed for another allele of the same nucleic acid sequence. In some embodiments, suppression of transcripts of a particular allele is at a level that is at least 1.1 fold greater than a level of suppression observed for another allele of the same nucleic acid sequence. In some embodiments, a level is at least 1.2 fold. In some embodiments, a level is at least 1.3 fold. In some embodiments, a level is at least 1.4 fold. In some embodiments, a level is at least 1.5 fold. In some embodiments, a level is at least 1.6 fold. In some embodiments, a level is at least 1.7 fold. In some embodiments, a level is at least 1.8 fold. In some embodiments, a level is at least 1.9 fold. In some embodiments, a level is at least 2 fold. In some embodiments, a level is at least 3 fold. In some embodiments, a level is at least 4 fold. In some embodiments, a level is at least 5 fold. In some embodiments, a level is at least 6 fold. In some embodiments, a level is at least 7 fold. In some

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 257

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THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
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NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

1. An oligonucleotide comprising a pattern of backbone chiral centers (linkage phosphorus) of:

(*O*p)n(*S*p)m,

wherein:

*S*p indicates the *S* configuration of a chiral linkage phosphorus of a chiral modified internucleotidic linkage;

*O*p indicates an achiral linkage phosphorus of a natural phosphate linkage; and

each of n and m is independently 1-20; and

each wing independently comprises one or more nucleobases.

2. The oligonucleotide of claim 1, wherein the pattern of backbone chiral centers comprises (*S*p)t[(*O*p/*R*p)n(*S*p)m]y, wherein t is 1-20.

3. The oligonucleotide of claim 1, wherein the pattern of backbone chiral centers comprises (*N*p)t[(*O*p/*R*p)n(*S*p)m]y, wherein t is 1-20, wherein *N*p is *S*p or *R*p, wherein *R*p indicates the *S* configuration of a chiral linkage phosphorus of a chiral modified internucleotidic linkage.

4. The oligonucleotide of any one of claims 1-3, wherein n is 1.

5. The oligonucleotide of claim 4, wherein m is 2 or greater.

6. The oligonucleotide of claim 5, wherein t is 2 or greater.

7. The oligonucleotide of claim 6, wherein the oligonucleotide comprises a wing-core-wing structure.

8. A composition comprising an oligonucleotide, wherein the oligonucleotide comprises a first wing, a second wing and a core in a format of first wing-core-second wing or second wing-core-first wing, wherein the first wing, the second wing and the core each comprise a different sugar or sugar modification(s) or combination or pattern thereof, and/or internucleotidic linkage(s) or combination or pattern thereof, and/or stereochemistry of internucleotidic linkage(s) or combination or pattern thereof.

9. The composition of any of the preceding claims, wherein the oligonucleotide is capable of decreasing the level, expression and/or activity of a target gene or a gene product thereof.

10. The composition of any of the preceding claims, wherein the oligonucleotide is capable of decreasing the level, expression and/or activity of a target gene or a gene product thereof via a mechanism involving RNase H.

11. The composition of any of the preceding claims, wherein the oligonucleotide is capable of decreasing the level, expression and/or activity of a target gene or a gene product thereof via a mechanism involving steric hindrance.

12. The composition of any of the preceding claims, wherein the oligonucleotide is capable of annealing to a target mRNA and decreasing the level of translation of the target mRNA.

13. The composition of any of the preceding claims, wherein the oligonucleotide is capable of annealing to a target RNA and decreasing the level of translation of the target RNA via a mechanism involving steric hindrance.

14. The composition of any of the preceding claims, wherein the core is capable of annealing to a target nucleic acid, forming a substrate for RNase H and allowing cleavage of the target nucleic acid by RNase H.

15. The composition of any of the preceding claims, wherein the core comprises one or more 2'-deoxyribose sugar moieties.

16. The composition of any of the preceding claims, wherein the core comprises one or more 2'-deoxyribose sugar moieties and is capable of annealing to a target nucleic acid, forming a substrate for RNase H and allowing cleavage of the target nucleic acid by RNase H.

17. The composition of any of the preceding claims, wherein the core comprises five or more 2'-deoxyribose sugar moieties and is capable of annealing to a target nucleic acid, forming a substrate for RNase H and allowing cleavage of the target nucleic acid by RNase H.

18. The composition of any of the preceding claims, wherein a sugar is a 2'-deoxyribose or a bicyclic sugar, and a sugar modification is 2'-MOE, 2'-OMe, or 2'-F.

19. The composition of any of the preceding claims, wherein an internucleotidic linkage is a phosphodiester linkage, a phosphorothioate, or a non-negatively-charged internucleotidic linkage.

20. The composition of any of the preceding claims, wherein the oligonucleotide comprises a stereorandom internucleotidic linkage.

21. The composition of any of the preceding claims, wherein the oligonucleotide comprises a chirally controlled internucleotidic linkage.

22. The composition of any of the preceding claims, wherein the pattern of backbone chiral centers of the oligonucleotide comprises a chiral internucleotidic linkage in the Rp conformation and/or a chiral internucleotidic linkage in the Sp conformation.

23. The composition of any of the preceding claims, wherein the oligonucleotide comprises a chiral internucleotidic linkage in the Sp conformation.

24. The composition of any of the preceding claims, wherein the oligonucleotide comprises a phosphorothioate linkage in the Sp conformation.

25. The composition of any of the preceding claims, wherein the first wing and second wing comprise a different sugar or sugar modification(s) or combination or pattern thereof.

26. The composition of any of the preceding claims, wherein the first wing and second wing comprise a different internucleotidic linkage(s) or combination or pattern thereof.

27. The composition of any of the preceding claims, wherein the first wing and second wing comprise a different stereochemistry of internucleotidic linkage(s) or combination or pattern thereof.

