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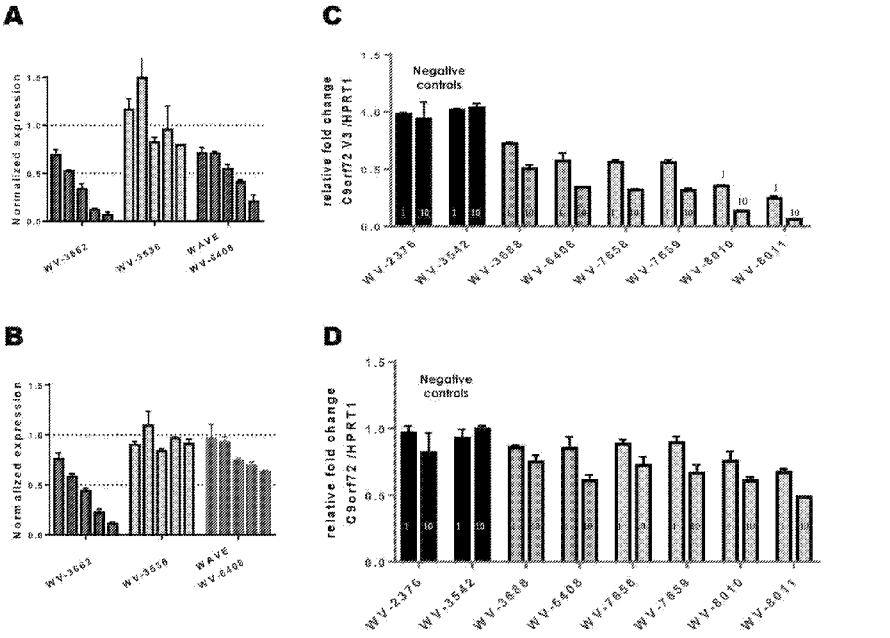
(54) Title: OLIGONUCLEOTIDE COMPOSITIONS AND METHODS THEREOF

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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OLIGONUCLEOTIDE COMPOSITIONS AND METHODS THEREOF

BACKGROUND

[0001] Oligonucleotides targeting the gene C9orf72 (e.g., C9orf72 oligonucleotides) are useful in various applications, e.g., therapeutic, diagnostic, and/or research applications, including but not limited to treatment of various C9orf72-related disorders.

SUMMARY

[0002] The present disclosure provides oligonucleotides, and compositions thereof, that can reduce levels of C9orf72 transcripts (or products thereof). In some embodiments, provided oligonucleotides and compositions can preferentially reduce levels of disease-associated transcripts of C9orf72 (or products thereof) over non-disease-associated transcripts of C9orf72 (see, *e.g.*, Figure 1). Example C9orf72 transcripts include transcripts from either strand of the C9orf72 gene and from various starting points. In some embodiments, at least some C9orf72 transcripts are translated into proteins; in some embodiments, at least some C9orf72 transcripts are not translated into proteins. In some embodiments, certain C9orf72 transcripts contain predominantly intronic sequences.

[0003] A hexanucleotide repeat expansion in C9orf72 (Chromosome 9, open reading frame 72) is reportedly the most frequent genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). C9orf72 gene variants comprising the repeat expansion and/or products thereof are also associated with other C9orf72-related disorders, such as corticobasal degeneration syndrome (CBD), atypical Parkinsonian syndrome, olivopontocerebellar degeneration (OPCD), primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), Huntington's disease (HD) phenocopy, Alzheimer's disease (AD), bipolar disorder, schizophrenia, and other non-motor disorders. In some embodiments, the present disclosure provides compositions and methods related to oligonucleotides which target a C9orf72 target (e.g., a C9orf72 oligonucleotide) and are capable of knocking down or decreasing expression, level and/or activity of the C9orf72 target gene and/or a gene product thereof (a transcript, particularly a repeat expansion containing transcript, a protein, *etc.*).

[0004] In some embodiments, an oligonucleotide targets a pathological or disease-associated C9orf72 mutation or variant comprising a repeat expansion. In some embodiments, a C9orf72 gene product is a RNA (e.g., a mRNA, mature RNA or pre-mRNA) transcribed from a C9orf72 gene, a protein translated from a C9orf72 RNA transcript (e.g., a dipeptide repeat protein translated from the hexanucleotide repeat), or a focus (plural: foci) (which reportedly comprises RNA comprising the repeat expansion bound by RNA-binding proteins). In some embodiments, a C9orf72 oligonucleotide is capable of mediating preferential knockdown of a repeat expansion-containing C9orf72 RNA relative to a non-

repeat expansion-containing C9orf72 RNA (a C9orf72 RNA which does not contain a repeat expansion). In some embodiments, a C9orf72 oligonucleotide decreases the expression, activity and/or level of a deleterious C9orf72 gene product (e.g., a RNA comprising a repeat expansion, a dipeptide repeat protein or a focus) without decreasing the expression, activity and/or level of a wild-type or non-deleterious C9orf72 gene product. In some embodiments, a C9orf72 oligonucleotide decreases the expression, activity and/or level of a deleterious C9orf72 gene product, but does not decrease the expression, activity and/or level of a wild-type or non-deleterious C9orf72 protein enough to eliminate or significantly suppress a beneficial and/or necessary biological activity or activities of C9orf72 protein. Beneficial and/or necessary activities of C9orf72 protein are widely known and include but not limited to restricting inflammation, preventing autoimmunity and preventing premature mortality.

[0005] Among other things, the present disclosure encompasses the recognition that controlling structural elements of C9orf72 oligonucleotides can have a significant impact on oligonucleotide properties and/or activities, including knockdown of a C9orf72 target gene. In some embodiments, knockdown of a target gene is mediated by RNase H or steric hindrance affecting translation. In some embodiments, controlled structural elements of C9orf72 oligonucleotides include but are not limited to: base sequence, chemical modifications (e.g., modifications of a sugar, base and/or internucleotidic linkage) or patterns thereof, alterations in stereochemistry (e.g., stereochemistry of a backbone chiral internucleotidic linkage) or patterns thereof, wing structure, core structure, wing-core structure, wing-core-wing structure, or core-wing structure, and/or conjugation with an additional chemical moiety (e.g., a carbohydrate moiety, a targeting moiety, etc.). In some embodiments, the present disclosure provides technologies (e.g., compounds, methods, etc.) for improving C9orf72 oligonucleotide stability while maintaining or increasing oligonucleotide activity, including compositions of improved-stability oligonucleotides. In some embodiments, provided oligonucleotides target C9orf72 or products thereof. In some embodiments, a target gene is a C9orf72.

[0006] In some embodiments, the present disclosure encompasses the recognition that various optional additional chemical moieties, such as carbohydrate moieties, targeting moieties, etc., when incorporated into c9orf72 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. These and other moieties are described in more detail herein, e.g., in Examples 1 and 2. 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 category (e.g., carbohydrate moiety, sugar moiety, targeting moiety, etc.) or not of the same category. In some embodiments, certain additional chemical moieties facilitate delivery of oligonucleotides to desired cells, tissues and/or organs, including but not limited to particular cells, parts or portions of the central nervous

system (e.g., cerebral cortex, hippocampus, spinal cord, etc.). In some embodiments, certain additional chemical moieties facilitate internalization of oligonucleotides. In some embodiments, certain additional chemical moieties increase oligonucleotide stability. In some embodiments, the present disclosure provides technologies for incorporating various additional chemical moieties into oligonucleotides. In some embodiments, the present disclosure provides, for example, reagents and methods, for introducing additional chemical moieties through internucleotidic linkages, sugars and/or nucleobases (e.g., by covalent linkage, optionally via a linker, to a site on a sugar, a nucleobase, or an internucleotidic linkage).

[0007] In some embodiments, the present disclosure demonstrates that surprisingly high target specificity can be achieved with oligonucleotides, e.g., C9orf72 oligonucleotides, whose structures include one or more features as described herein [including, but not limited to, base sequences disclosed herein (wherein each U can be optionally and independently substituted by T and vice versa), and/or chemical modifications and/or stereochemistry and/or patterns thereof and/or combinations thereof, e.g., examples illustrated in Figure 2].

[0008] In some embodiments, the present disclosure demonstrates that certain provided structural elements, technologies and/or features are particularly useful for oligonucleotides that knock down C9orf72. Regardless, however, the teachings of the present disclosure are not limited to oligonucleotides that participate in or operate via any particular biochemical mechanism. In some embodiments, the present disclosure provides oligonucleotides capable of operating via a mechanism such as double-stranded RNA interference, single-stranded RNA interference or which acts as an antisense oligonucleotide which decreases the expression, activity and/or level of a C9orf72 gene or a gene product thereof via a RNase H-mediated mechanism or steric hindrance of translation.

[0009] Further, the present disclosure pertains to any C9orf72 oligonucleotide which operates through any mechanism, and which comprises any sequence, structure or format (or portion thereof) described herein, wherein the oligonucleotide comprises at least one non-naturally-occurring modification of a base, sugar or internucleotidic linkage. In some embodiments, the present disclosure pertains to any C9orf72 oligonucleotide which comprises at least one stereocontrolled internucleotidic linkage (including but not limited to a phosphorothioate linkage in the Sp or Rp configuration). In some embodiments, the present disclosure pertains to any C9orf72 oligonucleotide which operates through any mechanism, and which comprises at least one stereocontrolled internucleotidic linkage (including but not limited to a phosphorothioate linkage in the Sp or Rp configuration). In some embodiments, the present disclosure provides a C9orf72 oligonucleotide which comprises any sequence, 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.

[0010] In some embodiments, a C9orf72 disorder-associated target allele contains a hexanucleotide repeat expansion in intron 1, including but not limited to G4C2 or (GGGGCC)ng, wherein ng is 30 or more. In some embodiments, ng is 50 or more. In some embodiments, ng is 100 or more. In some embodiments, ng is 150 or more. In some embodiments, ng is 200 or more. In some embodiments, ng is 300 or more. In some embodiments, ng is 500 or more.

[0011] The C9orf72 G4C2 repeat expansion in intron 1 reportedly accounts for 1 in 10 ALS cases among European-ancestry populations. G4C2 repeats are reportedly of only about ~10% of the transcripts (e.g., transcripts V3 and V1 of the pathological allele illustrated in Figure 1), with gain of function toxicities, at least partially mediated by the dipeptide repeat proteins and foci formation by, for example, repeat-expansion containing transcripts and/or spliced-out repeat-expansion containing introns and/or antisense transcription of the repeat-expansion containing region and various nucleic-acid binding proteins. In some embodiments, V1 is reportedly transcribed at very low levels (around 1% of the total C9orf72 transcript level) and does not contribute significantly to the levels of transcripts comprising hexanucleotide repeat expansions. Reportedly, intron nucleic acid containing repeat expansions can be retained as pre-mRNA, partially spliced RNA, and/or spliced out introns, and RNA foci comprising these nucleic acids are associated with RNA binding protein sequestration. C9orf72 RNA foci are described in, for example, Liu et al., 2017, Cell Chemical Biology 24, 1–8; Niblock et al. Acta Neuropathologica Communications (2016) 4:18. Aberrant protein products comprising dipeptide repeat proteins (DPR proteins) are reportedly produced from the repeat expansion, with toxicity to neurons. In some embodiment, the present disclosure provides oligonucleotides and compositions and methods thereof which target an intron sequence close to the G4C2 repeats, and can reduce levels of repeat expansion-containing transcripts, proteins encoded thereby, and/or related foci. In some embodiment, the present disclosure provides C9orf72 oligonucleotides and compositions thereof which target an intron sequence close to the G4C2 repeats, to specifically knockdown the repeat expansion-containing transcripts via RNAse-H, with minimal impact on normal C9orf 72 transcripts. In some embodiments, compared to existing data, the present disclosure demonstrates that provided technologies targeting an intron sequence (*e.g.*, between the repeats and exon 1b) can effectively and/or preferentially reduce levels of repeat expansion-containing products.

[0012] Without wishing to be bound by any particular theory, the present disclosure notes that several possible mechanisms for the deleterious and disease-associated effects of the repeat expansion have been proposed in the literature. See for example: Edbauer et al. 2016 Curr. Opin. Neurobiol. 36: 99-106; Conlon et al. Elife. 2016 Sep 13;5. pii: e17820; Xi et al. 2015 Acta Neuropathol. 129: 715-727; Cohen-Hada et al. 2015 Stem Cell Rep. 7: 927-940; and Burguete et al. eLife 2015;4:e08881. Among

other things, the present disclosure provides technologies that can reduce or remove one or more or all deleterious and disease-associated C9orf72 products and/or disease-associated effects.

[0013] Without wishing to be bound by any particular theory, the present disclosure notes that a possible mechanism of a deleterious effect of repeat expansion-containing C9orf72 transcripts is the generation of foci. Reportedly, the repeat expansion results in retention of intron 1-containing C9orf72 mRNA. The majority of intron 1-retaining C9orf72 mRNA accumulates in the nucleus where it is targeted to a specific degradation pathway unable to process G4C2 RNA repeats. The RNAs subsequently aggregate into foci, which also comprise RNA-binding proteins, sequestering them from their normal functions. Niblock Acta Neuropathol Commun. 2016; 4: 18. Reportedly antisense foci comprising antisense C9orf72 products are present at a significantly higher frequency in cerebellar Purkinje neurons and motor neurons, whereas sense foci are present at a significantly higher frequency in cerebellar granule neurons. Cooper-Knock et al. Acta Neuropathol (2015) 130:63–75. In some embodiments, the present disclosure provides technologies for reducing levels of foci. In some embodiments, provided technologies reduce levels of or remove antisense foci and/or sense foci in one or more types of neurons.

[0014] Without wishing to be bound by any particular theory, the present disclosure notes that another possible mechanism of a deleterious effect of repeat expansion-containing C9orf72 transcripts is the generation of dipeptide repeat (DPR) proteins. A small proportion of intron 1-retaining C9orf72 mRNA is exported to the cytoplasm for RAN (repeat-associated non-AUG translation) translation in all six reading frames into DPRs. Niblock Acta Neuropathol Commun. 2016; 4: 18. Cooper-Knock et al. also reported that inclusions containing sense or antisense derived dipeptide repeat proteins were present at significantly higher frequency in cerebellar granule neurons or motor neurons, respectively; and in motor neurons, which are the primary target of pathology in ALS, the presence of antisense foci but not sense foci correlated with mislocalisation of TDP-43, which is a hallmark of ALS neurodegeneration. In some embodiments, provided technologies reduce levels of one or more or all of C9orf72 DPR protein products.

[0015] In some embodiments, gain- and/or loss-of-function mechanisms lead to neurodegeneration in a C9orf72-related disorder. See, for example, : Mizielinska et al. 2014 Science 345: 1192-94; Chew et al. 2015 Science 348: 1151-1154; Jiang et al. 2016 Neuron 90: 535-550; and Liu et al. 2016 Neuron 90: 521-534; Gendron et al. Cold Spring Harb. Perspect. Med. 2017 Jan 27. pii: a024224; Haeusler et al. Nat Rev Neurosci. 2016 Jun; 17(6):383-95; Koppers et al. Ann. Neurol. 2015;78:426–438; Todd et al. J. Neurochem. 2016 138 (Suppl. 1) 145–162. In some embodiments, provided technologies reduce undesired gained functions, and/or restore or enhance desired functions.

[0016] In some embodiments, provided oligonucleotides and compositions and methods thereof

are useful for treatment of any of several C9orf72-related disorders, including but not limited to amyotrophic lateral sclerosis (ALS). In some embodiments, ALS is MIM: 612069. Amyotrophic lateral sclerosis (ALS) is a reportedly a fatal neurodegenerative disease characterized clinically by progressive paralysis leading to death, often from respiratory failure, typically within two to three years of symptom onset (Rowland and Shneider, N. Engl. J. Med., 2001, 344, 1688-1700). ALS reportedly is the third most common neurodegenerative disease in the Western world (Hirtz et al., Neurology, 2007, 68, 326-337), and there are currently no effective therapies. Approximately 10% of cases are familial in nature, whereas the bulk of patients diagnosed with the disease are classified as sporadic as they appear to occur randomly throughout the population (Chio et al., Neurology, 2008, 70, 533-537). Clinical, genetic, and epidemiological data reportedly support the hypothesis that ALS and frontotemporal dementia (FTD) represent an overlapping continuum of disease, characterized pathologically by the presence of TDP-43 positive inclusions throughout the central nervous system (Lillo and Hodges, J. Clin. Neurosci., 2009, 16, 1131-1135; Neumann et al., Science, 2006, 314, 130-133). A number of genes have been discovered as potentially causative for classical familial ALS, for example, SOD1, TARDBP, FUS, OPTN, and VCP (Johnson et al., Neuron, 2010, 68, 857-864; Kwiatkowski et al., Science, 2009, 323, 1205-1208; Maruyama et al., Nature, 2010, 465, 223-226; Rosen et al., Nature, 1993, 362, 59-62; Sreedharan et al., Science, 2008, 319, 1668-1672; Vance et al., Brain, 2009, 129, 868-876). Linkage analysis of kindreds involving multiple cases of ALS, FTD, and ALS-FTD had reportedly suggested that there was an important locus for the disease on the short arm of chromosome 9, identified as C9orf72 (Boxer et al., J. Neurol. Neurosurg. Psychiatry, 2011, 82, 196-203; Morita et al., Neurology, 2006, 66, 839-844; Pearson et al. J. Neurol., 2011, 258, 647-655; Vance et al., Brain, 2006, 129, 868-876). This mutation had been found to be the most common genetic cause of ALS and FTD. In some embodiments, ALS-FTD causing mutation is a large hexanucleotide (e.g., GGGGCC or G_4C_2) repeat expansion in the first intron of the C9orf72 gene on chromosome 9 (Renton et al., Neuron, 2011, 72, 257-268; DeJesus-Hernandez et al., Neuron, 2011, 72, 245-256). A founder haplotype, covering the C9orf72 gene, is present in the majority of cases linked to this region (Renton et al., Neuron, 2011, 72, 257-268). This locus on chromosome 9p21 accounts for nearly half of familial ALS and nearly one-quarter of all ALS cases in a cohort of 405 Finnish patients (Laaksovirta et al, Lancet Neurol., 2010, 9, 978-985). The incidence of ALS is reportedly 1:50,000. Familial ALS reportedly represents 5-10% of all ALS cases; C9orf72 mutations reportedly can be the most common cause of ALS (40-50%). ALS is reportedly associated with degeneration of both upper and lower motor neurons in the motor cortex of the brain, the brain stem, and the spinal cord. Symptoms of ALS reportedly include: muscle weakness and/or muscle atrophy, trouble swallowing or breathing, cramping, stiffness. Respiratory failure is reportedly the main cause of death. In some embodiments, provided technologies reduces severity and/or removes one or more of symptoms

related to ALS or other C9orf72 related conditions, disorders and/or diseases.