28. The composition of any of the preceding claims, wherein the first wing comprises a sugar or sugar modification not present in the core, and wherein the second wing comprises a sugar or sugar modification not present in the first wing or core.

29. The composition of any of the preceding claims, wherein the first wing comprises a first sugar or sugar modification not present in the core, and wherein the second wing comprises a first sugar or sugar modification not present in the first wing or core, and wherein the second wing further comprises a second sugar or sugar modification not present in the first wing or core.

30. The composition of any of the preceding claims, wherein the core does not comprise a 2'-OMe; the first wing comprises a 2'-OMe; and the second wing comprises a 2'-sugar modification which is not 2'-OMe and which is not present in the core.

31. The composition of any of the preceding claims, wherein the core does not comprise a 2'-MOE; the first wing comprises a 2'-MOE; and the second wing comprises a 2'-sugar modification which is not 2'-MOE and which is not present in the core.

32. The composition of any of the preceding claims, wherein the core does not comprise a 2'-F; the first wing comprises a 2'-F; and the second wing comprises a 2'-sugar modification which is not 2'-F and which is not present in the core.

33. The composition of any of the preceding claims, wherein the core does not comprise a bicyclic sugar; the first wing comprises a bicyclic sugar; and the second wing comprises a 2'-sugar modification which is not bicyclic sugar and which is not present in the core.

34. The composition of any of the preceding claims, wherein the core does not comprise a 2'-OMe or 2'-MOE; the first wing comprises a 2'-OMe and a 2'-MOE; and the second wing comprises a 2'-MOE and does not comprise a 2'-OMe.

35. The composition of any of the preceding claims, wherein the core does not comprise a 2'-OMe or 2'-MOE; the first wing comprises a 2'-OMe and a 2'-MOE; and the second wing comprises a 2'-OMe and does not comprise a 2'-MOE.

36. The composition of any of the preceding claims, wherein the core does not comprise a 2'-OMe, 2'-MOE or 2'-F; the first wing comprises a 2'-OMe and a 2'-MOE; and the second wing comprises a 2'-F and does not comprise both a 2'-MOE and a 2'-OMe.

37. The composition of any of the preceding claims, wherein the core does not comprise a 2'-OMe, 2'-MOE or 2'-F; the first wing comprises a 2'-OMe and not a 2'-MOE or a 2'-F; and the second wing comprises a 2'-MOE and does not comprise a 2'-OMe or a 2'-F.

38. The composition of any of the preceding claims, wherein the core does not comprise a 2'-OMe, 2'-MOE or 2'-F; the first wing comprises a 2'-F and not a 2'-MOE or a 2'-OMe; and the second wing comprises a 2'-OMe and does not comprise a 2'-MOE or a 2'-F.

39. The composition of any of the preceding claims, wherein the core does not comprise a 2'-OMe, 2'-MOE or 2'-F; the first wing comprises a 2'-F and not a 2'-MOE or a 2'-OMe; and the second wing comprises a 2'-MOE and does not comprise a 2'-OMe or a 2'-F.

40. A chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides which have:

a) a common base sequence;

b) a common pattern of backbone linkages;

c) a common pattern of backbone chiral centers;

wherein level of the plurality of oligonucleotides in the composition is not random; and

wherein each oligonucleotide of the particular oligonucleotide type is independently an oligonucleotide of any one of the preceding claims or a salt thereof.

41. An oligonucleotide composition comprising oligonucleotides of a particular oligonucleotide type characterized by:

a) a common base sequence;

b) a common pattern of backbone linkages;

c) a common pattern of backbone chiral centers;

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

wherein each oligonucleotide of the particular oligonucleotide type is independently an oligonucleotide of any one of the preceding claims or a salt thereof.

42. The composition of any one of claims 41-42, wherein at least 0.1%, 0.5%, 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% of all oligonucleotides in the composition that have common base sequence are oligonucleotides of the plurality or type.

43. The composition of any one of claims 41-43, wherein at least 0.1%, 0.5%, 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% of all oligonucleotides in the composition have the common base sequence.

44. The composition of any one of claims 42 or 43, wherein the percentage is at least 5%.

45. The composition of any one of claims 42 or 43, wherein the percentage is at least 10%.

46. A pharmaceutical composition comprising an oligonucleotide of any one of claims 1-39 or a pharmaceutically acceptable salt thereof.

47. The composition of claim 46, wherein the composition comprises a sodium salt of an oligonucleotide of any one of claims 1-39.

48. The composition or an oligonucleotide of any one of the preceding claims, wherein oligonucleotides of the composition or the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more non-negatively charged internucleotidic linkages.

49. A method for selective suppression of a transcript from a target nucleic acid sequence for which one or more similar sequences exist within a population, each of which contains a specific nucleotide characteristic sequence element that defines the target nucleic acid sequence relative to the similar sequences, the method comprising steps of:

contacting a sample comprising transcripts of the target nucleic acid sequence with a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides that have

1) a common base sequence;

2) a common pattern of backbone linkages;

3) a common pattern of backbone chiral centers;

wherein the common base sequence for the oligonucleotides of the particular oligonucleotide type is or comprises a sequence that is complementary to the characteristic sequence element that defines the target nucleic acid sequence.

50. The method of claim 49, wherein a characteristic sequence element is or comprises one or more nucleobases that differentiate the target nucleic acid sequence from similar sequence(s) in a genome and/or products encoded thereby.

51. The method of claim 49, wherein a characteristic sequence element is a nucleobase that differentiates the target nucleic acid sequence from similar sequence(s) in a genome and/or products encoded thereby.

52. The method of any one of claims 49-51, wherein a similar sequence shares at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% but less than 100% homology with the target nucleic acid sequence within the portion of the sequence that is complementary to the common base sequence.