[0017] In some embodiments, provided oligonucleotides and compositions and methods thereof are useful for treatment of any of several C9orf72-related disorders, including but not limited to frontotemporal dementia (FTD). In some embodiments, FTD is referred to as frontotemporal lobar degeneration or FTLD, MIM: 600274. Frontotemporal dementia, reportedly the second most common form of presenile dementia, is reportedly associated with focal atrophy of the frontal or temporal lobes. Boxer et al. 2005 Alzheimer Dis. Assoc. Disord. 19 (Suppl 1):S3–S6. FTD shares extensive clinical, pathological, and molecular overlap with amyotrophic lateral sclerosis. As reported by Gijselinck, Cold Spring Harb. Perspect. Med. 2017 Jan 27. pii: a026757, there are reportedly families and individual patients in which both diseases occur (ALS-FTD) (Lomen-Hoerth et al. 2002 Neurology 59:1077-1079), and TDP-43 inclusions (Arai et al. 2006 Biochem. Biophys. Res. Comm. 351: 602-611; Neumann et al. 2006 Science 314: 130-133) in ALS and FTLD patients can be indistinguishable (Tsuji et al. 2012 Brain 135: 3380-3391), despite the pathological distribution being different for ALS and FTLD patients. There is reportedly evidence that common disease pathways may be involved in ALS and FTLD because their clinical and pathological hallmarks overlap; hence, the pure forms of these diseases are considered the two extremes of one disease continuum (Lillo and Hodges 2009 J. Clin. Neurosci. 16: 1131-1135). Genetic studies reportedly identified mutations in the same genes in FTLD and ALS—for example, TBK1, TARDBP, FUS, VCP (Neumann et al. 2006; Kovacs et al. 2009 Mov. Disord. 24: 1843-1847; Johnson et al. 2010 Neuron 68: 857-864; Van Langenhove et al. 2010 Neurology 74: 366-371; Cirulli et al. 2015 Science 347: 1436-1441; Freischmidt et al. 2015 Nat. Neurosci. 18: 631-636; Pottier et al. 2015 Acta Neuropathol. 130: 77-92). Genetic evidence for a common disease pathomechanism was reportedly provided by the identification of the repeat expansion mutations in C9orf72 in patients with ALS, FTLD, and ALS-FTD (Gijselinck et al. 2010 Arch. Neurol. 67: 606-616; De Jesus-Hernandez et al. 2011 Neuron 72: 245-256; Renton et al. 2011 Neuron 72: 257-268).

[0018] In some embodiments, a C9orf72 target is a specific allele (e.g., one with a repeat expansion) and level, expression and/or activity of one or more products (e.g., RNA and/or protein products such as dipeptide repeat proteins or DPRs) are intended to be altered. In many embodiments, a C9orf72 target allele is one whose presence and/or expression is associated (e.g., correlated) with presence, incidence, and/or severity, of one or more diseases and/or conditions, including but not limited to ALS and FTD or other C9orf72-related disorders, or a symptom thereof. Alternatively or additionally, in some embodiments, a C9orf72 target allele is one for which alteration of expression, level and/or activity of one or more gene products correlates with improvement (e.g., delay of onset, reduction of severity, responsiveness to other therapy, etc.) in one or more aspects of a disease and/or condition, including but not limited to ALS and FTD or other C9orf72-related disorders.

[0019] In some embodiments, a neurological disease is characterized by neuronal hyperexcitability. In some embodiments, a 50% reduction in C9orf72 activity, due to and/or in the presence of the $(GGGGCC)_n$ expansion, reportedly increases neurotransmission through the glutamate receptors NMDA, AMPA, and kainite. In addition, glutamate receptors reportedly accumulate on neurons. The increased neurotransmission and accumulation of glutamate receptors reportedly leads to glutamate-induced excitotoxicity due to the neuronal hyperexcitability. Inhibiting glutamate receptors would reportedly treat the neuronal hyperexcitability. Clearance of dipeptide repeat proteins generated from the expansion reportedly is impaired, enhancing their neurotoxicity. C9orf72 reportedly promotes early endosomal trafficking through activation of RAB5, which requires phosphatidylinositol 3-phosphase (PI3P). PIKFYVE converts PI3P to phosphatidylinositol (3,5)-bisphosphate (PI(3,5)P2). Inhibiting PIKFYVE reportedly would compensate for altered RAB5 levels by increasing PI3P levels to enable early endosomal maturation, which would ultimately lead to the clearance of dipeptide repeat proteins. Neurons reportedly also use endosomal trafficking to regulate sodium and potassium ion channel localization. Inhibiting PIKFYVE reportedly may also treat neuronal hyperexcitability. In some embodiments, provided technologies reduce neuronal hyperexcitability. In some embodiments, provided technologies may be administered as part of the same treatment regime as an inhibitor of PIKFYVE.

[0020] In some embodiments, the present disclosure provides an oligonucleotide composition comprising a first plurality of oligonucleotides which share:

1) a common base sequence;

2) a common pattern of backbone linkages; and

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

[0021] In some embodiments, the present disclosure provides a C9orf72 oligonucleotide composition comprising a first plurality of oligonucleotides capable of directing C9orf72 knockdown, wherein oligonucleotides are of a particular oligonucleotide type characterized by:

1) a common base sequence and length;

2) a common pattern of backbone linkages; and

3) a common pattern of backbone chiral centers;

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

[0022] In some embodiments, a provided oligonucleotide (which can target C9orf72 or target a

target other than C9orf72) comprises one or more blocks. In some embodiments, a block comprises one or more consecutive nucleosides, and/or nucleotides, and/or sugars, or bases, and/or internucleotidic linkages. In some embodiments, a provided oligonucleotide comprises three or more blocks, wherein the blocks on either end are not identical and the oligonucleotide is thus asymmetric. In some embodiments, a block is a wing or a core.

[0023] In some embodiments, a c9orf72 oligonucleotide comprises at least one wing and at least one core, wherein a wing differs structurally from a core in that a wing comprises a structure [e.g., stereochemistry, additional chemical moiety, or chemical modification at a sugar, base or internucleotidic linkage (or pattern thereof)] different than the core, or vice versa. In some embodiments, a provided oligonucleotide comprises a wing-core-wing structure. In some embodiments, a provided oligonucleotide comprises a wing-core, core-wing, or wing-core-wing structure, wherein one wing differs in structure [e.g., stereochemistry, additional chemical moiety, or chemical modification at a sugar, base or internucleotidic linkage (or pattern thereof)] from the other wing and the core (for example, an asymmetrical oligonucleotide). In some embodiments, an oligonucleotide has or comprises a wing-core, core-wing, or wing-core-wing structure, and a block is a wing or core. In some embodiments, a core is also referenced to as a gap.

[0024] In general, properties of oligonucleotide compositions as described herein can be assessed using any appropriate assay.

[0025] Those of skill in the art will be aware of and/or will readily be able to develop appropriate assays for particular oligonucleotide compositions.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Figure 1. Figure 1 describes 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 targeting intron 1.

[0027] Figure 2. Figure 2 presents certain provided formats of oligonucleotides as examples.

[0028] Figure 3. Figures 3A and 3B present certain provided C9orf72 oligonucleotides as examples. Structural details of these oligonucleotides are further described in, for example, Table 1A.

[0029] Figure 4. Figure 4 presents example data demonstrating that provided C9orf72 oligonucleotides can provide preferential knockdown of repeat expansion-containing C9orf72 transcripts relative to total C9orf72 transcripts (including non-repeat expansion-containing C9orf72 transcripts). Figure 4A shows knockdown of repeating expansion-containing transcripts by administration of WV-3662 and WV-3536 (which represent the base sequence of SEQ ID NO: 0553 of WO2015054676, and

SEQ ID NO: 0057 of WO2016168592, respectively), and WV-6408, normalized to controls. Figure 4B shows knockdown of total C9orf72 transcripts by administration of WV-3662, WV-3536, and WV-6408. In Figures 4A and 4B, concentrations of oligonucleotides used were: 0.1, 0.3, 1, 3, and 10 μM from left to right. Figure 4C shows knockdown of repeating expansion-containing transcripts provided by control oligonucleotides WV-2376 and WV-3542, and example oligonucleotides WV-3688, WV-6408, WV-7658, WV-7659, WV-8010, and WV-8011. Concentrations were 1 (left column) and 10 μM (right column). Figure 4D shows knockdown of total transcripts by administration of control oligonucleotides WV-2376 and WV-3542. Concentrations were 1 (left column) and 10 μM (right column).

[0030] Figure 5. Figure 5 presents example data demonstrating in vivo potency of provided C9orf72 oligonucleotides in the C9-BAC mouse spinal cord. WV-2376 is a negative control oligonucleotide. Present data were those of WV-6408, WV-8009, WV-8010, WV-8011, and WV-8012. Figure 5A shows knockdown of total transcripts (including repeat expansion-containing and non-repeat expansion-containing transcripts). Figure 5B shows knockdown of V3 (repeat expansion-containing) transcripts. Figure 5C shows knockdown of Intron/AS transcripts (with probes targeting a region 3' to the repeat transcript expansion, the detected area includes both sense and antisense transcripts of the intronic region). PBS, phosphate buffered saline (negative control).

[0031] Figure 6. Figure 6 presents example data demonstrating the in vivo potency of some C9orf72 oligonucleotides in the C9-BAC mouse cortex. WV-2376 is a negative control oligonucleotide which does not target C9orf72; presented data were those of: WV-6408, WV-8009, WV-8010, WV-8011, and WV-8012. Figure 6A shows knockdown of total transcripts (including repeat expansion-containing and non-repeat expansion-containing transcripts). Figure 6B shows knockdown of V3 (repeat expansion-containing) transcripts. Figure 6C shows knockdown of Intron/AS transcripts (with probes targeting a region 3' to the repeat transcript expansion, the detected area includes both sense and antisense transcripts of the intronic region).

[0032] Figure 7. Figures 7A to 7D present example data on the activity of provided Malat1 oligonucleotides conjugated to various chemical moieties, for example, sulfonamide or anisamide. Figure 7A shows example data of Malat1 oligonucleotides in knocking down Malat1 in spinal cord; Figure 7B shows example distribution data of various Malat1 oligonucleotides (ASO or antisense oligonucleotides) in spinal cord; Figure 7C shows the knockdown of Malat1 in cortex; and Figure 7D shows the distribution of the test oligonucleotides in cortex. Presented data were those of: WV-3174, WV-7558, WV-7559, and WV-7560, administered ICV, 1 x 50 μg.

[0033] Figure 8. Figures 8A to H show the effect of certain provided C9orf72 oligonucleotides on C9orf72 transcripts in C9-BAC mice. C9orf72 oligonucleotides tested were: WV-6408, WV-8009, WV-8010, WV-8011, and WV-8012. Negative controls were PBS (phosphate-buffered saline) and WV-

2376, which does not target C9orf72. Transcripts were analyzed from the cerebral cortex (Figures 8A to D) and spinal cord (Figures 8E to H). Transcripts analyzed were: All transcripts (Figures 8A and E); V3 (Figures 8B and F); V3 (exon 1a) (Figures 8C and G); and Intron1/AS (Figures 8D and H). The data in Figure 9 and Figure 10 are from the same in-vivo mouse study.

[0034] Figure 9. Figures 9A and 9B show example distribution data of C9orf72 oligonucleotides in spinal cord (Figure 9A) and cerebral cortex (Figure 9B) of C9-BAC mice. C9orf72 oligonucleotides tested were: WV-6408, WV-8009, WV-8010, WV-8011, and WV-8012. Negative controls were PBS (phosphate-buffered saline) and WV-2376, which does not target C9orf72.

[0035] Figure 10. Figure 10 shows example data of C9orf72 oligonucleotides on the level of polyGP (a dipeptide repeat protein) in the hippocampus of C9-BAC mice. C9orf72 oligonucleotides tested were: WV-6408, WV-8009, WV-8010, WV-8011, and WV-8012. Negative controls were PBS (phosphate-buffered saline) and WV-2376, which does not target C9orf72.

[0036] Figure 11. Figure 11A shows an example hybridization ELISA assay for measuring oligonucleotide levels, e.g., in tissues and fluids, including but not limited to animal biopsies. Figure 11B shows example chemistry for binding a primary amine-labeled capture probe to an amino-reactive solid support, such as a plate comprising maleic anhydride.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

Definitions

[0037] 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.

[0038] *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.

[0039] *Alkenyl*: As used herein, the term "alkenyl" refers to an alkyl group, as defined herein, having one or more double bonds.

[0040] *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).

[0041] *Alkynyl*: As used herein, the term "alkynyl" refers to an alkyl group, as defined herein, having one or more triple bonds.

[0042] *Animal:* As used herein, the term "animal" refers to any member of the animal kingdom. In some embodiments, "animal" refers to humans, at any stage of development. In some embodiments, "animal" refers to non-human animals, at any stage of development. In certain embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate and/or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish and/or worms. In some embodiments, an animal may be a transgenic animal, a genetically-engineered animal and/or a clone.

[0043] *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.

[0044] *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.

[0045] *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.

[0046] *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.

[0047] *Dosing regimen:* As used herein, a "dosing regimen" or "therapeutic regimen" refers to a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by periods of time. In some embodiments, a given therapeutic agent has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which are separated from one another by a time period of the same length; in some embodiments, a dosing regime comprises a plurality of doses and at least two different time periods separating individual doses. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from the first dose amount. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount same as the first dose amount.

[0048] *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.

[0049] *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.

[0050] *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.

[0051] *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.).

[0052] *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.

[0053] *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).

[0054] *In vivo:* As used herein, the term "*in vivo*" refers to events that occur within an organism (*e.g.*, animal, plant and/or microbe).

[0055] *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.

[0056] Suitable monovalent substituents on a substitutable atom, *e.g.*, a suitable carbon atom, are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^o$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR$, $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-Si(R^\circ)_3$; $-OSi(R^\circ)_3$; $-B(R^\circ)_2$; $-OB(R^\circ)_2$; $-OB(OR^\circ)_2$; $-P(R^\circ)_2$; $-P(OR^\circ)_2$; $-OP(R^\circ)_2$; $-OP(OR^\circ)_2$; $-P(O)(R^\circ)_2$; $-P(O)(OR^\circ)_2$; $-OP(O)(R^\circ)_2$;

$-OP(O)(OR°)_2$; $-OP(O)(OR°)(SR°)$; $-SP(O)(R°)_2$; $-SP(O)(OR°)_2$; $-N(R°)P(O)(R°)_2$; $-N(R°)P(O)(OR°)_2$; $-P(R°)_2[B(R°)_3]$; $-P(OR°)_2[B(R°)_3]$; $-OP(R°)_2[B(R°)_3]$; $-OP(OR°)_2[B(R°)_3]$; $-(C_{1-4}$ 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] *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.

[0061] *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.

[0062] *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.

[0063] *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.

[0064] *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.

[0065] *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.

[0066] *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).

[0067] *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.

[0068] 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.

[0069] 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.

[0070] 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. 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.

[0071] *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.

[0072] *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.

[0073] *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.

[0074] *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.

[0075] *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.

[0076] *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.

[0077] *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.

[0078] *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.

[0079] *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.

[0080] *Unsaturated:* The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[0081] *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.

[0082] *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).

[0083] *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.

[0084] *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.

[0085] *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.

[0086] *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.

[0087] *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.

[0088] *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.

[0089] *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.

[0090] *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.

[0091] *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.

[0092] *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.

[0093] *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.

[0094] *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.

[0095] *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.

[0096] *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).

[0097] *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.

[0098] 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).

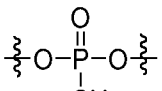
[0099] *Identity*: As used herein, "identity" means the percentage of identical nucleotide residues at corresponding positions in two or more sequences when the sequences are aligned to maximize sequence matching, *i.e.*, taking into account gaps and insertions. Identity can be readily calculated by known methods, including but not limited to those known in the art, including but not limited to those cited in WO2017/192679.

[00100] *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.

[00101] 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.

[00102] *Internucleotidic linkage:* As used herein, the phrase "internucleotidic linkage" refers

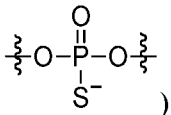
generally to a linkage linking nucleoside units of an oligonucleotide or a nucleic acid. In some embodiments, an internucleotidic linkage is a phosphodiester linkage, as found in naturally occurring DNA and RNA molecules (natural phosphate linkage). In some embodiments, an internucleotidic linkage includes 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



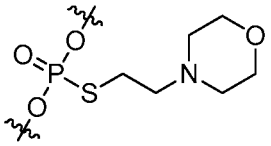
linkage ( ), or modified phosphorothioate triester linkage. In some embodiments, an internucleotidic linkage is one of, *e.g.*, PNA (peptide nucleic acid) or PMO (phosphorodiamidate Morpholino oligomer) linkage. It is understood by a person of ordinary skill in the art that an internucleotidic linkage may exist as an anion or cation at a given pH due to the existence of acid or base moieties in the linkage.

[00103] 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.

[00104] 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.

[00105] *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.

[00106] 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.

[00107] *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.

[00108] *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 a oligonucleotide type, which composition comprises a non-random or controlled level of a plurality of oligonucleotides of the oligonucleotide type.

[00109] *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.

[00110] *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.

[00111] *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.

[00112] *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.

[00113] *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.

[00114] 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."

[00115] 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.

[00116] 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.

[00117] 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.

[00118] *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.

[00119] In some embodiments, an altmer is a "stereoaltmer," *e.g.*, no two consecutive nucleotide units have the same stereochemistry at the linkage phosphorus.

[00120] 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.

[00121] 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.

[00122] *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.

[00123] In some embodiments, a unimer is a "stereounimer," *e.g.*, all nucleotide units have the same stereochemistry at the linkage phosphorus.

[00124] In some embodiments, a unimer is a "P-modification unimer", *e.g.*, all nucleotide units have the same modification at the linkage phosphorus.

[00125] 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.

[00126] *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.

[00127] *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.

[00128] 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.

[00129] 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

[00130] Oligonucleotides provide useful molecular tools in a wide variety of applications. For example, oligonucleotides (e.g., oligonucleotides which target C9orf72) are useful in therapeutic, diagnostic, and research applications, including the treatment of a variety of conditions, disorders, and diseases. The use of naturally occurring nucleic acids (*e.g.*, unmodified DNA or RNA) is limited, for example, by their susceptibility to endo- and exo-nucleases. As such, various synthetic counterparts have been developed to circumvent these shortcomings. These include synthetic oligonucleotides that contain chemical modifications, *e.g.*, base modifications, sugar modifications, backbone modifications, etc., which, among other things, render these molecules less susceptible to degradation and improve other properties of oligonucleotides. From a structural point of view, modifications to internucleotidic linkages can introduce chirality, and certain properties of oligonucleotides may be affected by configurations of phosphorus atoms that form the backbone of oligonucleotides. For example, *in vitro* studies have shown that properties of antisense oligonucleotides, such as binding affinity, sequence specific binding to complementary RNA, stability to nucleases, are affected by, inter alia, chirality of backbone phosphorus atoms. Various modifications are efficacious for C9orf72 oligonucleotides.

Oligonucleotides and Compositions

[00131] 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.

[00132] In some embodiments, as demonstrated in the present disclosure, such oligonucleotides provide improved properties, *e.g.*, improved stability, and/or activities.

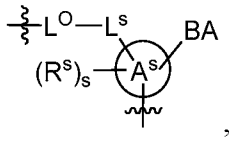
[00133] In some embodiments, y is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, y is 1. In some embodiments, y is 2. In some embodiments, y is 3. In some embodiments, y is 4. In some embodiments, y is 5. In some embodiments, y is 6. In some embodiments, y is 7. In some embodiments, y is 8. In some embodiments, y is 9. In some embodiments, y is 10.

[00134] 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.

[00135] 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.

[00136] 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, $-C\equiv C-$, $-C(R')_2-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$,

−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 is an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms;

s is 0-20;

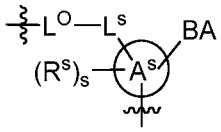
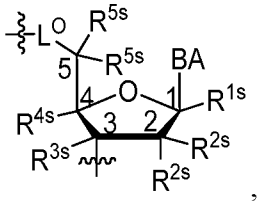
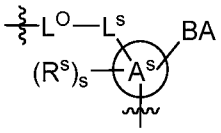
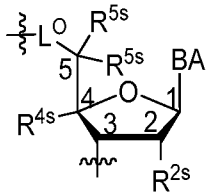
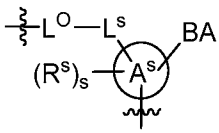
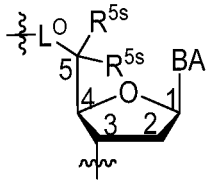
each R' is independently −R, −C(O)R, −C(O)OR, or −S(O)$_2$R; and

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.

[00137] 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.

[00138] 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–.

[00139] In some embodiments, a region of consecutive nucleotidic units comprises a pattern of backbone chiral centers (linkage phosphorus) of (*N*p)t[(*O*p)n(*S*p)m]y, wherein each variable is independently as described in the present disclosure. In some embodiments, a region of consecutive nucleotidic units comprises a pattern of backbone chiral centers (linkage phosphorus) of (*S*p)t[(*O*p)n(*S*p)m]y, wherein each variable is independently as described in the present disclosure.

[00140] In some embodiments, the present disclosure provides oligonucleotides that comprise one or two wings and a core, and comprise or are of a wing-core-wing, a core-wing, or a wing-core structure. In some embodiments, provided oligonucleotides comprise or are of a wing-core-wing structure. In some embodiments, provided oligonucleotides comprise or are of a core-wing structure. In some embodiments, provided oligonucleotides comprise or are of a wing-core structure. In some embodiments, a core of is a region of consecutive nucleotidic unit as described in the present disclosure. In some embodiments, each wing independently comprises one or more nucleobases as described in the present disclosure.

[00141] 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. In some embodiments, an oligonucleotide described herein has or comprises a wing-core or core-wing structure of, for example 5-10, 8-4, 4-12, 12-4, 3-14, 16-2, 18-1, 10-3, 2-10, 1-10, 8-2, 2-13, 5-13, 5-8, or 6-8. In some embodiments, a wing or a core is a block, and a wing-core, core-wing, or wing-core-wing structure is a blockmer comprising two or three blocks.

[00142] 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.

[00143] In some embodiments, the present disclosure provides an oligonucleotide comprising or of a wing-core-wing, core-wing or wing-core structure, wherein:

the core comprises a pattern of backbone chiral centers (linkage phosphorus) of:

(*N*p)t[(*O*p/*R*p)n(*S*p)m]y,

wherein:

*N*p is either *R*p or *S*p;

*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

*R*p indicates the *S* configuration of a chiral linkage phosphorus of a chiral modified internucleotidic linkage; and

each wing independently comprises one or more nucleobases.

[00144] In some embodiments, the present disclosure provides an oligonucleotide comprising or of a wing-core-wing, core-wing or wing-core structure, wherein:

the core is or comprises a region of consecutive nucleotidic units $(Nu^M)t[(Nu^O)n(Nu^M)m]y$, which region of consecutive nucleotidic units has a pattern of backbone chiral centers (linkage phosphorus) of (*N*p)t[(*O*p)n(*S*p)m]y,

wherein each variable is independently as described in the present disclosure.

[00145] In some embodiments, (*N*p)t[(*O*p/*R*p)n(*S*p)m]y comprises at least one *O*p. In some embodiments, (*N*p)t[(*O*p/*R*p)n(*S*p)m]y comprises at least one *R*p. In some embodiments, (*N*p)t[(*O*p/*R*p)n(*S*p)m]y is (*N*p)t[(*O*p)n(*S*p)m]y. In some embodiments, (*N*p)t[(*O*p/*R*p)n(*S*p)m]y is

(*N*p)t[(*R*p)n(*S*p)m]y.

[00146] 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.

[00147] In some embodiments, certain sugar modifications, e.g., 2'-MOE, provides more stability under otherwise identical conditions than 2'-OMe. 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 (*e.g.*, see WV-7127, WV-7128, *etc.*). In some embodiments, such a wing is a 5'-wing. In some embodiments, such a wing is a 3'-wing.

[00148] 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.

[00149] Among other things, the present disclosure encompasses the recognition that 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.

[00150] 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.

[00151] 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.

[00152] 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.

[00153] 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.

[00154] 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.

[00155] 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.

[00156] 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.

[00157] 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.

[00158] 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.

[00159] 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.

[00160] 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.

[00161] 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.

[00162] 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.

[00163] 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 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 bicyclic sugar and, in the other wing, at least one sugar comprises a 2'-MOE and at least one sugar are a bicyclic sugar, 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'-MOE and, in the other wing, at least one sugar comprises a 2'-MOE and at least one sugar 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'-MOE and, in the other wing, at least one sugar comprises a 2'-MOE and at least one sugar are a bicyclic sugar, 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 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.

[00166] 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.

[00167] 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.

[00168] 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.

[00169] In some embodiments, a bicyclic sugar is a LNA, a cEt or BNA.

[00170] 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.

[00171] 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.

[00172] 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.

[00173] 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.

[00174] 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.

[00175] 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.

[00176] 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.

[00177] 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.

[00178] 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.

[00179] 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.

[00180] 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 are 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 are 2'-F, and the majority of the sugars in the core comprise a 2'-deoxy.

[00181] 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 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'-MOE and, in the other wing, at least one sugar comprises a 2'-MOE and at least one sugar are 2'-F, and the majority of the sugars in the core comprise a 2'-deoxy.

[00182] 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.

[00183] 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.

[00184] 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.

[00185] 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.

[00186] In some embodiments, a C9orf72 oligonucleotides has a wing-core-wing structure and has an asymmetrical format. In some embodiments of a C9orf72 oligonucleotide having an asymmetrical format, one wing differs from another. In some embodiments of a C9orf72 oligonucleotide having an asymmetrical format, one wing differs from another in the sugar modifications or pattern thereof, or the backbone internucleotidic linkages or pattern thereof, or the backbone chiral centers 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 C9orf72 oligonucleotides having an asymmetrical format are shown herein. In some embodiments of a C9orf72 oligonucleotide 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. 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 wing are the same or different lengths.

[00187] In some embodiments, an oligonucleotide having an asymmetrical structure (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 structure wherein both wings have the same pattern of chemical modifications; or a different asymmetrical structure). 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 asymmetrical structure 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 asymmetrical structure 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 asymmetrical structure 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 asymmetrical structure comprises a bicyclic sugar or two or more bicyclic sugars.

[00188] In some embodiments, a core comprises no 2'-substitution, and each sugar unit 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. 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 *S*p configuration, and the core also contains 1, 2, 3, 4, or 5 internucleotidic linkages selected from modified internucleotidic linkages of *R*p configuration and natural phosphate linkages. In some embodiments, the core also contains 1 or 2 internucleotidic linkages selected from modified internucleotidic linkages of *R*p 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 *R*p configuration and a natural phosphate linkage, and the rest internucleotidic linkages are independently modified internucleotidic linkages of *S*p 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 *R*p configuration and a natural phosphate linkage, and the rest internucleotidic linkages are independently modified internucleotidic linkages of *S*p 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 *S*p 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 *S*p configuration. In some embodiments, the core also contains 1 and no more than 1 modified internucleotidic linkage of *R*p configuration, and the rest internucleotidic linkages are independently modified internucleotidic linkages of *S*p configuration. In some embodiments, the core also contains 2 and no more than 2 modified internucleotidic linkages of *R*p configuration, and the rest internucleotidic linkages are independently modified internucleotidic linkages of *S*p configuration. In some embodiments, the two natural phosphate linkages, or the two modified internucleotidic linkages of *R*p configuration, are separated by two or more modified internucleotidic linkages of *S*p configuration. In some embodiments, a modified internucleotidic linkage is of formula I. In some embodiments, a modified internucleotidic linkage is a phosphorothioate diester linkage.

[00189] Core 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.

[00190] In some embodiments, the present disclosure provides oligonucleotides comprising additional chemistry moieties, optionally connected to the oligonucleotide moiety through a linker. In some embodiments, the present disclosure provides oligonucleotides comprising $(R^D)b-L^{M1}-L^{M2}-L^{M3}-$, wherein:

each R^D is independently a chemical moiety;

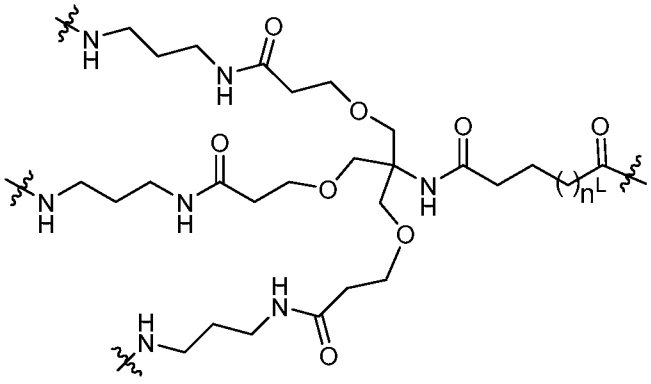
each of L^{M1}, L^{M2}, and L^{M3} is independently a covalent bond, or a bivalent or multivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, $-C(R')_2-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$, $-OP(O)(NR')O-$, $-OP(OR')O-$, $-OP(SR')O-$, $-OP(NR')O-$, $-OP(R')O-$, or $-OP(OR')[B(R')_3]O-$; and one or more carbon atoms are optionally and independently replaced with Cy^L;

each Cy^L is independently an optionally substituted 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; and

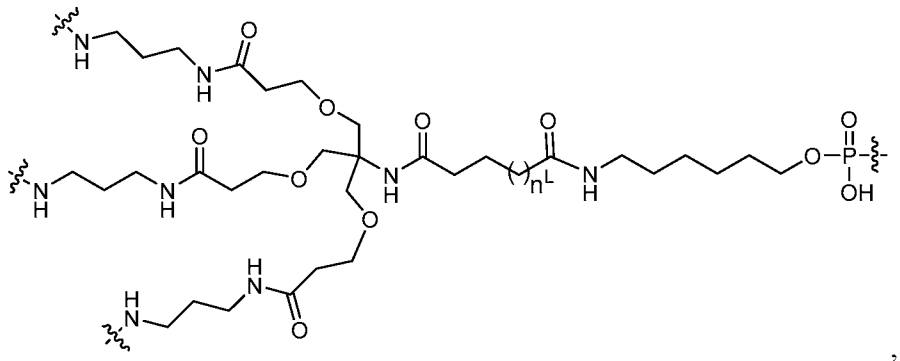
b is 1-1000.

[00191] In some embodiments, each of L^{M1}, L^{M2}, and L^{M3} is independently a covalent bond, or a bivalent or multivalent, optionally substituted, linear or branched group selected from a C_{1-10} aliphatic group and a C_{1-10} heteroaliphatic group having 1-5 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡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.

[00192] In some embodiments, L^{M1} comprises one or more $-N(R')-$ and one or more $-C(O)-$. In some embodiments, a linker or L^{M1} is or comprises

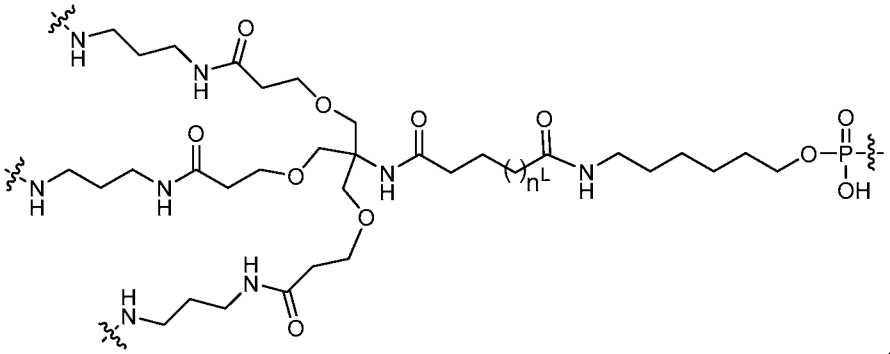


, wherein n^L is 1-8. In some embodiments, a linker or $-L^{M1}-L^{M2}-L^{M3}-$ is



,

or a salt form thereof, wherein n^L is 1-8. In some embodiments, a linker or $-L^{M1}-L^{M2}-L^{M3}-$ is



,

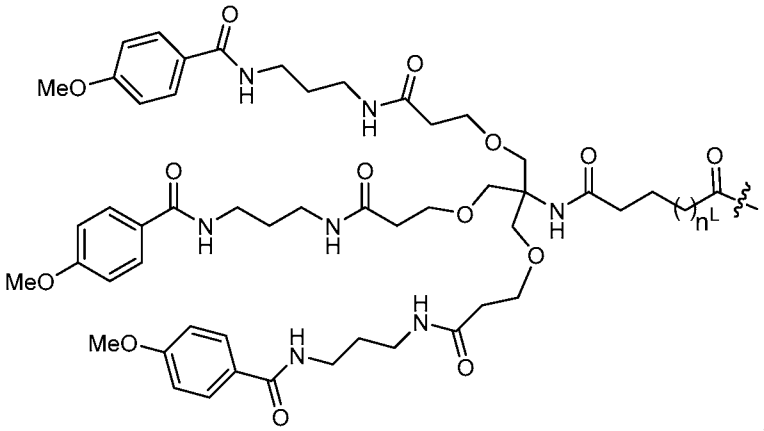
or a salt form thereof, wherein:

n^L is 1-8.

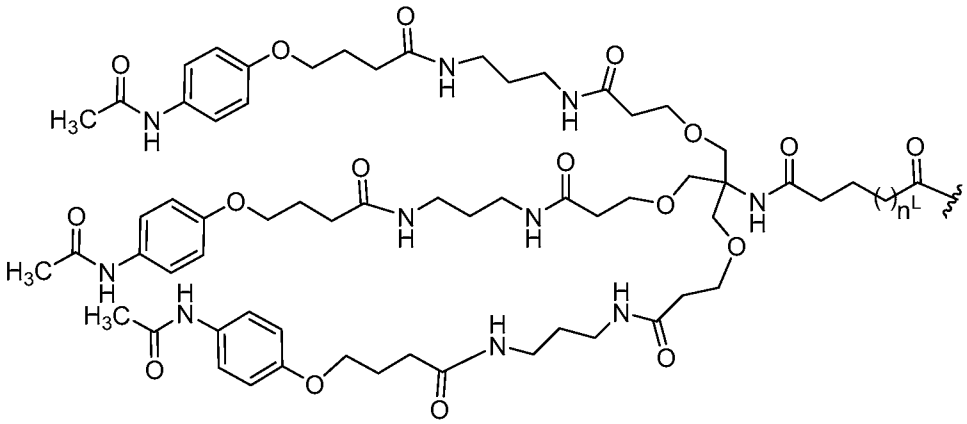
each amino group independently connects to a moiety; and

the P atom connects to the 5'-OH of the oligonucleotide.

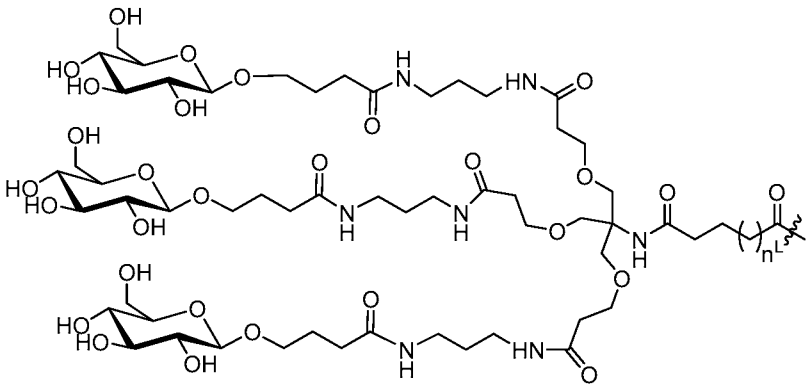
In some embodiments, the moiety and the linker, or $(R^D)b-L^{M1}-L^{M2}-L^{M3}-$, is or comprises



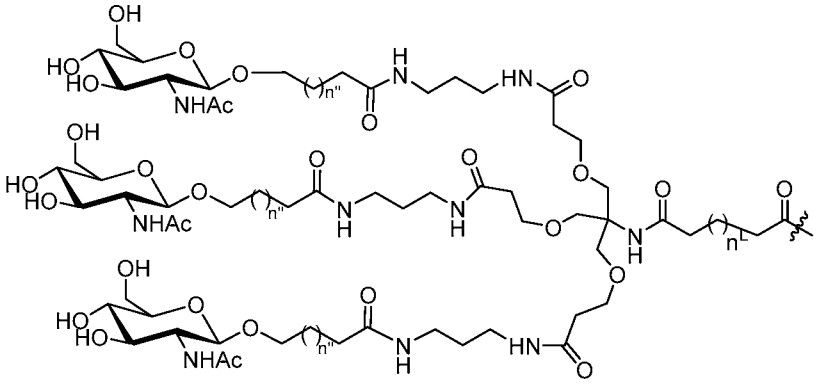
. In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



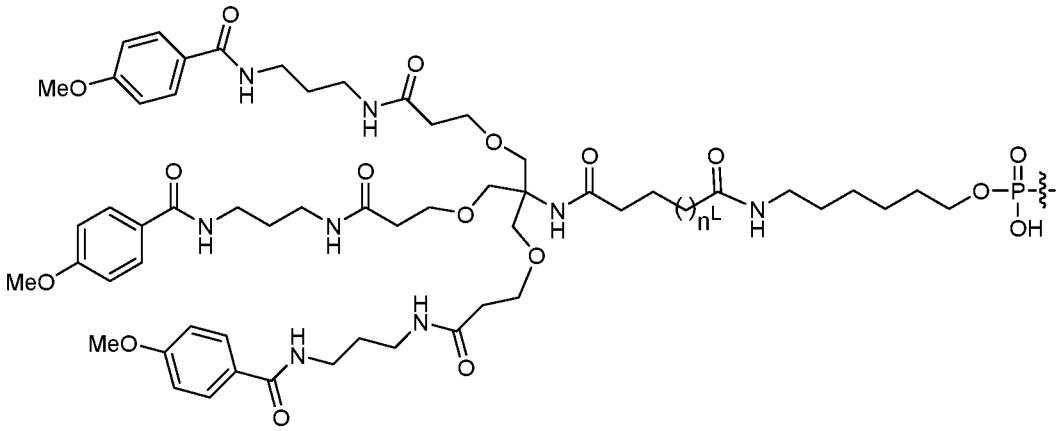
. In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