53. The method of any one of claims 49-52, wherein a similar sequence differs at no more than 5, 4, 3, 2, or 1 nucleobases from but not identical with the target nucleic acid sequence within the portion of the sequence that is complementary to the common base sequence.

54. The method of any one of claims 49-52, wherein a similar sequence differs at only 1 nucleobases from the target nucleic acid sequence within the portion of the sequence that is complementary to the common base sequence.

55. A method for allele-specific suppression of a transcript from a target nucleic acid sequence for which a plurality of alleles exist within a population, each of which contains a specific nucleotide characteristic sequence element that defines the allele relative to other alleles of the same target nucleic acid sequence, the method comprising steps of:

contacting a sample comprising transcripts of the target nucleic acid sequence with a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides that have

1) a common base sequence;

2) a common pattern of backbone linkages;

3) a common pattern of backbone chiral centers;

wherein the common base sequence for the oligonucleotides of the particular oligonucleotide type is or comprises a sequence that is complementary to the characteristic sequence element that defines a particular allele.

56. The method of any one of claims 49-55, wherein a characteristic sequence element is a SNP.

57. The method of any one of claims 49-55, wherein a characteristic sequence element is a mutation.

58. The method of any one of claims 49-57, wherein the composition provides suppression of the transcript at a level that is greater than when the composition is absent.

59. The method of any one of claims 49-58, wherein the composition provides suppression of the transcript at a level that is greater than a level of suppression observed for another allele or a similar sequence.

60. The method of any one of claims 49-59, wherein the chirally controlled oligonucleotide composition is a chirally controlled oligonucleotide composition of an oligonucleotide of any one of claims 1-39 and 48 or a composition of any one of claims 40-48.

61. A method for reducing a level of a transcript or a protein encoded thereby in a system, comprising administering an oligonucleotide or a composition of any one of the preceding claims.