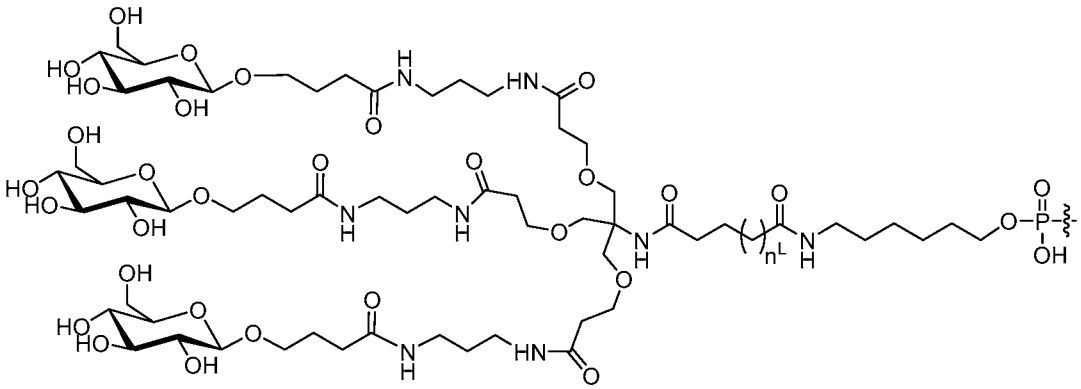
. In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



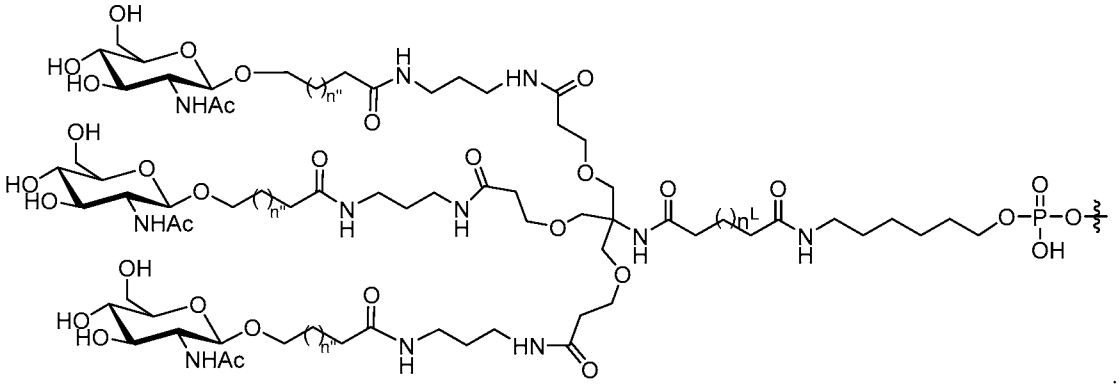
. In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



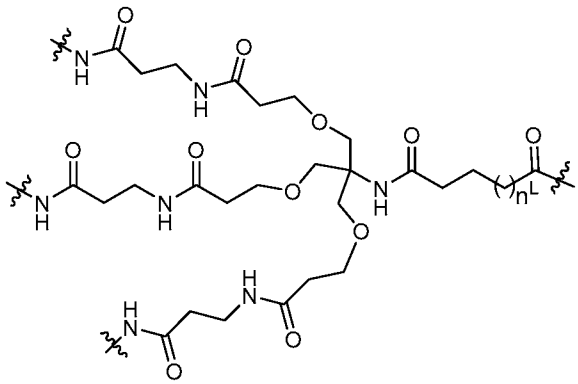
. In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



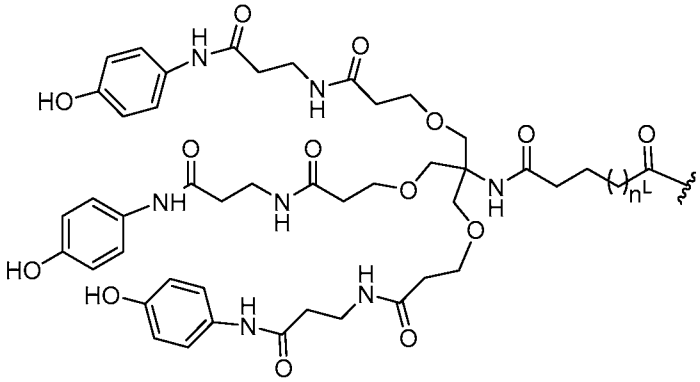
. In some embodiments, the moiety and the linker, or $(R^D)b–L^{M1}–L^{M2}–L^{M3}–$, is or comprises



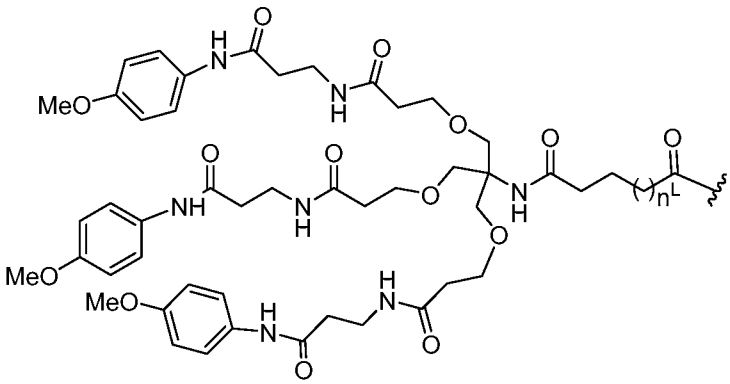
. In some embodiments, the linker, or L^{M1}, is or comprises



. In some embodiments, the moiety and linker, or $(R^D)b-L^{M1}-L^{M2}-L^{M3}-$, is or comprises:



. In some embodiments, the moiety and linker, or $(R^D)b-L^{M1}-L^{M2}-L^{M3}-$, is or comprises:



.

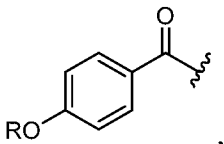
[00193] In some embodiments, n^L is 1-8. In some embodiments, n^L is 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments, n^L is 1. In some embodiments, n^L is 2. In some embodiments, n^L is 3. In some embodiments, n^L is 4. In some embodiments, n^L is 5. In some embodiments, n^L is 6. In some embodiments, n^L is 7. In some embodiments, n^L is 8.

[00194] In some embodiments, L^{M2} is a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-10} aliphatic group and a C_{1-10} heteroaliphatic group having 1-5 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, $-C(R')_2-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$, $-OP(O)(NR')O-$, $-OP(OR')O-$, $-OP(SR')O-$, $-OP(NR')O-$, $-OP(R')O-$, or $-OP(OR')[B(R')_3]O-$; and one or more carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L^{M2} is a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-10} aliphatic group and a C_{1-10} heteroaliphatic group having 1-5 heteroatoms, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, $-C(R')_2-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, or $-P(O)(R')-$. In some embodiments, L^{M2} is is a covalent bond, or a bivalent, optionally substituted, linear or branched C_{1-10} aliphatic wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, $-C(R')_2-$, $-O-$, $-S-$, $-N(R')-$, or $-C(O)-$. In some embodiments, L^{M2} is $-NH-(CH_2)_6-$, wherein $-NH-$ is bonded to L^{M1}.

[00195] In some embodiments, L^{M3} is is $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')-$, $-OP(O)(SR')-$, $-OP(O)(R')-$, $-OP(O)(NR')-$, $-OP(S)(OR')-$, $-OP(S)(SR')-$, $-OP(S)(R')-$, $-OP(S)(NR')-$, $-OP(R')-$, $-OP(OR')-$, $-OP(SR')-$, $-OP(NR')-$, or $-OP(OR')[B(R')_3]-$. In some embodiments, L^{M3} is $-OP(O)(OR')-$, or $-OP(O)(SR')-$, wherein $-O-$ is bonded to L^{M2}. In some embodiments, the P atom is connected to a sugar unit, a nucleobase unit, or an internucleotidic linkage. In some embodiments, the P atom is connected to a $-OH$ group through formation of a P–O bond. In some embodiments, the P atom is connected to the 5'–OH group through formation of a P–O bond.

[00196] In some embodiments, L^{M1} is a covalent bond. In some embodiments, L^{M2} is a covalent bond. In some embodiments, L^{M3} is a covalent bond. In some embodiments, L^{M1} is L^{M2} as described in

the present disclosure. In some embodiments, L^{M1} is L^{M3} as described in the present disclosure. In some embodiments, L^{M2} is L^{M1} as described in the present disclosure. In some embodiments, L^{M2} is L^{M3} as described in the present disclosure. In some embodiments, L^{M3} is L^{M1} as described in the present disclosure. In some embodiments, L^{M3} is L^{M2} as described in the present disclosure. In some embodiments, L^{M} is L^{M1} as described in the present disclosure. In some embodiments, L^{M} is L^{M2} as described in the present disclosure. In some embodiments, L^{M} is L^{M3} as described in the present disclosure. In some embodiments, L^{M} is L^{M1}–L^{M2}, wherein each of L^{M1} and L^{M2} is independently as described in the present disclosure. In some embodiments, L^{M} is L^{M1}–L^{M3}, wherein each of L^{M1} and L^{M3} is independently as described in the present disclosure. In some embodiments, L^{M} is L^{M2}–L^{M3}, wherein each of L^{M2} and L^{M3} is independently as described in the present disclosure. In some embodiments, L^{M} is L^{M1}–L^{M2}–L^{M3}, wherein each of L^{M1}, L^{M2} and L^{M3} is independently as described in the present disclosure.

[00197] In some embodiments, each R^{D} is independently a chemical moiety as described in the present disclosure. In some embodiments, R^{D} is targeting moiety. In some embodiments, R^{D} is or comprises a carbohydrate moiety. In some embodiments, R^{D} is or comprises a lipid moiety. In some embodiments, R^{D} is or comprises a ligand moiety for, e.g., cell receptors such as a sigma receptor, an asialoglycoprotein receptor, etc. In some embodiments, a ligand moiety is or comprises an anisamide moiety, which may be a ligand moiety for a sigma receptor. In some embodiments, a ligand moiety is or comprises a GalNAc moiety, which may be a ligand moiety for an asialoglycoprotein receptor. In some embodiments, R^{D} is selected from optionally substituted phenyl, 

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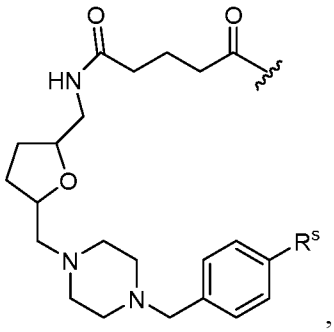

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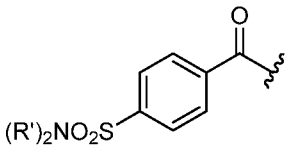

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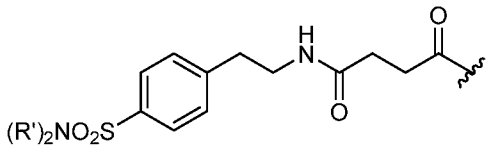

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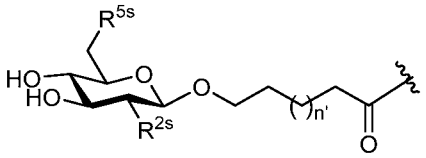

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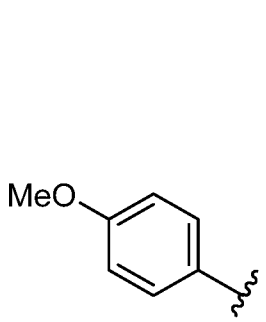
wherein n' is 0 or 1, and each other variable is independently as described in the present disclosure. In some embodiments, R^{s} is F. In some embodiments, R^{s} is OMe. In some embodiments, R^{s} is OH. In

some embodiments, R^s is NHAc. In some embodiments, R^s is $NHCOCF_3$. In some embodiments, R' is H. In some embodiments, R is H. In some embodiments, R^{2s} is NHAc, and R^{5s} is OH. In some embodiments, R^{2s} is p-anisoyl, and R^{5s} is OH. In some embodiments, R^{2s} is NHAc and R^{5s} is p-anisoyl. In some embodiments, R^{2s} is OH, and R^{5s} is p-anisoyl. In some embodiments, R^D is selected from



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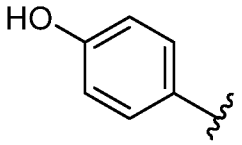

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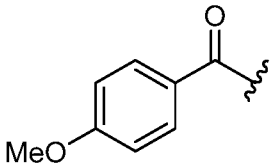

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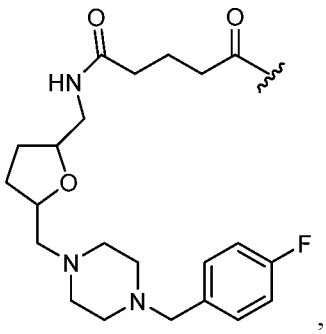

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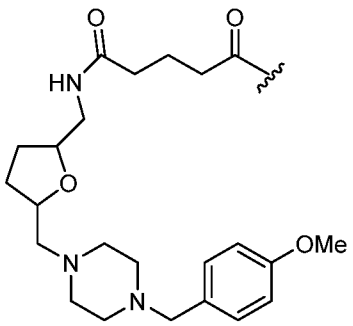

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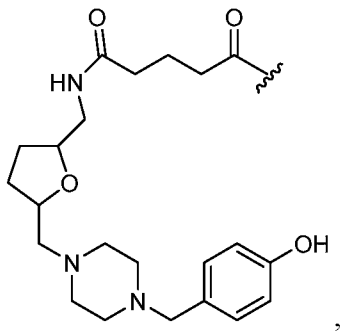

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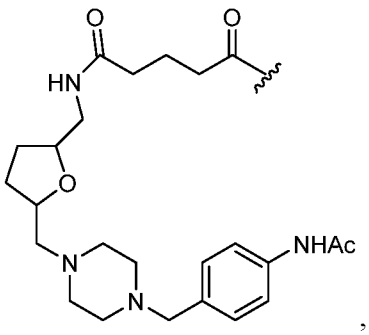

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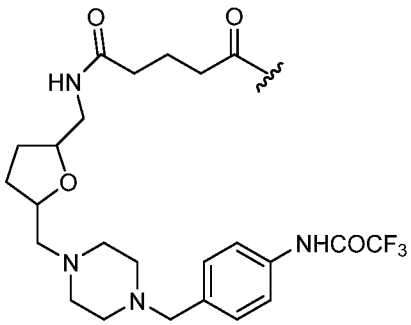

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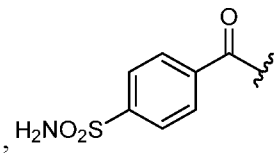

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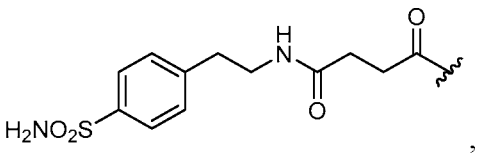

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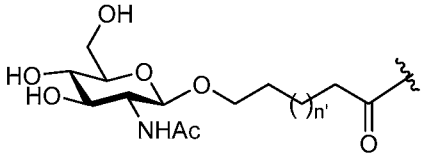

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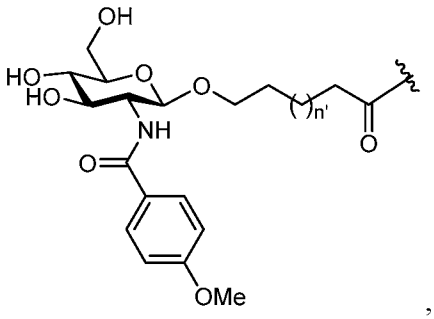

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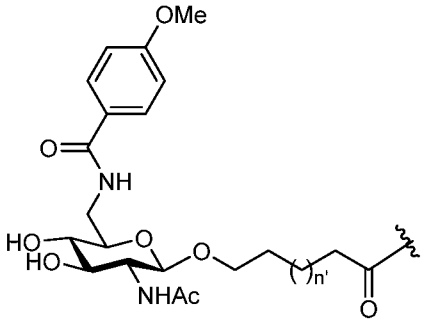

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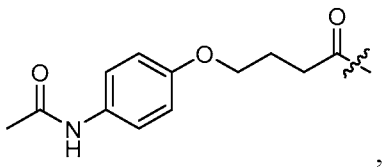

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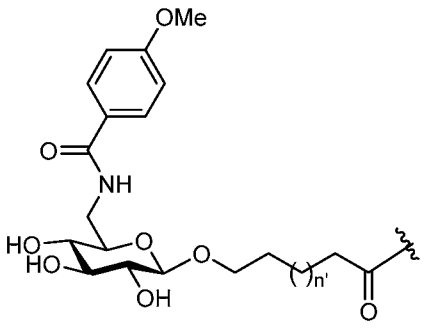
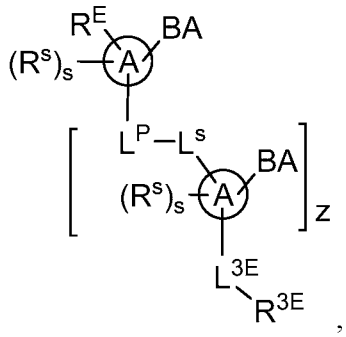


. Further embodiments of R^D includes additional chemical moiety embodiments, *e.g.*, those described in Example, Example 2, *etc.*

[00198] In some embodiments, n' is 1. In some embodiments, n' is 0.

[00199] In some embodiments, n" is 1. In some embodiments, n" is 2.

[00200] In some embodiments, the present disclosure provides a provided compound, *e.g.*, an oligonucleotide of a provided composition, having the structure of formula **O-I**:



,

O-I

or a salt thereof, wherein:

R^E is a 5'-end group;

each BA is independently an optionally substituted group selected from C_{3-30} cycloaliphatic, C_{6-30} aryl, C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{3-30} heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus, boron and silicon, a natural nucleobase moiety, and a modified nucleobase moiety;

each 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 $-O-L-N(R')_2$;

s is 0-20;

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

each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms 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;

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

each Ring A is independently an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon;

each L^P is independently an internucleotidic linkage;

z is 1-1000;

L^{3E} is L or −L−L−;

R^{3E} is −R', −L−R', −OR', or a solid support;

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

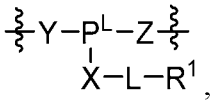
each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10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

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

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

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

[00201] In some embodiments, each L^P independently has the structure of formula **I**:



I

or a salt form thereof, wherein:

P^L is P(=W), P, or P→B(R')$_3$;

W is O, S or Se;

R^1 is −L−R, halogen, −CN, −NO_2, −Si(R')$_3$, −OR', −SR', or −N(R')$_2$;

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

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

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)−, −$S(O)_2$−, −$S(O)_2$N(R')−, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, −P(OR')[B(R')$_3$]−, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or −OP(OR')[B(R')$_3$]O−; and one or more carbon atoms are optionally and independently replaced with Cy^L;

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

having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, or

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

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

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

[00202] In some embodiments, each L^P independently has the structure of formula **I**, and R^E is $-C(R^{5s})_3$, $-L-P^{DB}$, $-C(R^{5s})_2OH$, $-L-R^{5s}$, or $-L-P^{5s}-L-R^{5s}$, or a salt form thereof, wherein each variable is independently as described in the present disclosure.

[00203] In some embodiments, each L^P independently has the structure of formula **I**, and R^E is $-C(R^{5s})_3$, $-L-P^{DB}$, $-C(R^{5s})_2OH$, $-L-R^{5s}$, or $-L-P^{5s}-L-R^{5s}$, or a salt form thereof, wherein each variable is independently as described in the present disclosure.

[00204] In some embodiments, R^E is $-C(R^{5s})_3$, $-C(R^{5s})_2OH$, or $-L-R^{5s}$;

each BA is independently an optionally substituted group selected from C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and C_{3-30} heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus, boron and silicon;

each Ring A is independently an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon; and

each L^P independently has the structure of formula **I**, wherein each variable is independently as described in the present disclosure.

[00205] In some embodiments, R^E is $-C(R^{5s})_3$, $-C(R^{5s})_2OH$, or $-L-R^{5s}$

each BA is independently an optionally substituted C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein the heteroaryl comprises one or more heteroatoms selected from oxygen and nitrogen;

each Ring A is independently an optionally substituted 5-10 membered monocyclic or bicyclic saturated ring having 0-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus

and silicon, wherein the ring comprises at least one oxygen atom; and

each L^P independently has the structure of formula **I**, wherein each variable is independently as described in the present disclosure.

[00206] In some embodiments, R^E is $-C(R^{5s})_3$, $-C(R^{5s})_2OH$, or $-L-R^{5s}$;

each BA is independently an optionally substituted or protected nucleobase selected from adenine, cytosine, guanosine, thymine, and uracil;

each Ring A is independently an optionally substituted 5-7 membered monocyclic or bicyclic saturated ring having one or more oxygen atoms; and

each L^P independently has the structure of formula **I**, wherein each variable is independently as described in the present disclosure.

[00207] In some embodiments, R^E is a 5'-end group as described herein. In some embodiments, R^E is $-C(R^{5s})_3$, $-L-P^{DB}$, $-C(R^{5s})_2OH$, $-L-R^{5s}$, or $-L-P^{5s}-L-R^{5s}$, or a salt form thereof, wherein each variable is independently as described in the present disclosure. In some embodiments, R^E is $-CH_2OH$. In some embodiments, R^E is $-CH_2OP(O)(OR)_2$ or a salt form thereof, wherein each R is independently as described in the present disclosure. In some embodiments, R^E is $-CH_2OP(O)(OH)_2$ or a salt form thereof. In some embodiments, R^E is $-CH_2OP(O)(OR)(SR)$ or a salt form thereof, wherein each R is independently as described in the present disclosure. In some embodiments, R^E is $-CH_2OP(O)(SH)(OH)$ or a salt form thereof. In some embodiments, R^E is (*E*)-$CH{=}CHP(O)(OR)_2$ or a salt form thereof, wherein each R is independently as described in the present disclosure. In some embodiments, R^E is (*E*)-$CH{=}CHP(O)(OH)_2$.

[00208] In some embodiments, R^E is $-CH_2OH$. In some embodiments, R^E is $-CH_2OP(O)(R)_2$ or a salt form thereof, wherein each R is independently as described in the present disclosure. In some embodiments, R^E is $-CH_2OP(O)(OR)_2$ or a salt form thereof, wherein each R is independently as described in the present disclosure. In some embodiments, R^E is $-CH_2OP(O)(OH)_2$ or a salt form thereof. In some embodiments, R^E is $-CH_2OP(O)(OR)(SR)$ or a salt form thereof, wherein each R is independently as described in the present disclosure. In some embodiments, R^E is $-CH_2OP(O)(SH)(OH)$ or a salt form thereof. In some embodiments, R^E is (*E*)-$CH{=}CHP(O)(OR)_2$ or a salt form thereof, wherein each R is independently as described in the present disclosure. In some embodiments, R^E is (*E*)-$CH{=}CHP(O)(OH)_2$.

[00209] In some embodiments, R^E is $-CH(R^{5s})-OH$, wherein R^{5s} is as described in the present disclosure. In some embodiments, R^E is $-CH(R^{5s})-OP(O)(R)_2$ or a salt form thereof, wherein each R^{5s} and R is independently as described in the present disclosure. In some embodiments, R^E is $-CH(R^{5s})-OP(O)(OR)_2$ or a salt form thereof, wherein each R^{5s} and R is independently as described in the present disclosure. In some embodiments, R^E is $-CH(R^{5s})-OP(O)(OH)_2$ or a salt form thereof. In some

embodiments, R^E is $-CH(R^{5s})-OP(O)(OR)(SR)$ or a salt form thereof. In some embodiments, R^E is $-CH(R^{5s})-OP(O)(OH)(SH)$ or a salt form thereof. In some embodiments, R^E is $-(R)-CH(R^{5s})-OH$, wherein R^{5s} is as described in the present disclosure. In some embodiments, R^E is $-(R)-CH(R^{5s})-OP(O)(R)_2$ or a salt form thereof, wherein each R^{5s} and R is independently as described in the present disclosure. In some embodiments, R^E is $-(R)-CH(R^{5s})-OP(O)(OR)_2$ or a salt form thereof, wherein each R^{5s} and R is independently as described in the present disclosure. In some embodiments, R^E is $-(R)-CH(R^{5s})-OP(O)(OH)_2$ or a salt form thereof. In some embodiments, R^E is $-(R)-CH(R^{5s})-OP(O)(OR)(SR)$ or a salt form thereof. In some embodiments, R^E is $-(R)-CH(R^{5s})-OP(O)(OH)(SH)$ or a salt form thereof. In some embodiments, R^E is $-(S)-CH(R^{5s})-OH$, wherein R^{5s} is as described in the present disclosure. In some embodiments, R^E is $-(S)-CH(R^{5s})-OP(O)(R)_2$ or a salt form thereof, wherein each R^{5s} and R is independently as described in the present disclosure. In some embodiments, R^E is $-(S)-CH(R^{5s})-OP(O)(OR)_2$ or a salt form thereof, wherein each R^{5s} and R is independently as described in the present disclosure. In some embodiments, R^E is $-(S)-CH(R^{5s})-OP(O)(OH)_2$ or a salt form thereof. In some embodiments, R^E is $-(S)-CH(R^{5s})-OP(O)(OR)(SR)$ or a salt form thereof. In some embodiments, R^E is $-(S)-CH(R^{5s})-OP(O)(OH)(SH)$ or a salt form thereof. In some embodiments, R^{5s} is optionally substituted C_1, C_2, C_3, or C_4 aliphatic. In some embodiments, R^{5s} is C_1, C_2, C_3, or C_4 aliphatic or haloaliphatic. In some embodiments, R^{5s} is optionally substituted $-CH_3$. In some embodiments, R^{5s} is $-CH_3$.

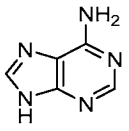
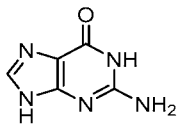
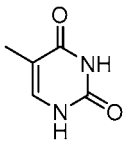
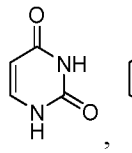
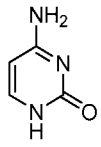
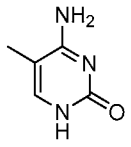
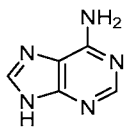
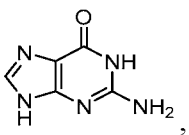
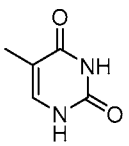
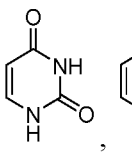
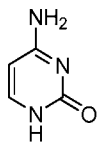
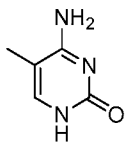
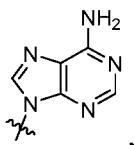
[00210] In some embodiments, BA is an optionally substituted group selected from C_{3-30} cycloaliphatic, C_{6-30} aryl, C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{3-30} heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, a natural nucleobase moiety, and a modified nucleobase moiety. In some embodiments, BA is an optionally substituted group selected from C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{3-30} heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, a natural nucleobase moiety, and a modified nucleobase moiety. In some embodiments, BA is an optionally substituted group selected from C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, a natural nucleobase moiety, and a modified nucleobase moiety. In some embodiments, BA is optionally substituted C_{5-30} heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, BA is optionally substituted natural nucleobases and tautomers thereof. In some embodiments, BA is protected natural nucleobases and tautomers thereof. Various nucleobase protecting groups for oligonucleotide synthesis are known and can be utilized in accordance with the

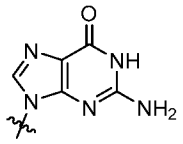
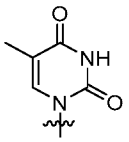
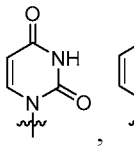
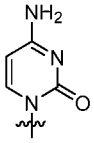
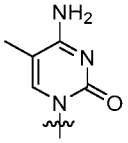
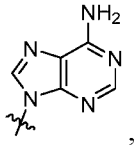
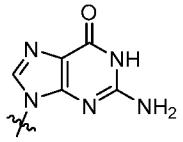
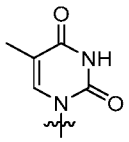
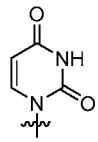
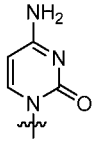
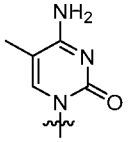
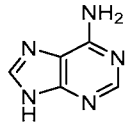
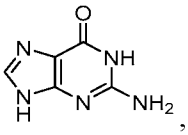
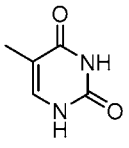
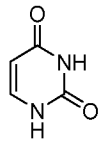
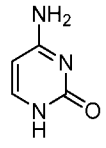
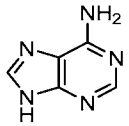
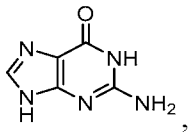
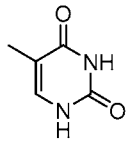
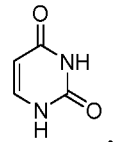
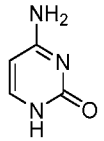
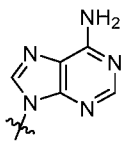
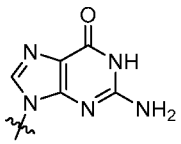
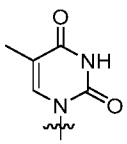
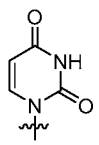
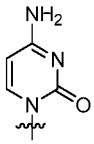
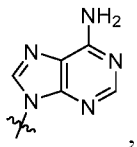
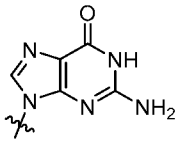
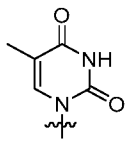
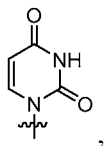
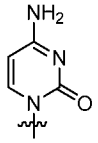
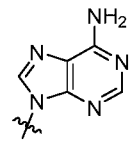
present disclosure. In some embodiments, BA is an optionally substituted nucleobase selected from adenine, cytosine, guanosine, thymine, and uracil, and tautomers thereof. In some embodiments, BA is an optionally protected nucleobase selected from adenine, cytosine, guanosine, thymine, and uracil, and tautomers thereof.

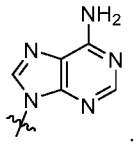
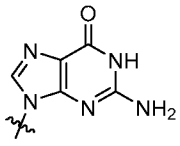
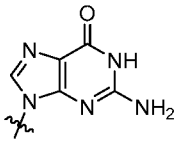
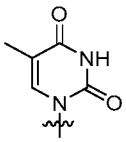
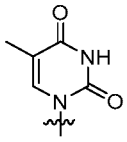
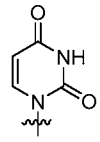
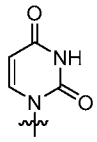
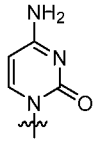
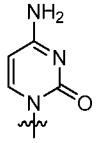
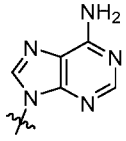
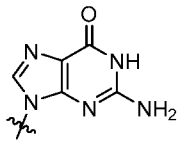
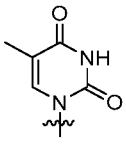
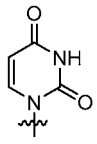
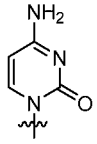
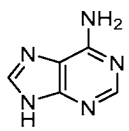
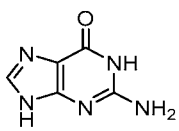
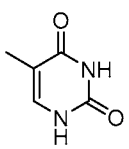
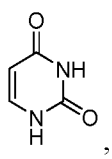
[00211] In some embodiments, BA is optionally substituted C_{3-30} cycloaliphatic. In some embodiments, BA is optionally substituted C_{6-30} aryl. In some embodiments, BA is optionally substituted C_{3-30} heterocyclyl. In some embodiments, BA is optionally substituted C_{5-30} heteroaryl. In some embodiments, BA is an optionally substituted natural base moiety. In some embodiments, BA is an optionally substituted modified base moiety. BA is an optionally substituted group selected from C_{3-30} cycloaliphatic, C_{6-30} aryl, C_{3-30} heterocyclyl, and C_{5-30} heteroaryl. In some embodiments, BA is an optionally substituted group selected from C_{3-30} cycloaliphatic, C_{6-30} aryl, C_{3-30} heterocyclyl, C_{5-30} heteroaryl, and a natural nucleobase moiety.

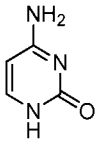
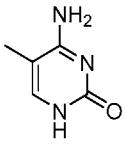
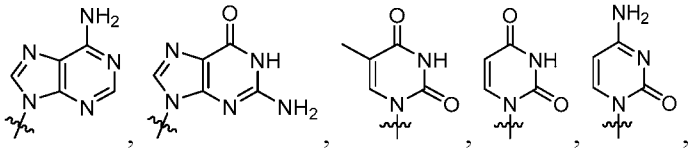
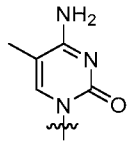
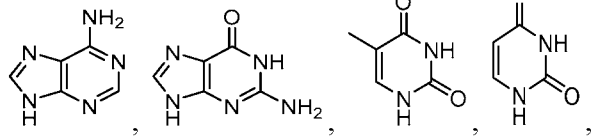
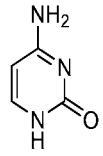
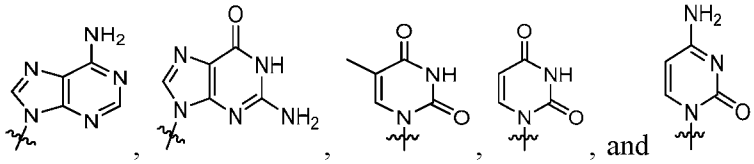
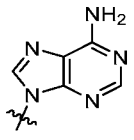
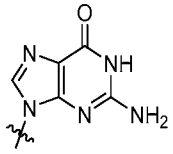
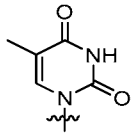
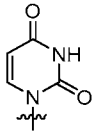
[00212] In some embodiments, BA is connected through an aromatic ring. In some embodiments, BA is connected through a heteroatom. In some embodiments, BA is connected through a ring heteroatom of an aromatic ring. In some embodiments, BA is connected through a ring nitrogen atom of an aromatic ring.

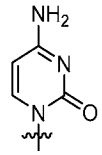
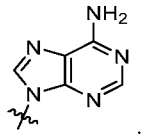
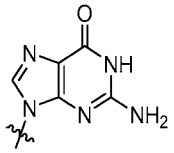
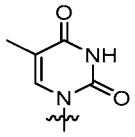
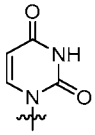
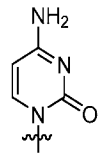
[00213] In some embodiments, BA is a natural nucleobase moiety. In some embodiments, BA is an optionally substituted natural nucleobase moiety. In some embodiments, BA is a substituted natural nucleobase moiety. In some embodiments, BA is natural nucleobase A, T, C, U, or G. In some embodiments, BA is an optionally substituted group selected from natural nucleobases A, T, C, U, and G.