62. A compound, oligonucleotide, composition, or method of any one of embodiments 1-431.

FIG. 1A

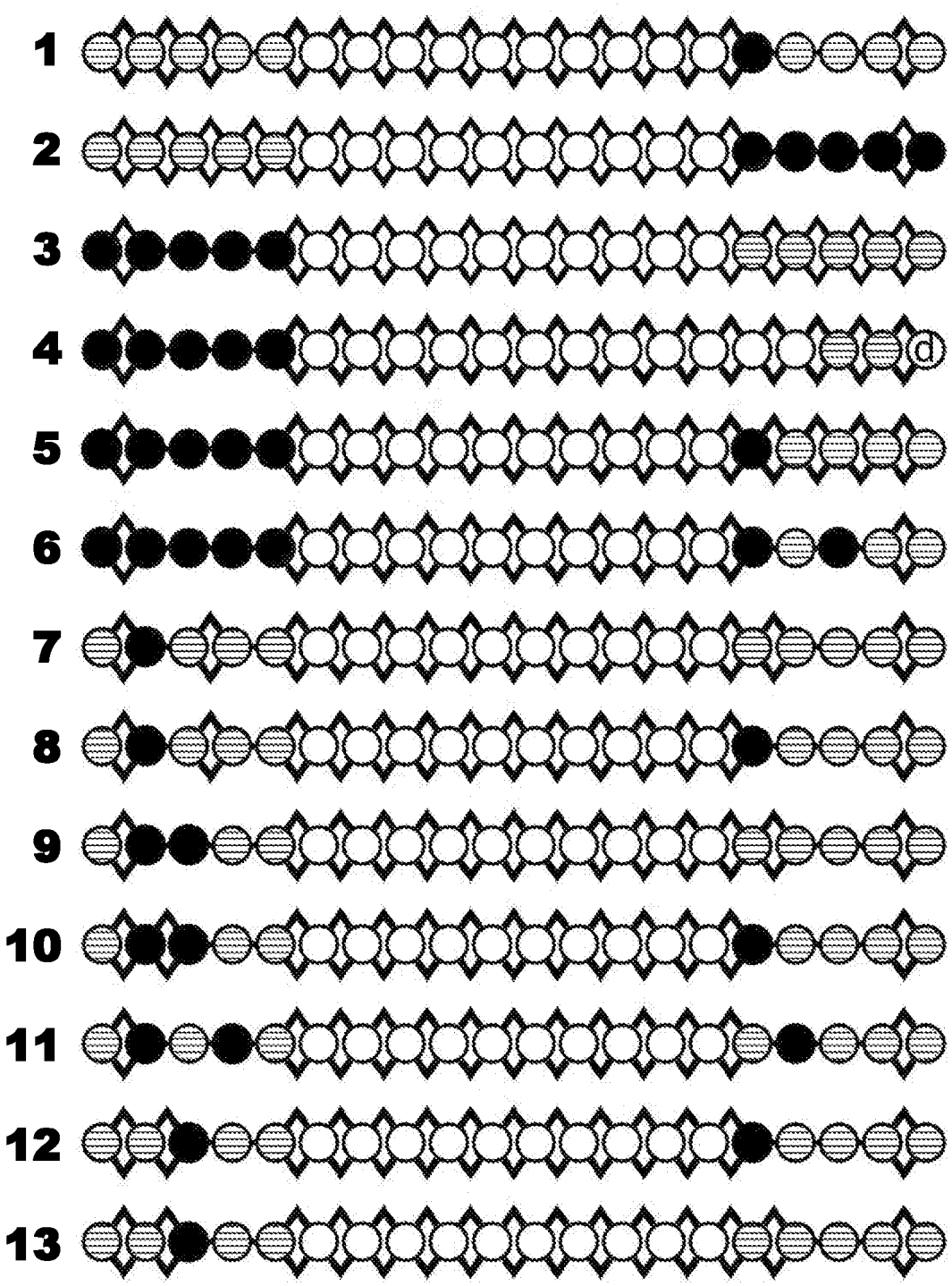


FIG. 1B

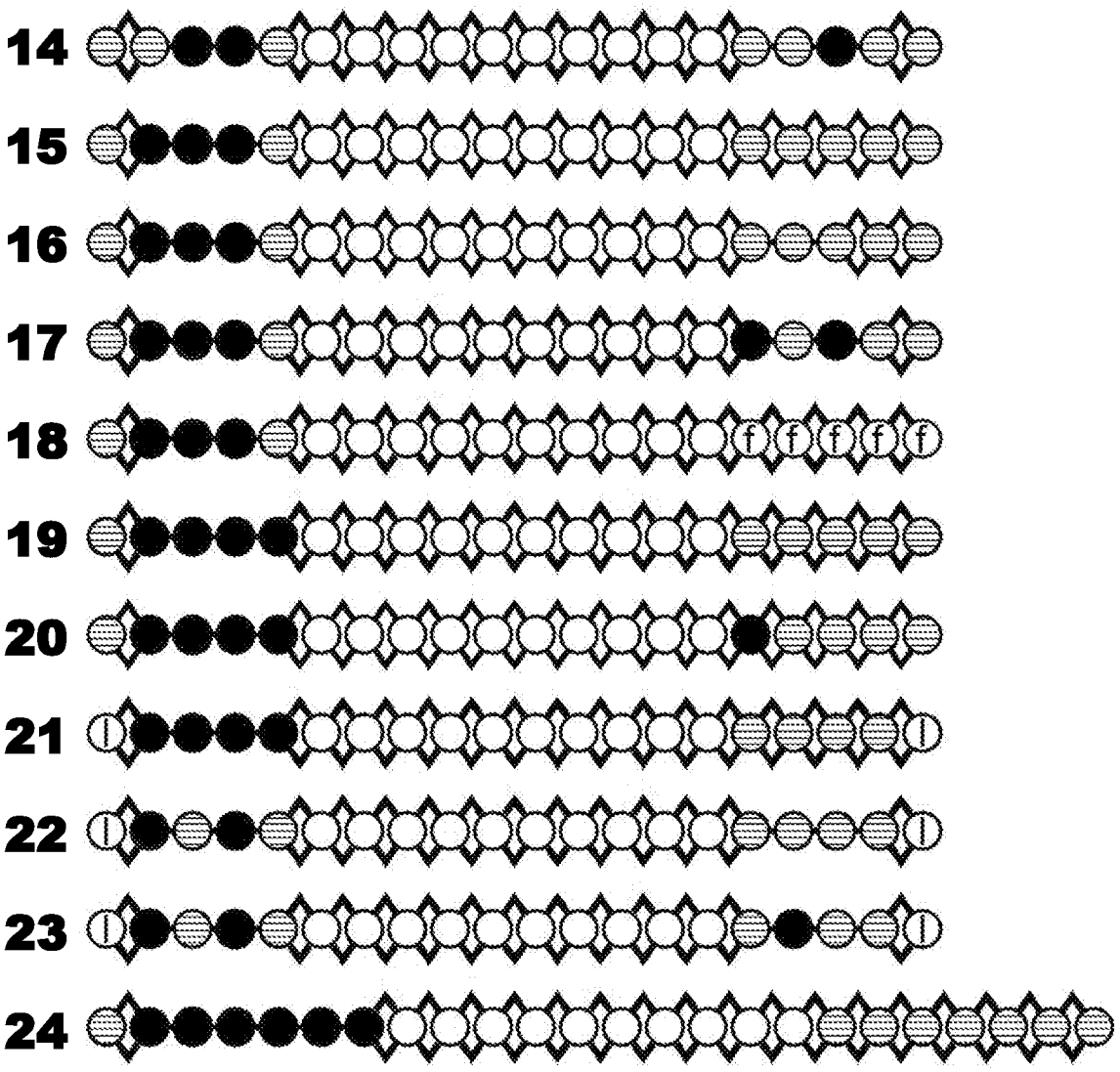


FIG. 1C

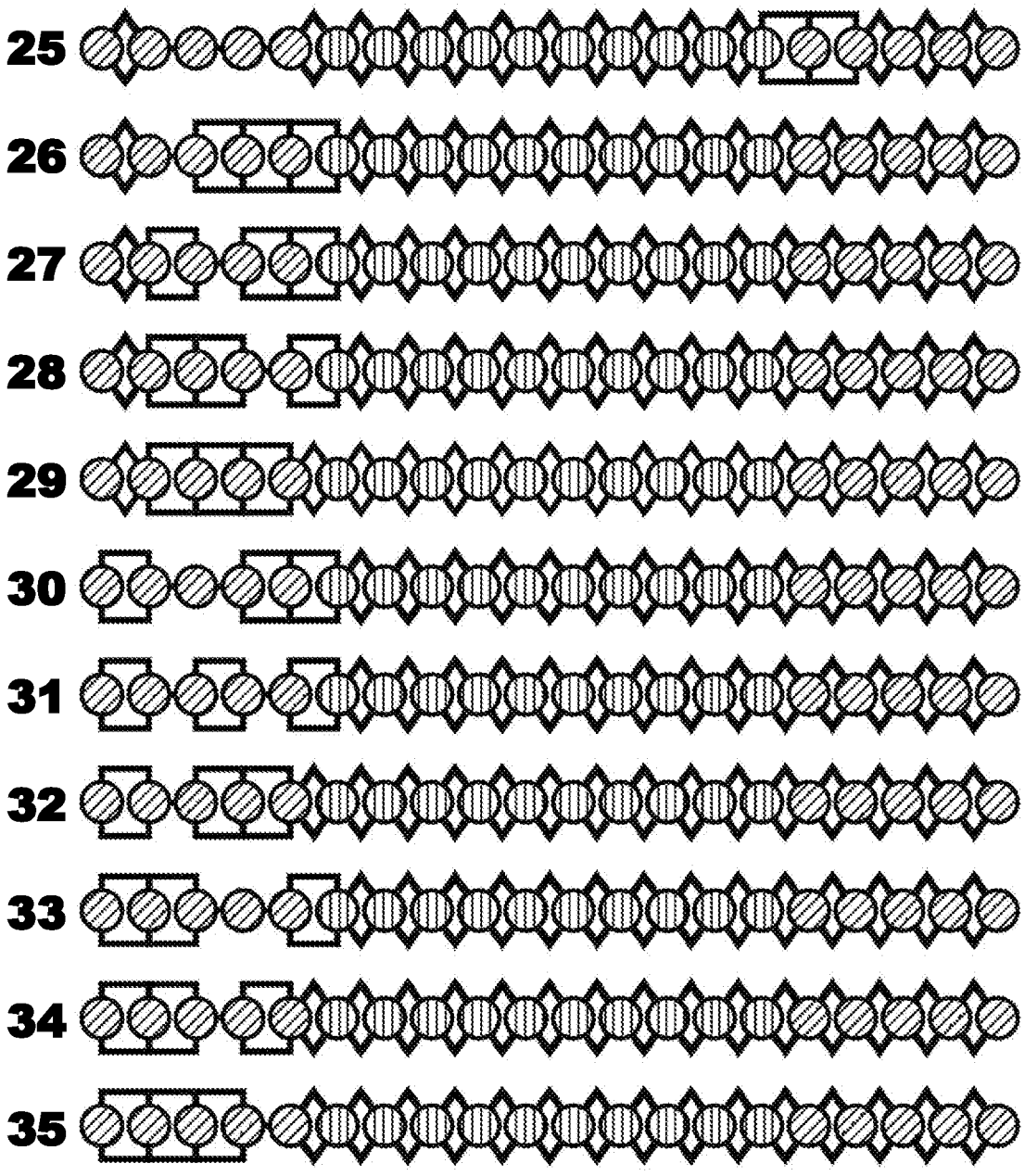


FIG. 1D

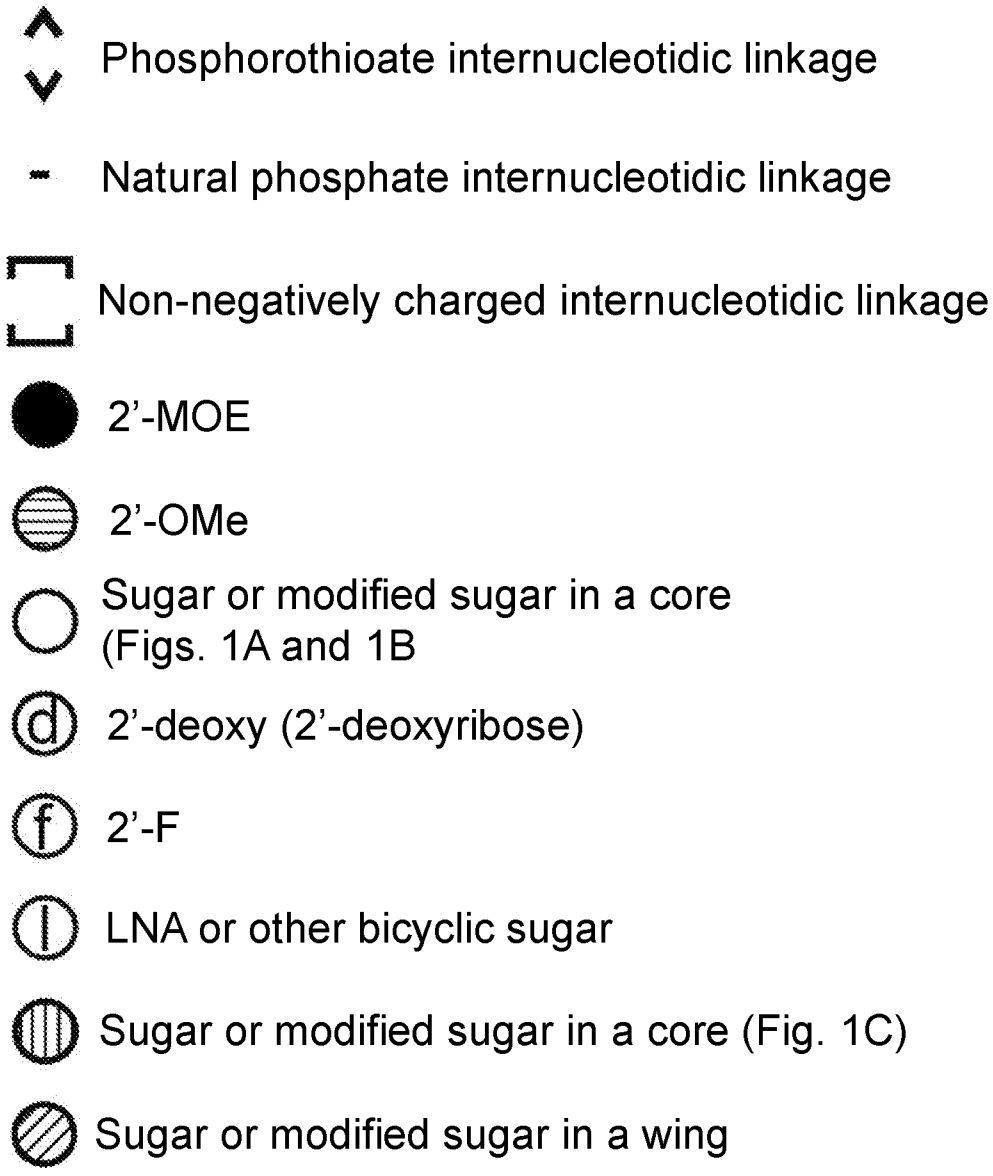

Phosphorothioate internucleotidic linkage
Natural phosphate internucleotidic linkage
Non-negatively charged internucleotidic linkage
2'-MOE
2'-OMe
Sugar or modified sugar in a core (Figs. 1A and 1B
2'-deoxy (2'-deoxyribose)
2'-F
LNA or other bicyclic sugar
Sugar or modified sugar in a core (Fig. 1C)
Sugar or modified sugar in a wing