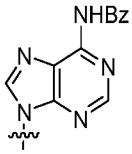
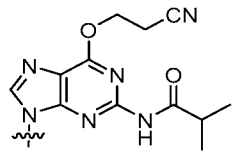
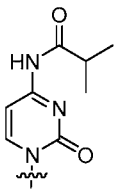
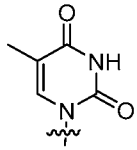
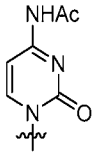
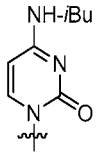
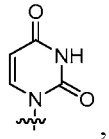
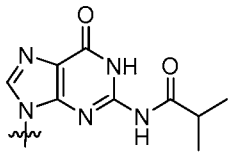
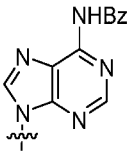
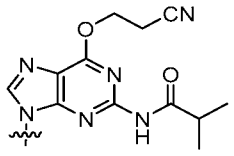
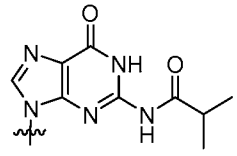
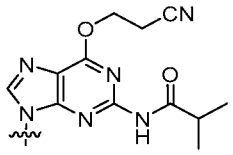
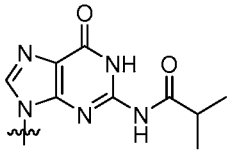
[00214] In some embodiments, BA is an optionally substituted group, which group is formed by removing a −H from  ,  ,  ,  ,  , or  , or a tautomer thereof. In some embodiments, BA is an optionally substituted group, which group is formed by removing a −H from  ,  ,  ,  ,  , or  . In some embodiments, BA is an optionally substituted group which group is selected from  ,

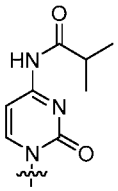
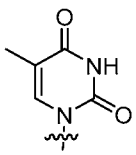
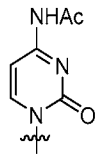
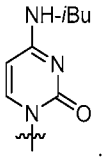
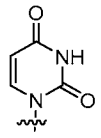
 ,  ,  ,  , and  , and tautomeric forms thereof. In some embodiments, BA is an optionally substituted group which group is selected from  ,  ,  ,  ,  , and  . In some embodiments, BA is an optionally substituted group, which group is formed by removing a −H from  ,  ,  ,  , and  , and tautomers thereof. In some embodiments, BA is an optionally substituted group, which group is formed by removing a −H from  ,  ,  ,  , and  . In some embodiments, BA is an optionally substituted group which group is selected from  ,  ,  ,  , and  , and tautomeric forms thereof. In some embodiments, BA is an optionally substituted group which group is selected from  ,  ,  ,  , and  . In some embodiments, BA is optionally substituted  or a tautomeric form thereof. In some embodiments, BA is optionally substituted


. In some embodiments, BA is optionally substituted  or a tautomeric form thereof. In some embodiments, BA is optionally substituted  . In some embodiments, BA is optionally substituted  or a tautomeric form thereof. In some embodiments, BA is optionally substituted  . In some embodiments, BA is optionally substituted  or a tautomeric form thereof. In some embodiments, BA is optionally substituted  . In some embodiments, BA is optionally substituted  or a tautomeric form thereof. In some embodiments, BA is optionally substituted  . In some embodiments, BA is  . In some embodiments, BA is  . In some embodiments, BA is  . In some embodiments, BA is  . In some embodiments, BA is  . In some embodiments, BA of the 5'-end nucleoside unit of a provided oligonucleotide, *e.g.*, an oligonucleotide of formula **VIII**, is an optionally substituted group, which group is formed by removing a −H from  ,  ,  ,  ,

 , and  . In some embodiments, BA of the 5'-end nucleoside unit is an optionally substituted group which group is selected from  , and  . In some embodiments, BA of the 5'-end nucleoside unit is an optionally substituted group, which group is formed by removing a −H from  , and  . In some embodiments, BA of the 5'-end nucleoside unit is an optionally substituted group which group is selected from  , and . In some embodiments, BA of the 5'-end nucleoside unit is optionally substituted  . In some embodiments, BA of the 5'-end nucleoside unit is optionally substituted  . In some embodiments, BA of the 5'-end nucleoside unit is optionally substituted  . In some embodiments, BA of the 5'-end nucleoside unit is optionally substituted  . In some embodiments,

BA of the 5'-end nucleoside unit is optionally substituted  . In some embodiments, BA of the 5'-end nucleoside unit is  . In some embodiments, BA of the 5'-end nucleoside unit is  . In some embodiments, BA of the 5'-end nucleoside unit is  . In some embodiments, BA of the 5'-end nucleoside unit is  . In some embodiments, BA of the 5'-end nucleoside unit is  .

[00215] In some embodiments, BA is  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, BA is  . In some embodiments, BA is  or  . In some embodiments, BA is  . In some embodiments, BA is  . In some embodiments, BA is


. In some embodiments, BA is 
. In some embodiments, BA is 
. In some embodiments, BA is 
. In some embodiments, BA is 
. In some embodiments, a protection group is −Ac. In some embodiments, a protection group is −Bz. In some embodiments, a protection group is -*i*Bu for nucleobase.

[00216] In some embodiments, BA is an optionally substituted purine base residue. In some embodiments, BA is a protected purine base residue. In some embodiments, BA is an optionally substituted adenine residue. In some embodiments, BA is a protected adenine residue. In some embodiments, BA is an optionally substituted guanine residue. In some embodiments, BA is a protected guanine residue. In some embodiments, BA is an optionally substituted cytosine residue. In some embodiments, BA is a protected cytosine residue. In some embodiments, BA is an optionally substituted thymine residue. In some embodiments, BA is a protected thymine residue. In some embodiments, BA is an optionally substituted uracil residue. In some embodiments, BA is a protected uracil residue. In some embodiments, BA is an optionally substituted 5-methylcytosine residue. In some embodiments, BA is a protected 5-methylcytosine residue.

[00217] In some embodiments, BA is a protected base residue as used in oligonucleotide preparation. In some embodiments, BA is a base residue illustrated in US 2011/0294124, US 2015/0211006, US 2015/0197540, and WO 2015/107425, each of which is incorporated herein by reference.

[00218] In some embodiments, BA is a modified nucleobase illustrated in WO 2017/192679.

[00219] In some embodiments, each R^s is independently −H, halogen, −CN, $-N_3$, −NO, $-NO_2$, $-L^s-R'$, $-L^s-Si(R)_3$, $-L^s-OR'$, $-L^s-SR'$, $-L^s-N(R')_2$, $-O-L^s-R'$, $-O-L^s-Si(R)_3$, $-O-L^s-OR'$, $-O-L^s-SR'$, or $-O-L^s-N(R')_2$ as described in the present disclosure. In some embodiments, R^s is −H. In some embodiments, R^s is not −H.

[00220] In some embodiments, R^s is R', wherein R is as described in the present disclosure. In some embodiments, R^s is R, wherein R is as described in the present disclosure. In some embodiments, R^s is optionally substituted C_{1-30} heteroaliphatic. In some embodiments, R^s comprises one or more silicon atoms. In some embodiments, R^s is $-CH_2Si(Ph)_2CH_3$.

[00221] In some embodiments, R^s is $-L^s-R'$. In some embodiments, R^s is $-L^s-R'$ wherein $-L^s-$

is a bivalent, optionally substituted C_{1-30} heteroaliphatic group. In some embodiments, R^s is $-CH_2Si(Ph)_2CH_3$.

[00222] In some embodiments, R^s is $-F$. In some embodiments, R^s is $-Cl$. In some embodiments, R^s is $-Br$. In some embodiments, R^s is $-I$. In some embodiments, R^s is $-CN$. In some embodiments, R^s is $-N_3$. In some embodiments, R^s is $-NO$. In some embodiments, R^s is $-NO_2$. In some embodiments, R^s is $-L^s-Si(R)_3$. In some embodiments, R^s is $-Si(R)_3$. In some embodiments, R^s is $-L^s-R'$. In some embodiments, R^s is $-R'$. In some embodiments, R^s is $-L^s-OR'$. In some embodiments, R^s is $-OR'$. In some embodiments, R^s is $-L^s-SR'$. In some embodiments, R^s is $-SR'$. In some embodiments, R^s is $-L^s-N(R')_2$. In some embodiments, R^s is $-N(R')_2$. In some embodiments, R^s is $-O-L^s-R'$. In some embodiments, R^s is $-O-L^s-Si(R)_3$. In some embodiments, R^s is $-O-L^s-OR'$. In some embodiments, R^s is $-O-L^s-SR'$. In some embodiments, R^s is $-O-L^s-N(R')_2$. In some embodiments, R^s is a 2'-modification as described in the present disclosure. In some embodiments, R^s is $-OR$, wherein R is as described in the present disclosure. In some embodiments, R^s is $-OR$, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, R^s is $-OMe$. In some embodiments, R^s is $-OCH_2CH_2OMe$.

[00223] In some embodiments, s is 0-20. In some embodiments, s is 1-20. In some embodiments, s is 1-5. In some embodiments, s is 1. In some embodiments, s is 2. In some embodiments, s is 3. In some embodiments, s is 4. In some embodiments, s is 5. In some embodiments, s is 6. In some embodiments, s is 7. In some embodiments, s is 8. In some embodiments, s is 9. In some embodiments, s is 10. In some embodiments, s is 11. In some embodiments, s is 12. In some embodiments, s is 13. In some embodiments, s is 14. In some embodiments, s is 15. In some embodiments, s is 16. In some embodiments, s is 17. In some embodiments, s is 18. In some embodiments, s is 19. In some embodiments, s is 20.

[00224] In some embodiments, L^s is L, wherein L is as described in the present disclosure. In some embodiments, L is a bivalent optionally substituted methylene group.

[00225] As described herein, 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, $-C\equiv C-$, $-C(R')_2-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$, $-OP(O)(NR')O-$, $-OP(OR')O-$, $-OP(SR')O-$,

−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.

[00226] In some embodiments, L is a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, −C(R')$_2$−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, −S(O)$_2$−, −S(O)$_2$N(R')−, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, −P(OR')[B(R')$_3$]−, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or −OP(OR')[B(R')$_3$]O−, and one or more carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L is a covalent bond, or a bivalent, optionally substituted, linear or branched C_{1-30} aliphatic group, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, −C(R')$_2$−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, −S(O)$_2$−, −S(O)$_2$N(R')−, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, −P(OR')[B(R')$_3$]−, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or −OP(OR')[B(R')$_3$]O−, and one or more carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L is a covalent bond, or a bivalent, optionally substituted, linear or branched C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, −C(R')$_2$−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, −S(O)$_2$−, −S(O)$_2$N(R')−, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, −P(OR')[B(R')$_3$]−, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or −OP(OR')[B(R')$_3$]O−, and one or more carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L is a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and

silicon, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, $-C(R')_2-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, or $-C(O)O-$, and one or more carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L is a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-10} aliphatic group and a C_{1-10} heteroaliphatic group having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, $-C(R')_2-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, and $-C(O)O-$, and one or more carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L is a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-10} aliphatic group and a C_{1-10} heteroaliphatic group having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from $-C(R')_2-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, and $-C(O)O-$.

[00227] In some embodiments, L is a covalent bond. In some embodiments, L is optionally substituted bivalent C_{1-30} aliphatic. In some embodiments, L is optionally substituted bivalent C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from boron, oxygen, nitrogen, sulfur, phosphorus and silicon.

[00228] In some embodiments, aliphatic moieties, *e.g.* those of L, R, *etc.*, either monovalent or bivalent or multivalent, and can contain any number of carbon atoms (before any optional substitution) within its range, *e.g.*, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, C_{25}, C_{26}, C_{27}, C_{28}, C_{29}, C_{30}, *etc.* In some embodiments, heteroaliphatic moieties, *e.g.* those of L, R, *etc.*, either monovalent or bivalent or multivalent, and can contain any number of carbon atoms (before any optional substitution) within its range, *e.g.*, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, C_{25}, C_{26}, C_{27}, C_{28}, C_{29}, C_{30}, *etc.*

[00229] In some embodiments, one or more methylene unit is optionally and independently substituted with $-O-$, $-S-$, $-N(R')-$, $-C(O)-$, $-S(O)-$, $-S(O)_2-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(S)(OR')-$, or $-P(S)(OR')-$. In some embodiments, a methylene unit is replaced with $-O-$. In some embodiments, a methylene unit is replaced with $-S-$. In some embodiments, a methylene unit is replaced with $-N(R')-$. In some embodiments, a methylene unit is replaced with $-C(O)-$. In some embodiments, a methylene unit is replaced with $-S(O)-$. In some embodiments, a methylene unit is replaced with

$-S(O)_2-$. In some embodiments, a methylene unit is replaced with $-P(O)(OR')-$. In some embodiments, a methylene unit is replaced with $-P(O)(SR')-$. In some embodiments, a methylene unit is replaced with $-P(O)(R')-$. In some embodiments, a methylene unit is replaced with $-P(O)(NR')-$. In some embodiments, a methylene unit is replaced with $-P(S)(OR')-$. In some embodiments, a methylene unit is replaced with $-P(S)(SR')-$. In some embodiments, a methylene unit is replaced with $-P(S)(R')-$. In some embodiments, a methylene unit is replaced with $-P(S)(NR')-$. In some embodiments, a methylene unit is replaced with $-P(R')-$. In some embodiments, a methylene unit is replaced with $-P(OR')-$. In some embodiments, a methylene unit is replaced with $-P(SR')-$. In some embodiments, a methylene unit is replaced with $-P(NR')-$. In some embodiments, a methylene unit is replaced with $-P(OR')[B(R')_3]-$. In some embodiments, one or more methylene unit is optionally and independently substituted with $-O-$, $-S-$, $-N(R')-$, $-C(O)-$, $-S(O)-$, $-S(O)_2-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(S)(OR')-$, or $-P(S)(OR')-$. In some embodiments, a methylene unit is replaced with $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$, $-OP(O)(NR')O-$, $-OP(OR')O-$, $-OP(SR')O-$, $-OP(NR')O-$, $-OP(R')O-$, or $-OP(OR')[B(R')_3]O-$, each of which may independently be an internucleotidic linkage.

[00230] In some embodiments, L, *e.g.*, when connected to R, is $-CH_2-$. In some embodiments, L is $-C(R)_2-$, wherein at least one R is not hydrogen. In some embodiments, L is $-CHR-$. In some embodiments, R is hydrogen. In some embodiments, L is $-CHR-$, wherein R is not hydrogen. In some embodiments, C of $-CHR-$ is chiral. In some embodiments, L is $-(R)-CHR-$, wherein C of $-CHR-$ is chiral. In some embodiments, L is $-(S)-CHR-$, wherein C of $-CHR-$ is chiral. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted C_{1-5} aliphatic. In some embodiments, R is optionally substituted C_{1-5} alkyl. In some embodiments, R is optionally substituted C_{1-4} aliphatic. In some embodiments, R is optionally substituted C_{1-4} alkyl. In some embodiments, R is optionally substituted C_{1-3} aliphatic. In some embodiments, R is optionally substituted C_{1-3} alkyl. In some embodiments, R is optionally substituted C_2 aliphatic. In some embodiments, R is optionally substituted methyl. In some embodiments, R is C_{1-6} aliphatic. In some embodiments, R is C_{1-6} alkyl. In some embodiments, R is C_{1-5} aliphatic. In some embodiments, R is C_{1-5} alkyl. In some embodiments, R is C_{1-4} aliphatic. In some embodiments, R is C_{1-4} alkyl. In some embodiments, R is C_{1-3} aliphatic. In some embodiments, R is C_{1-3} alkyl. In some embodiments, R is C_2 aliphatic. In some embodiments, R is methyl. In some embodiments, R is C_{1-6} haloaliphatic. In some embodiments, R is C_{1-6} haloalkyl. In some embodiments, R is C_{1-5} haloaliphatic. In some embodiments, R is C_{1-5} haloalkyl. In some embodiments, R is C_{1-4} haloaliphatic. In some embodiments, R is C_{1-4} haloalkyl. In some embodiments, R is C_{1-3} haloaliphatic. In some embodiments, R is C_{1-3} haloalkyl. In some embodiments, R is C_2 haloaliphatic. In some embodiments, R is methyl substituted with one or more halogen. In some embodiments, R is $-CF_3$. In

some embodiments, L is optionally substituted −CH=CH−. In some embodiments, L is optionally substituted (*E*)−CH=CH−. In some embodiments, L is optionally substituted (*Z*)−CH=CH−. In some embodiments, L is −C≡C−.

[00231] In some embodiments, L comprises at least one phosphorus atom. In some embodiments, at least one methylene unit of L is replaced with −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, −P(OR')[B(R')$_3$]−, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or −OP(OR')[B(R')$_3$]O−.

[00232] In some embodiments, Cy^L is an optionally substituted tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus, boron and silicon.

[00233] In some embodiments, Cy^L is monocyclic. In some embodiments, Cy^L is bicyclic. In some embodiments, Cy^L is polycyclic.

[00234] In some embodiments, Cy^L is saturated. In some embodiments, Cy^L is partially unsaturated. In some embodiments, Cy^L is aromatic. In some embodiments, Cy^L is or comprises a saturated ring moiety. In some embodiments, Cy^L is or comprises a partially unsaturated ring moiety. In some embodiments, Cy^L is or comprises an aromatic ring moiety.

[00235] In some embodiments, Cy^L is an optionally substituted C_{3-20} cycloaliphatic ring as described in the present disclosure (for example, those described for R but tetravalent). In some embodiments, a ring is an optionally substituted saturated C_{3-20} cycloaliphatic ring. In some embodiments, a ring is an optionally substituted partially unsaturated C_{3-20} cycloaliphatic ring. A cycloaliphatic ring can be of various sizes as described in the present disclosure. In some embodiments, a ring is 3, 4, 5, 6, 7, 8, 9, or 10-membered. In some embodiments, a ring is 3-membered. In some embodiments, a ring is 4-membered. In some embodiments, a ring is 5-membered. In some embodiments, a ring is 6-membered. In some embodiments, a ring is 7-membered. In some embodiments, a ring is 8-membered. In some embodiments, a ring is 9-membered. In some embodiments, a ring is 10-membered. In some embodiments, a ring is an optionally substituted cyclopropyl moiety. In some embodiments, a ring is an optionally substituted cyclobutyl moiety. In some embodiments, a ring is an optionally substituted cyclopentyl moiety. In some embodiments, a ring is an optionally substituted cyclohexyl moiety. In some embodiments, a ring is an optionally substituted cycloheptyl moiety. In some embodiments, a ring is an optionally substituted cyclooctanyl moiety. In some embodiments, a cycloaliphatic ring is a cycloalkyl ring. In some embodiments, a cycloaliphatic ring

is monocyclic. In some embodiments, a cycloaliphatic ring is bicyclic. In some embodiments, a cycloaliphatic ring is polycyclic. In some embodiments, a ring is a cycloaliphatic moiety as described in the present disclosure for R with more valences.

[00236] In some embodiments, Cy^L is an optionally substituted 6-20 membered aryl ring. In some embodiments, a ring is an optionally substituted tetravalent phenyl moiety. In some embodiments, a ring is a tetravalent phenyl moiety. In some embodiments, a ring is an optionally substituted naphthalene moiety. A ring can be of different size as described in the present disclosure. In some embodiments, an aryl ring is 6-membered. In some embodiments, an aryl ring is 10-membered. In some embodiments, an aryl ring is 14-membered. In some embodiments, an aryl ring is monocyclic. In some embodiments, an aryl ring is bicyclic. In some embodiments, an aryl ring is polycyclic. In some embodiments, a ring is an aryl moiety as described in the present disclosure for R with more valences.

[00237] In some embodiments, Cy^L is an optionally substituted 5-20 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, Cy^L is an optionally substituted 5-20 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, as described in the present disclosure, heteroaryl rings can be of various sizes and contain various numbers and/or types of heteroatoms. In some embodiments, a heteroaryl ring contains no more than one heteroatom. In some embodiments, a heteroaryl ring contains more than one heteroatom. In some embodiments, a heteroaryl ring contains no more than one type of heteroatom. In some embodiments, a heteroaryl ring contains more than one type of heteroatoms. In some embodiments, a heteroaryl ring is 5-membered. In some embodiments, a heteroaryl ring is 6-membered. In some embodiments, a heteroaryl ring is 8-membered. In some embodiments, a heteroaryl ring is 9-membered. In some embodiments, a heteroaryl ring is 10-membered. In some embodiments, a heteroaryl ring is monocyclic. In some embodiments, a heteroaryl ring is bicyclic. In some embodiments, a heteroaryl ring is polycyclic. In some embodiments, a heteroaryl ring is a nucleobase moiety, *e.g.*, A, T, C, G, U, *etc.* In some embodiments, a ring is a heteroaryl moiety as described in the present disclosure for R with more valences.