FIG. 2

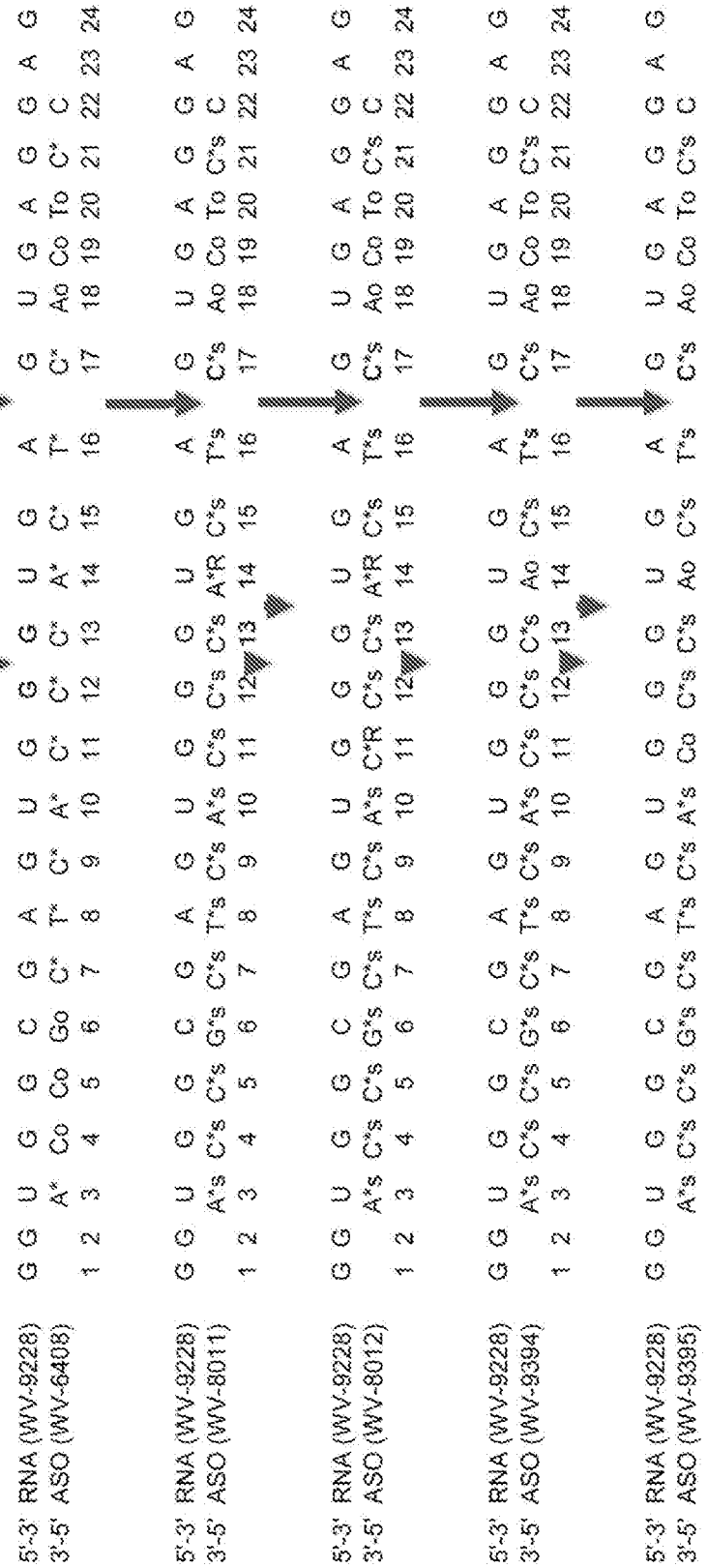

5'-3' RNA (WV-9228)
3'-5' ASO (WV-6408)
5'-3' RNA (WV-9228)
3'-5' ASO (WV-8011)
5'-3' RNA (WV-9228)
3'-5' ASO (WV-8012)
5'-3' RNA (WV-9228)
3'-5' ASO (WV-9394)
5'-3' RNA (WV-9228)
3'-5' ASO (WV-9395)

FIG. 3

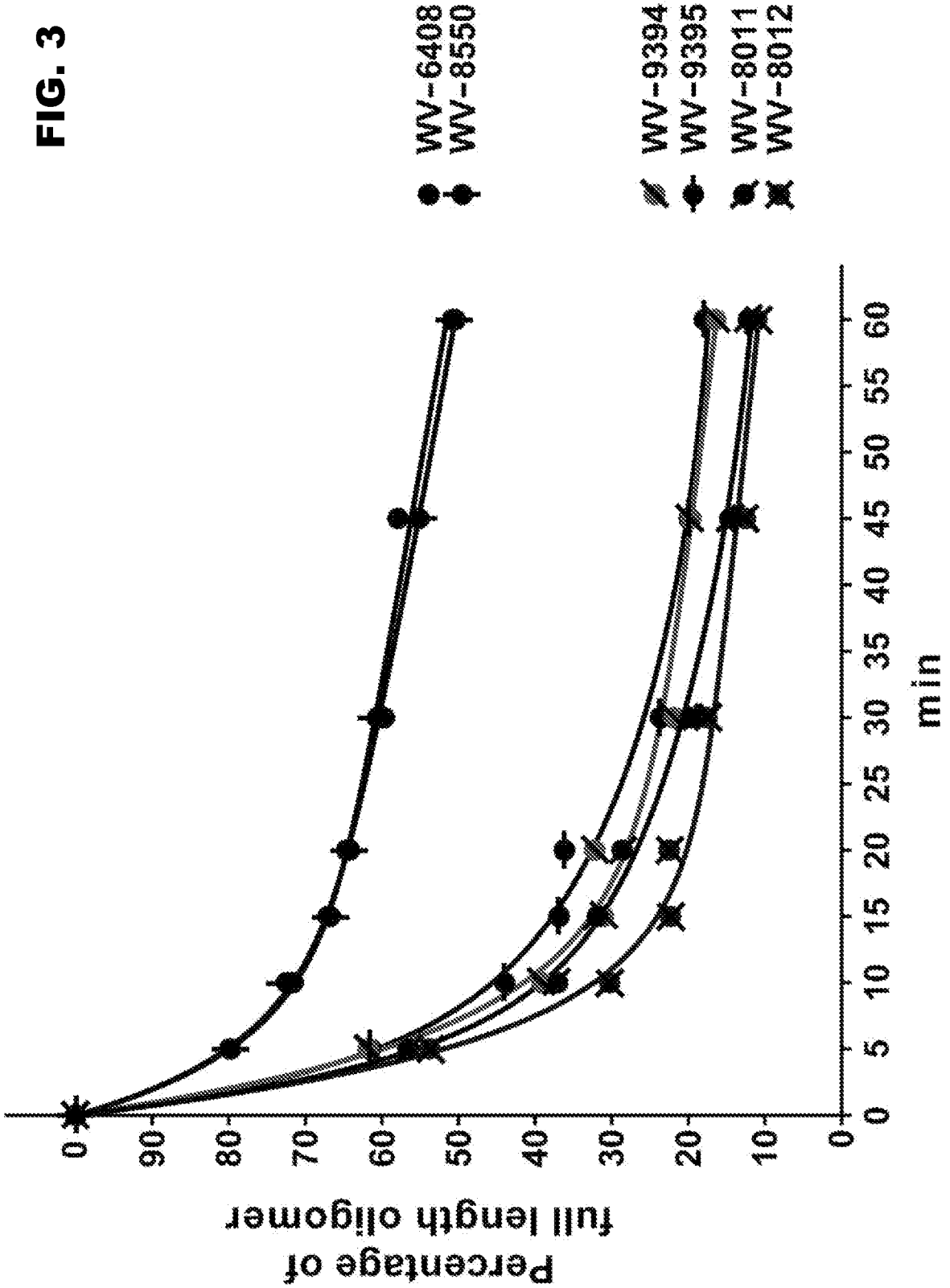

WV-6408
WV-8550
WV-9394
WV-9395
WV-8011
WV-8012
Percentage of full length oligomer
0
10
20
30
40
50
60
70
80
90
0
5
10
15
20
25
30
35
40
45
50
55
60
min