[00238] In some embodiments, Cy^L is a 3-20 membered heterocyclyl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, Cy^L is a 3-20 membered heterocyclyl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, a heterocyclyl ring is saturated. In some embodiments, a heterocyclyl ring is partially unsaturated. A heterocyclyl ring can be of various sizes as described in the present disclosure. In some embodiments, a ring is 3, 4, 5, 6, 7, 8, 9, or 10-membered. In some embodiments, a ring is 3-membered. In some embodiments, a ring is 4-membered. In some

embodiments, a ring is 5-membered. In some embodiments, a ring is 6-membered. In some embodiments, a ring is 7-membered. In some embodiments, a ring is 8-membered. In some embodiments, a ring is 9-membered. In some embodiments, a ring is 10-membered. Heterocyclyl rings can contain various numbers and/or types of heteroatoms. In some embodiments, a heterocyclyl ring contains no more than one heteroatom. In some embodiments, a heterocyclyl ring contains more than one heteroatom. In some embodiments, a heterocyclyl ring contains no more than one type of heteroatom. In some embodiments, a heterocyclyl ring contains more than one type of heteroatoms. In some embodiments, a heterocyclyl ring is monocyclic. In some embodiments, a heterocyclyl ring is bicyclic. In some embodiments, a heterocyclyl ring is polycyclic. In some embodiments, a ring is a heterocyclyl moiety as described in the present disclosure for R with more valences.

[00239] As readily appreciated by a person having ordinary skill in the art, many suitable ring moieties are extensively described in and can be used in accordance with the present disclosure, for example, those described for R (which may have more valences for Cy^L).

[00240] In some embodiments, Cy^L is a sugar moiety in a nucleic acid. In some embodiments, Cy^L is an optionally substituted furanose moiety. In some embodiments, Cy^L is a pyranose moiety. In some embodiments, Cy^L is an optionally substituted furanose moiety found in DNA. In some embodiments, Cy^L is an optionally substituted furanose moiety found in RNA. In some embodiments, Cy^L is an optionally substituted 2'-deoxyribofuranose moiety. In some embodiments, Cy^L is an optionally substituted ribofuranose moiety. In some embodiments, substitutions provide sugar modifications as described in the present disclosure. In some embodiments, an optionally substituted 2'-deoxyribofuranose moiety and/or an optionally substituted ribofuranose moiety comprise substitution at a 2'-position. In some embodiments, a 2'-position is a 2'-modification as described in the present disclosure. In some embodiments, a 2'-modification is −F. In some embodiments, a 2'-modification is −OR, wherein R is as described in the present disclosure. In some embodiments, R is not hydrogen. In some embodiments, Cy^L is a modified sugar moiety, such as a sugar moiety in LNA. In some embodiments, Cy^L is a modified sugar moiety, such as a sugar moiety in ENA. In some embodiments, Cy^L is a terminal sugar moiety of an oligonucleotide, connecting an internucleotidic linkage and a nucleobase. In some embodiments, Cy^L is a terminal sugar moiety of an oligonucleotide, for example, when that terminus is connected to a solid support optionally through a linker. In some embodiments, Cy^L is a sugar moiety connecting two internucleotidic linkages and a nucleobase. Example sugars and sugar moieties are extensively described in the present disclosure.

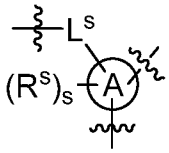
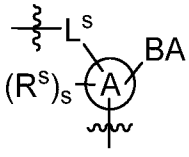
[00241] In some embodiments, Cy^L is a nucleobase moiety. In some embodiments, a nucleobase is a natural nucleobase, such as A, T, C, G, U, *etc.* In some embodiments, a nucleobase is a modified nucleobase. In some embodiments, Cy^L is optionally substituted nucleobase moiety selected from A, T,

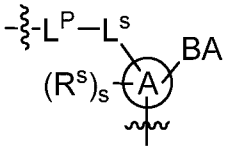
C, G, U, and 5mC. Example nucleobases and nucleobase moieties are extensively described in the present disclosure.

[00242] In some embodiments, two Cy^L moieties are bonded to each other, wherein one Cy^L is a sugar moiety and the other is a nucleobase moiety. In some embodiments, such a sugar moiety and nucleobase moiety forms a nucleoside moiety. In some embodiments, a nucleoside moiety is natural. In some embodiments, a nucleoside moiety is modified. In some embodiments, Cy^L is an optionally substituted natural nucleoside moiety selected from adenosine, 5-methyluridine, cytidine, guanosine, uridine, 5-methylcytidine, 2'-deoxyadenosine, thymidine, 2'-deoxycytidine, 2'-deoxyguanosine, 2'-deoxyuridine, and 5-methyl-2'-deoxycytidine. Example nucleosides and nucleosides moieties are extensive described in the present disclosure.

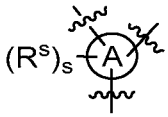
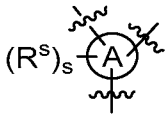
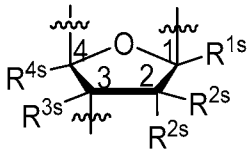
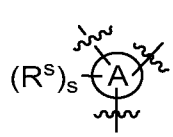
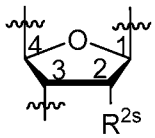
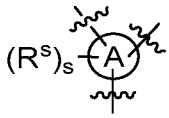
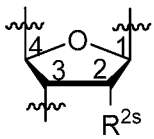
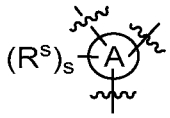
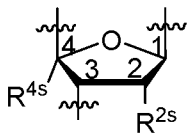
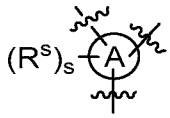
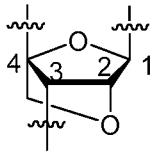
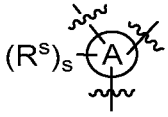
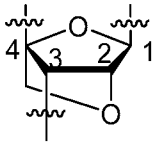
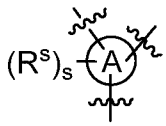
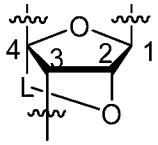
[00243] In some embodiments, for example in L^s, Cy^L is an optionally substituted nucleoside moiety bonded to an internucleotidic linkage, for example, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, −OP(OR')[B(R')$_3$]O−, *etc.*, which may form an optionally substituted nucleotidic unit. Example nucleotides and nucleosides moieties are extensive described in the present disclosure.

[00244] In some embodiments, each Ring A is independently an optionally substituted 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, Ring A is an optionally substituted ring, which ring is as described in the present disclosure. In some embodiments, a ring is . In some embodiments, a ring is . In some embodiments, Ring A is or comprises a ring of a sugar moiety. In some embodiments, Ring A is or comprises a ring of a modified sugar moiety.

[00245] In some embodiments, a sugar unit is of the structure  , wherein each variable is independently as described in the present disclosure. In some embodiments, a nucleoside unit is of the structure  , wherein each variable is independently as described in the present disclosure. In some embodiments, a nucleotide unit, *e.g.*, Nu^M, Nu^O, *etc.*, is of the structure



, wherein each variable is independently as described in the present disclosure. In some embodiments, for Nu^O, L^P is a natural phosphate linkage, and L^s is $-C(R^{5s})_2-$ as described in the present disclosure.

[00246] In some embodiments, L^s is $-C(R^{5s})_2-$ and  is as described in the present disclosure. In some embodiments,  is  , BA is connected at C1, and each of R^{1s}, R^{2s}, R^{3s}, R^{4s} and R^{5s} is independently as described in the present disclosure. In some embodiments,  is  , wherein R^{2s} is as described in the present disclosure. In some embodiments,  is  , wherein R^{2s} is not $-OH$. In some embodiments,  is  , wherein R^{2s} and R^{4s} are R, and the two R groups are taken together with their intervening atoms to form an optionally substituted ring. In some embodiments,  , or Ring A, is optionally substituted  . In some embodiments,  , or Ring A, is  . In some embodiments,  , or Ring A, is  .

[00247] In some embodiments, each of R^{1s}, R^{2s}, R^{3s}, R^{4s}, and R^{5s} is independently R^s, wherein R^s is as described in the present disclosure.

[00248] In some embodiments, R^{1s} is R^s wherein R^s is as described in the present disclosure. In some embodiments, R^{1s} is at 1'-position (BA is at 1'-position). In some embodiments, R^{1s} is −H. In some embodiments, R^{1s} is −F. In some embodiments, R^{1s} is −Cl. In some embodiments, R^{1s} is −Br. In some embodiments, R^{1s} is −I. In some embodiments, R^{1s} is −CN. In some embodiments, R^{1s} is $-N_3$. In some embodiments, R^{1s} is −NO. In some embodiments, R^{1s} is $-NO_2$. In some embodiments, R^{1s} is −L−R'. In some embodiments, R^{1s} is −R'. In some embodiments, R^{1s} is −L−OR'. In some embodiments, R^{1s} is −OR'. In some embodiments, R^{1s} is −L−SR'. In some embodiments, R^{1s} is −SR'. In some embodiments, R^{1s} is L−L−$N(R')_2$. In some embodiments, R^{1s} is $-N(R')_2$. In some embodiments, R^{1s} is −OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{1s} is −OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{1s} is −OMe. In some embodiments, R^{1s} is −MOE. In some embodiments, R^{1s} is hydrogen. In some embodiments, R^s at one 1'-position is hydrogen, and R^s at the other 1'-position is not hydrogen as described herein. In some embodiments, R^s at both 1'-positions are hydrogen. In some embodiments, R^s at one 1'-position is hydrogen, and the other 1'-position is connected to an internucleotidic linkage. In some embodiments, R^{1s} is −F. In some embodiments, R^{1s} is −Cl. In some embodiments, R^{1s} is −Br. In some embodiments, R^{1s} is −I. In some embodiments, R^{1s} is −CN. In some embodiments, R^{1s} is $-N_3$. In some embodiments, R^{1s} is −NO. In some embodiments, R^{1s} is $-NO_2$. In some embodiments, R^{1s} is −L−R'. In some embodiments, R^{1s} is −R'. In some embodiments, R^{1s} is −L−OR'. In some embodiments, R^{1s} is −OR'. In some embodiments, R^{1s} is −L−SR'. In some embodiments, R^{1s} is −SR'. In some embodiments, R^{1s} is −L−$N(R')_2$. In some embodiments, R^{1s} is $-N(R')_2$. In some embodiments, R^{1s} is −OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{1s} is −OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{1s} is −OH. In some embodiments, R^{1s} is −OMe. In some embodiments, R^{1s} is −MOE. In some embodiments, R^{1s} is hydrogen. In some embodiments, one R^{1s} at a 1'-position is hydrogen, and the other R^{1s} at the other 1'-position is not hydrogen as described herein. In some embodiments, R^{1s} at both 1'-positions are hydrogen. In some embodiments, R^{1s} is −O−L^s−OR'. In some embodiments, R^{1s} is −O−L^s−OR', wherein L^s is optionally substituted C_{1-6} alkylene, and R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{1s} is −O−(optionally substituted C_{1-6} alkylene)−OR'. In some embodiments, R^{1s} is −O−(optionally substituted C_{1-6} alkylene)−OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{1s} is $-OCH_2CH_2OMe$.

[00249] In some embodiments, R^{2s} is R^s wherein R^s is as described in the present disclosure. In some embodiments, if there are two R^{2s} at the 2'-position, one R^{2s} is −H and the other is not. In some embodiments, R^{2s} is at 2'-position (BA is at 1'-position). In some embodiments, R^{2s} is −H. In some embodiments, R^{2s} is −F. In some embodiments, R^{2s} is −Cl. In some embodiments, R^{2s} is −Br. In some embodiments, R^{2s} is −I. In some embodiments, R^{2s} is −CN. In some embodiments, R^{2s} is $-N_3$. In some

embodiments, R^{2s} is −NO. In some embodiments, R^{2s} is $-NO_2$. In some embodiments, R^{2s} is −L−R'. In some embodiments, R^{2s} is −R'. In some embodiments, R^{2s} is −L−OR'. In some embodiments, R^{2s} is −OR'. In some embodiments, R^{2s} is −L−SR'. In some embodiments, R^{2s} is −SR'. In some embodiments, R^{2s} is L−L−$N(R')_2$. In some embodiments, R^{2s} is $-N(R')_2$. In some embodiments, R^{2s} is −OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{2s} is −OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{2s} is −OMe. In some embodiments, R^{2s} is −MOE. In some embodiments, R^{2s} is hydrogen. In some embodiments, R^s at one 2'-position is hydrogen, and R^s at the other 2'-position is not hydrogen as described herein. In some embodiments, R^s at both 2'-positions are hydrogen. In some embodiments, R^s at one 2'-position is hydrogen, and the other 2'-position is connected to an internucleotidic linkage. In some embodiments, R^{2s} is −F. In some embodiments, R^{2s} is −Cl. In some embodiments, R^{2s} is −Br. In some embodiments, R^{2s} is −I. In some embodiments, R^{2s} is −CN. In some embodiments, R^{2s} is $-N_3$. In some embodiments, R^{2s} is −NO. In some embodiments, R^{2s} is $-NO_2$. In some embodiments, R^{2s} is −L−R'. In some embodiments, R^{2s} is −R'. In some embodiments, R^{2s} is −L−OR'. In some embodiments, R^{2s} is −OR'. In some embodiments, R^{2s} is −L−SR'. In some embodiments, R^{2s} is −SR'. In some embodiments, R^{2s} is −L−$N(R')_2$. In some embodiments, R^{2s} is $-N(R')_2$. In some embodiments, R^{2s} is −OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{2s} is −OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{2s} is −OH. In some embodiments, R^{2s} is −OMe. In some embodiments, R^{2s} is −MOE. In some embodiments, R^{2s} is hydrogen. In some embodiments, one R^{2s} at a 2'-position is hydrogen, and the other R^{2s} at the other 2'-position is not hydrogen as described herein. In some embodiments, R^{2s} at both 2'-positions are hydrogen. In some embodiments, R^{2s} is −O−L^s−OR'. In some embodiments, R^{2s} is −O−L^s−OR', wherein L^s is optionally substituted C_{1-6} alkylene, and R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{2s} is −O−(optionally substituted C_{1-6} alkylene)−OR'. In some embodiments, R^{2s} is −O−(optionally substituted C_{1-6} alkylene)−OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{2s} is $-OCH_2CH_2OMe$.

[00250] In some embodiments, R^{3s} is R^s wherein R^s is as described in the present disclosure. In some embodiments, R^{3s} is at 3'-position (BA is at 1'-position). In some embodiments, R^{3s} is −H. In some embodiments, R^{3s} is −F. In some embodiments, R^{3s} is −Cl. In some embodiments, R^{3s} is −Br. In some embodiments, R^{3s} is −I. In some embodiments, R^{3s} is −CN. In some embodiments, R^{3s} is $-N_3$. In some embodiments, R^{3s} is −NO. In some embodiments, R^{3s} is $-NO_2$. In some embodiments, R^{3s} is −L−R'. In some embodiments, R^{3s} is −R'. In some embodiments, R^{3s} is −L−OR'. In some embodiments, R^{3s} is −OR'. In some embodiments, R^{3s} is −L−SR'. In some embodiments, R^{3s} is −SR'. In some embodiments, R^{3s} is −L−$N(R')_2$. In some embodiments, R^{3s} is $-N(R')_2$. In some embodiments, R^{3s} is −OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{3s} is −OR', wherein

R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{3s} is −OMe. In some embodiments, R^{3s} is −MOE. In some embodiments, R^{3s} is hydrogen. In some embodiments, R^s at one 3'-position is hydrogen, and R^s at the other 3'-position is not hydrogen as described herein. In some embodiments, R^s at both 3'-positions are hydrogen. In some embodiments, R^s at one 3'-position is hydrogen, and the other 3'-position is connected to an internucleotidic linkage. In some embodiments, R^{3s} is −F. In some embodiments, R^{3s} is −Cl. In some embodiments, R^{3s} is −Br. In some embodiments, R^{3s} is −I. In some embodiments, R^{3s} is −CN. In some embodiments, R^{3s} is $-N_3$. In some embodiments, R^{3s} is −NO. In some embodiments, R^{3s} is $-NO_2$. In some embodiments, R^{3s} is −L−R'. In some embodiments, R^{3s} is −R'. In some embodiments, R^{3s} is −L−OR'. In some embodiments, R^{3s} is −OR'. In some embodiments, R^{3s} is −L−SR'. In some embodiments, R^{3s} is −SR'. In some embodiments, R^{3s} is L−L−$N(R')_2$. In some embodiments, R^{3s} is $-N(R')_2$. In some embodiments, R^{3s} is −OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{3s} is −OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{3s} is −OH. In some embodiments, R^{3s} is −OMe. In some embodiments, R^{3s} is −MOE. In some embodiments, R^{3s} is hydrogen.

[00251] In some embodiments, R^{4s} is R^s wherein R^s is as described in the present disclosure. In some embodiments, R^{4s} is at 4'-position (BA is at 1'-position). In some embodiments, R^{4s} is −H. In some embodiments, R^{4s} is −F. In some embodiments, R^{4s} is −Cl. In some embodiments, R^{4s} is −Br. In some embodiments, R^{4s} is −I. In some embodiments, R^{4s} is −CN. In some embodiments, R^{4s} is $-N_3$. In some embodiments, R^{4s} is −NO. In some embodiments, R^{4s} is $-NO_2$. In some embodiments, R^{4s} is −L−R'. In some embodiments, R^{4s} is −R'. In some embodiments, R^{4s} is −L−OR'. In some embodiments, R^{4s} is −OR'. In some embodiments, R^{4s} is −L−SR'. In some embodiments, R^{4s} is −SR'. In some embodiments, R^{4s} is −L−$N(R')_2$. In some embodiments, R^{4s} is $-N(R')_2$. In some embodiments, R^{4s} is −OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{4s} is −OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{4s} is −OMe. In some embodiments, R^{4s} is −MOE. In some embodiments, R^{4s} is hydrogen. In some embodiments, R^s at one 4'-position is hydrogen, and R^s at the other 4'-position is not hydrogen as described herein. In some embodiments, R^s at both 4'-positions are hydrogen. In some embodiments, R^s at one 4'-position is hydrogen, and the other 4'-position is connected to an internucleotidic linkage. In some embodiments, R^{4s} is −F. In some embodiments, R^{4s} is −Cl. In some embodiments, R^{4s} is −Br. In some embodiments, R^{4s} is −I. In some embodiments, R^{4s} is −CN. In some embodiments, R^{4s} is $-N_3$. In some embodiments, R^{4s} is −NO. In some embodiments, R^{4s} is $-NO_2$. In some embodiments, R^{4s} is −L−R'. In some embodiments, R^{4s} is −R'. In some embodiments, R^{4s} is −L−OR'. In some embodiments, R^{4s} is −OR'. In some embodiments, R^{4s} is −L−SR'. In some embodiments, R^{4s} is −SR'. In some embodiments, R^{4s} is L−L−$N(R')_2$. In some embodiments, R^{4s} is $-N(R')_2$. In some embodiments, R^{4s} is −OR', wherein R' is optionally substituted

C_{1-6} aliphatic. In some embodiments, R^{4s} is −OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{4s} is −OH. In some embodiments, R^{4s} is −OMe. In some embodiments, R^{4s} is −MOE. In some embodiments, R^{4s} is hydrogen.