FIG. 4

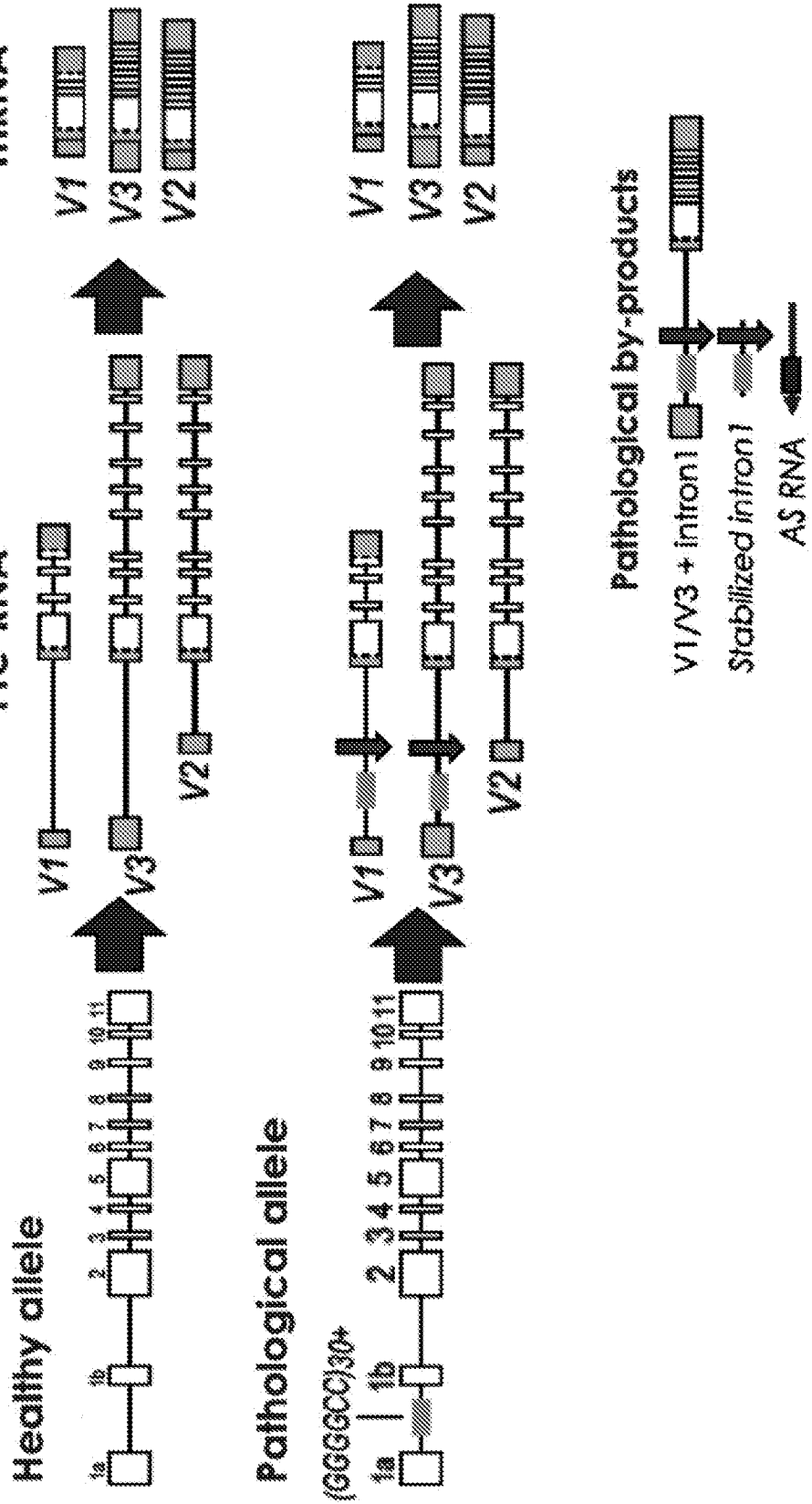
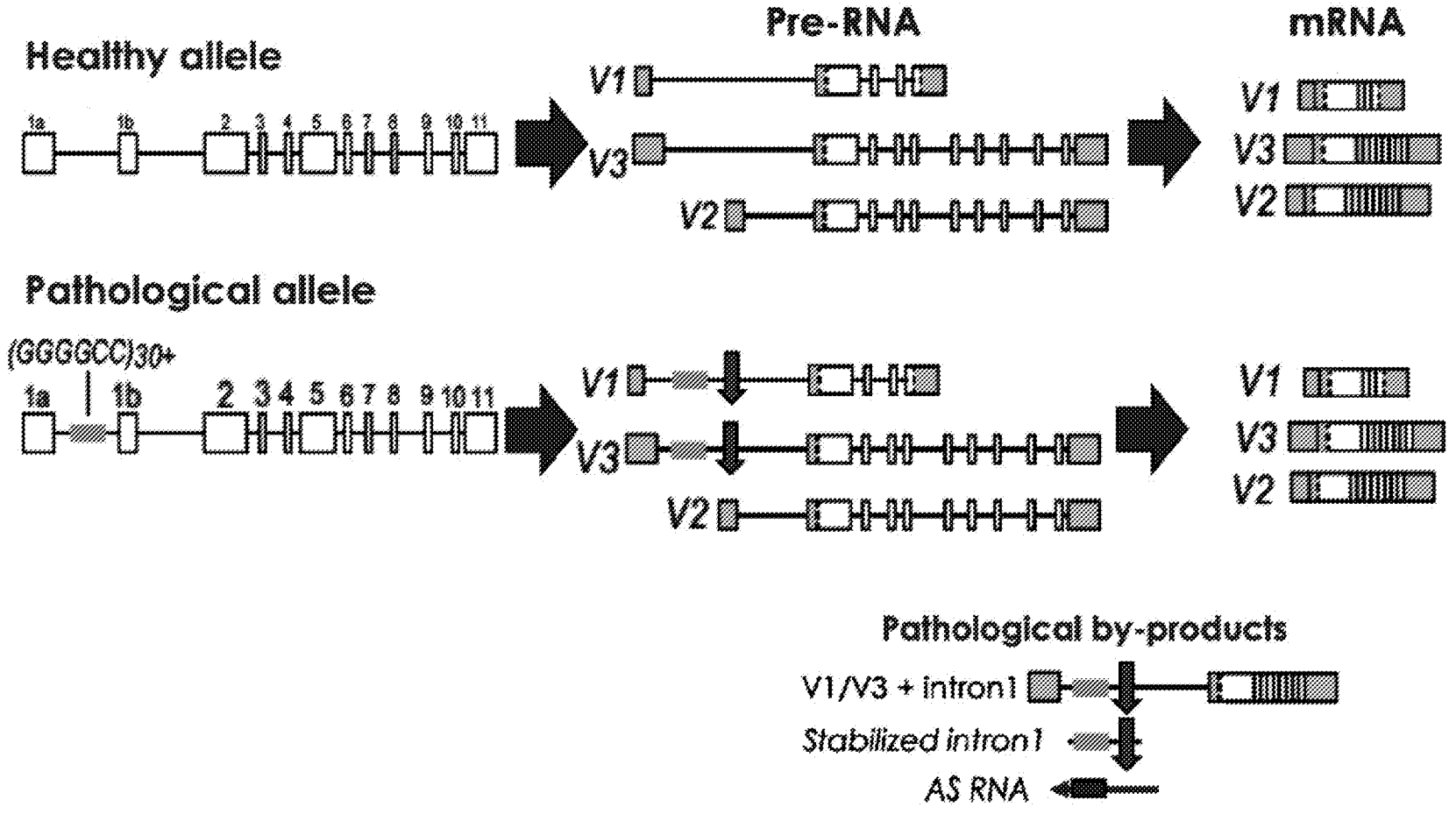

mRNA
V1
V3
V2
Pre-RNA
Healthy allele
1a
1b
2
3
4
5
6
7
8
9
10
11
Pathological allele
(GGGGCC)30+
Pathological by-products
V1/V3 + intron1
Stabilized intron1
AS RNA

FIG. 4


Healthy allele
Pre-RNA
mRNA
1a
1b
2
3
4
5
6
7
8
9
10
11
V1
V3
V2
Pathological allele
(GGGGCC)30+
Pathological by-products
V1/V3 + intron1
Stabilized intron1
AS RNA