[00252] In some embodiments, R^{5s} is R^s wherein R^s is as described in the present disclosure. In some embodiments, R^{5s} is R' wherein R' is as described in the present disclosure. In some embodiments, R^{5s} is −H. In some embodiments, two or more R^{5s} are connected to the same carbon atom, and at least one is not −H. In some embodiments, R^{5s} is not −H. In some embodiments, R^{5s} is −F. In some embodiments, R^{5s} is −Cl. In some embodiments, R^{5s} is −Br. In some embodiments, R^{5s} is −I. In some embodiments, R^{5s} is −CN. In some embodiments, R^{5s} is $-N_3$. In some embodiments, R^{5s} is −NO. In some embodiments, R^{5s} is $-NO_2$. In some embodiments, R^{5s} is −L−R'. In some embodiments, R^{5s} is −R'. In some embodiments, R^{5s} is −L−OR'. In some embodiments, R^{5s} is −OR'. In some embodiments, R^{5s} is −L−SR'. In some embodiments, R^{5s} is −SR'. In some embodiments, R^{5s} is L−L−$N(R')_2$. In some embodiments, R^{5s} is $-N(R')_2$. In some embodiments, R^{5s} is −OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{5s} is −OR', wherein R' is optionally substituted C_{1-6} alkyl. In some embodiments, R^{5s} is −OH. In some embodiments, R^{5s} is −OMe. In some embodiments, R^{5s} is −MOE. In some embodiments, R^{5s} is hydrogen.

[00253] In some embodiments, R^{5s} is optionally substituted C_{1-6} aliphatic as described in the present disclosure, *e.g.*, C_{1-6} aliphatic embodiments described for R or other variables. In some embodiments, R^{5s} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{5s} is methyl. In some embodiments, R^{5s} is ethyl.

[00254] In some embodiments, R^{5s} is a protected hydroxyl group suitable for oligonucleotide synthesis. In some embodiments, R^{5s} is −OR', wherein R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{5s} is DMTrO−. Example protecting groups are widely known for use in accordance with the present disclosure. For additional examples, see Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, 2nd ed.; Wiley: New York, 1991, and WO/2011/005761, WO/2013/012758, WO/2014/012081, WO/2015/107425, WO/2010/064146, WO/2014/010250, WO/2011/108682, WO/2012/039448, and WO/2012/073857, protecting groups of each of which are hereby incorporated by reference.

[00255] In some embodiments, two or more of R^{1s}, R^{2s}, R^{3s}, R^{4s}, and R^{5s} are R and can be taken together with intervening atom(s) to form a ring as described in the present disclosure. In some embodiments, R^{2s} and R^{4s} are R taken together to form a ring, and a sugar moiety can be a bicyclic sugar moiety, *e.g.*, a LNA sugar moiety.

[00256] In some embodiments, L^s is $-C(R^{5s})_2-$, wherein each R^{5s} is independently as described in the present disclosure. In some embodiments, one of R^{5s} is H and the other is not H. In some

embodiments, none of R^{5s} is H. In some embodiments, L^s is $-CHR^{5s}-$, wherein each R^{5s} is independently as described in the present disclosure. In some embodiments, $-C(R^{5s})_2-$ is 5'-C, optionally substituted, of a sugar moiety. In some embodiments, the C of $-C(R^{5s})_2-$ is connected to linkage phosphorus and a sugar wing moiety. In some embodiments, the C of $-C(R^{5s})_2-$ is of *R* configuration. In some embodiments, the C of $-C(R^{5s})_2-$ is of *S* configuration. As described in the present disclosure, in some embodiments, R^{5s} is optionally substituted C_{1-6} aliphatic; in some embodiments, R^{5s} is methyl.

[00257] In some embodiments, provided compounds comprise one or more bivalent or multivalent optionally substituted rings, *e.g.*, Ring A, Cy^L, those formed by two or more R groups (R and (combinations of) variables that can be R) taken together, *etc.* In some embodiments, a ring is a cycloaliphatic, aryl, heteroaryl, or heterocyclyl group as described for R but bivalent or multivalent. As appreciated by those skilled in the art, ring moieties described for one variable, *e.g.*, Ring A, can also be applicable to other variables, *e.g.*, Cy^L, if requirements of the other variables, *e.g.*, number of heteroatoms, valence, *etc.*, are satisfied. Example rings are extensively described in the present disclosure.

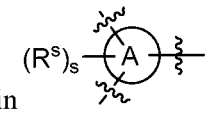
[00258] In some embodiments, a ring, *e.g.*, in Ring A, R, *etc.* which is optionally substituted, is a 3-20 membered monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[00259] In some embodiments, a ring can be of any size within its range, *e.g.*, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20-membered.

[00260] In some embodiments, a ring is monocyclic. In some embodiments, a ring is saturated and monocyclic. In some embodiments, a ring is monocyclic and partially saturated. In some embodiments, a ring is monocyclic and aromatic.

[00261] In some embodiments, a ring is bicyclic. In some embodiments, a ring is polycyclic. In some embodiments, a bicyclic or polycyclic ring comprises two or more monocyclic ring moieties, each of which can be saturated, partially saturated, or aromatic, and each which can contain no or 1-10 heteroatoms. In some embodiments, a bicyclic or polycyclic ring comprises a saturated monocyclic ring. In some embodiments, a bicyclic or polycyclic ring comprises a saturated monocyclic ring containing no heteroatoms. In some embodiments, a bicyclic or polycyclic ring comprises a saturated monocyclic ring comprising one or more heteroatoms. In some embodiments, a bicyclic or polycyclic ring comprises a partially saturated monocyclic ring. In some embodiments, a bicyclic or polycyclic ring comprises a partially saturated monocyclic ring containing no heteroatoms. In some embodiments, a bicyclic or polycyclic ring comprises a partially saturated monocyclic ring comprising one or more heteroatoms. In some embodiments, a bicyclic or polycyclic ring comprises an aromatic monocyclic ring. In some embodiments, a bicyclic or polycyclic ring comprises an aromatic monocyclic ring containing no

heteroatoms. In some embodiments, a bicyclic or polycyclic ring comprises an aromatic monocyclic ring comprising one or more heteroatoms. In some embodiments, a bicyclic or polycyclic ring comprises a saturated ring and a partially saturated ring, each of which independently contains one or more heteroatoms. In some embodiments, a bicyclic ring comprises a saturated ring and a partially saturated ring, each of which independently comprises no, or one or more heteroatoms. In some embodiments, a bicyclic ring comprises an aromatic ring and a partially saturated ring, each of which independently comprises no, or one or more heteroatoms. In some embodiments, a polycyclic ring comprises a saturated ring and a partially saturated ring, each of which independently comprises no, or one or more heteroatoms. In some embodiments, a polycyclic ring comprises an aromatic ring and a partially saturated ring, each of which independently comprises no, or one or more heteroatoms. In some embodiments, a polycyclic ring comprises an aromatic ring and a saturated ring, each of which independently comprises no, or one or more heteroatoms. In some embodiments, a polycyclic ring comprises an aromatic ring, a saturated ring, and a partially saturated ring, each of which independently comprises no, or one or more heteroatoms. In some embodiments, a ring comprises at least one heteroatom. In some embodiments, a ring comprises at least one nitrogen atom. In some embodiments, a ring comprises at least one oxygen atom. In some embodiments, a ring comprises at least one sulfur atom.

[00262] As appreciated by those skilled in the art in accordance with the present disclosure, a ring is typically optionally substituted. In some embodiments, a ring is unsubstituted. In some embodiments, a ring is substituted. In some embodiments, a ring is substituted on one or more of its carbon atoms. In some embodiments, a ring is substituted on one or more of its heteroatoms. In some embodiments, a ring is substituted on one or more of its carbon atoms, and one or more of its heteroatoms. In some embodiments, two or more substituents can be located on the same ring atom. In some embodiments, all available ring atoms are substituted. In some embodiments, not all available ring atoms are substituted. In some embodiments, in provided structures where rings are indicated to be connected to other structures (*e.g.*, Ring A in ), "optionally substituted" is to mean that, besides those structures already connected, remaining substitutable ring positions, if any, are optionally substituted.

[00263] In some embodiments, a ring is a bivalent or multivalent C_{3-30} cycloaliphatic ring. In some embodiments, a ring is a bivalent or multivalent C_{3-20} cycloaliphatic ring. In some embodiments, a ring is a bivalent or multivalent C_{3-10} cycloaliphatic ring. In some embodiments, a ring is a bivalent or multivalent 3-30 membered saturated or partially unsaturated carbocyclic ring. In some embodiments, a ring is a bivalent or multivalent 3-7 membered saturated or partially unsaturated carbocyclic ring. In

some embodiments, a ring is a bivalent or multivalent 3-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, a ring is a bivalent or multivalent 4-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, a ring is a bivalent or multivalent 5-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, a ring is a bivalent or multivalent 6-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, a ring is a bivalent or multivalent 7-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, a ring is a bivalent or multivalent cyclohexyl ring. In some embodiments, a ring is a bivalent or multivalent cyclopentyl ring. In some embodiments, a ring is a bivalent or multivalent cyclobutyl ring. In some embodiments, a ring is a bivalent or multivalent cyclopropyl ring.

[00264] In some embodiments, a ring is a bivalent or multivalent C_{6-30} aryl ring. In some embodiments, a ring is a bivalent or multivalent phenyl ring.

[00265] In some embodiments, a ring is a bivalent or multivalent 8-10 membered bicyclic saturated, partially unsaturated or aryl ring. In some embodiments, a ring is a bivalent or multivalent 8-10 membered bicyclic saturated ring. In some embodiments, a ring is a bivalent or multivalent 8-10 membered bicyclic partially unsaturated ring. In some embodiments, a ring is a bivalent or multivalent 8-10 membered bicyclic aryl ring. In some embodiments, a ring is a bivalent or multivalent naphthyl ring.

[00266] In some embodiments, a ring is a bivalent or multivalent 5-30 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, a ring is a bivalent or multivalent 5-30 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 5-30 membered heteroaryl ring having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, a ring is a bivalent or multivalent 5-30 membered heteroaryl ring having 1-5 heteroatoms independently selected from oxygen, nitrogen, and sulfur.

[00267] In some embodiments, a ring is a bivalent or multivalent 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, sulfur, and oxygen.

[00268] In some embodiments, a ring is a bivalent or multivalent 5-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur. In some embodiments, a ring is a bivalent or multivalent 6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00269] In certain embodiments, a ring is a bivalent or multivalent 8–10 membered bicyclic heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In

some embodiments, a ring is a bivalent or multivalent 5,6–fused heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 5,6–fused heteroaryl ring having 1–5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, a ring is a bivalent or multivalent 6,6–fused heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

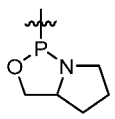
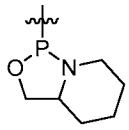
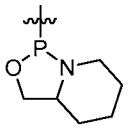
[00270] In some embodiments, a ring is a bivalent or multivalent 3-30 membered heterocyclic ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, a ring is a bivalent or multivalent 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, a ring is a bivalent or multivalent 5–7 membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, a ring is a bivalent or multivalent 5–6 membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, a ring is a bivalent or multivalent 5-membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, a ring is a bivalent or multivalent 6-membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, a ring is a bivalent or multivalent 7-membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 3-membered heterocyclic ring having one heteroatom selected from nitrogen, oxygen or sulfur. In some embodiments, a ring is a bivalent or multivalent 4-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 5-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 6-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 7-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

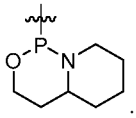
[00271] In some embodiments, a ring is a bivalent or multivalent 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a ring is a bivalent or multivalent 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00272] In some embodiments, a ring is a bivalent or multivalent 5,6–fused heteroaryl ring having 1–5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, a ring is a bivalent or multivalent 6,6–fused heteroaryl ring having 1–5 heteroatoms independently selected

from nitrogen, oxygen, and sulfur.

[00273] In some embodiments, a ring formed by two or more groups taken together, which is typically optionally substituted, is a monocyclic saturated 5-7 membered ring having no additional heteroatoms in addition to intervening heteroatoms, if any. In some embodiments, a ring formed by two or more groups taken together is a monocyclic saturated 5-membered ring having no additional heteroatoms in addition to intervening heteroatoms, if any. In some embodiments, a ring formed by two or more groups taken together is a monocyclic saturated 6-membered ring having no additional heteroatoms in addition to intervening heteroatoms, if any. In some embodiments, a ring formed by two or more groups taken together is a monocyclic saturated 7-membered ring having no additional heteroatoms in addition to intervening heteroatoms, if any.

[00274] In some embodiments, a ring formed by two or more groups taken together is a bicyclic, saturated, partially unsaturated, or aryl 5-30 membered ring having, in addition to the intervening heteroatoms, if any, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, a ring formed by two or more groups taken together is a bicyclic, saturated, partially unsaturated, or aryl 5-30 membered ring having, in addition to the intervening heteroatoms, if any, 0-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, a ring formed by two or more groups taken together is a bicyclic and saturated 8-10 membered bicyclic ring having no additional heteroatoms in addition to intervening heteroatoms, if any. In some embodiments, a ring formed by two or more groups taken together is a bicyclic and saturated 8-membered bicyclic ring having no additional heteroatoms in addition to intervening heteroatoms, if any. In some embodiments, a ring formed by two or more groups taken together is a bicyclic and saturated 9-membered bicyclic ring having no additional heteroatoms in addition to intervening heteroatoms, if any. In some embodiments, a ring formed by two or more groups taken together is a bicyclic and saturated 10-membered bicyclic ring having no additional heteroatoms in addition to intervening heteroatoms, if any. In some embodiments, a ring formed by two or more groups taken together is bicyclic and comprises a 5-membered ring fused to a 5-membered ring. In some embodiments, a ring formed by two or more groups taken together is bicyclic and comprises a 5-membered ring fused to a 6-membered ring. In some embodiments, the 5-membered ring comprises one or more intervening nitrogen, phosphorus and oxygen atoms as ring atoms. In some embodiments, a ring formed by two or more groups taken together comprises a ring system having the backbone structure of  ,  ,  , or



[00275] In some embodiments, a ring formed by two or more groups taken together is a polycyclic, saturated, partially unsaturated, or aryl 3-30 membered ring having, in addition to the intervening heteroatoms, if any, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, a ring formed by two or more groups taken together is a polycyclic, saturated, partially unsaturated, or aryl 3-30 membered ring having, in addition to the intervening heteroatoms, if any, 0-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur.

[00276] In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 5-10 membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 5-9 membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 5-8 membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 5-7 membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 5-6 membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms.

[00277] In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 5-membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 6-membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 7-membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 8-membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is

monocyclic, bicyclic or polycyclic and comprises a 9-membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 10-membered monocyclic ring whose ring atoms comprise one or more intervening nitrogen, phosphorus and/or oxygen atoms.

[00278] In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 5-membered ring whose ring atoms consist of carbon atoms and the intervening nitrogen, phosphorus and oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 6-membered ring whose ring atoms consist of carbon atoms and the intervening nitrogen, phosphorus and oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 7-membered ring whose ring atoms consist of carbon atoms and the intervening nitrogen, phosphorus and oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 8-membered ring whose ring atoms consist of carbon atoms and the intervening nitrogen, phosphorus and oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 9-membered ring whose ring atoms consist of carbon atoms and the intervening nitrogen, phosphorus and oxygen atoms. In some embodiments, a ring formed by two or more groups taken together is monocyclic, bicyclic or polycyclic and comprises a 10-membered ring whose ring atoms consist of carbon atoms and the intervening nitrogen, phosphorus and oxygen atoms.

[00279] In some embodiments, rings described herein are unsubstituted. In some embodiments, rings described herein are substituted. In some embodiments, substituents are selected from those described in example compounds provided in the present disclosure.

[00280] As described herein, each L^P is independently an internucleotidic linkage as described in the present disclosure, *e.g.*, a natural phosphate linkage, a phosphorothioate diester linkage, a modified internucleotidic linkage, a chiral internucleotidic linkage, *etc.*, In some embodiments, each L^P is independently a linkage having the structure of formula IIn some embodiments, L^{3E} is $-L^s-$ or $-L^s-L^s-$. In some embodiments, L^{3E} is $-L^s-$. In some embodiments, L^{3E} is $-L^s-L^s-$. In some embodiments, L^{3E} is a covalent bond. In some embodiments, L^{3E} is a linker used in oligonucleotide synthesis. In some embodiments, L^{3E} is a linker used in solid phase oligonucleotide synthesis. Various types of linkers are known and can be utilized in accordance with the present disclosure. In some embodiments, a linker is a succinate linker ($-O-C(O)-CH_2-CH_2-C(O)-$). In some embodiments, a linker is an oxalyl linker ($-O-C(O)-C(O)-$). In some embodiments, L^{3E} is a succinyl-piperidine linker (SP) linker. In some embodiments, L^{3E} is a succinyl linker. In some embodiments, L^{3E} is a Q-linker.

[00281] In some embodiments, R^{3E} is −R', $-L^s-R'$, −OR', or a solid support. In some embodiments, R^{3E} is −R'. In some embodiments, R^{3E} is $-L^s-R'$. In some embodiments, R^{3E} is −OR'. In some embodiments, R^{3E} is a solid support. In some embodiments, R^{3E} is −H. In some embodiments, $-L^3-R^{3E}$ is −H. In some embodiments, R^{3E} is −OH. In some embodiments, $-L^3-R^{3E}$ is −OH. In some embodiments, R^{3E} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{3E} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{3E} is −OR'. In some embodiments, R^{3E} is −OH. In some embodiments, R^{3E} is −OR', wherein R' is not hydrogen. In some embodiments, R^{3E} is −OR', wherein R' is optionally substituted C_{1-6} alkyl.

In some embodiments, R^{3E} is a 3'-end cap (*e.g.*, those used in RNAi technologies).

[00282] In some embodiments, R^{3E} is a solid support. In some embodiments, R^{3E} is a solid support for oligonucleotide synthesis. Various types of solid support are known and can be utilized in accordance with the present disclosure. In some embodiments, a solid support is HCP. In some embodiments, a solid support is CPG.

[00283] In some embodiments, R' is −R, −C(O)R, −C(O)OR, or $-S(O)_2R$, wherein R is as described in the present disclosure. In some embodiments, R' is R, wherein R is as described in the present disclosure. In some embodiments, R' is −C(O)R, wherein R is as described in the present disclosure. In some embodiments, R' is −C(O)OR, wherein R is as described in the present disclosure. In some embodiments, R' is $-S(O)_2R$, wherein R is as described in the present disclosure. In some embodiments, R' is hydrogen. In some embodiments, R' is not hydrogen. In some embodiments, R' is R, wherein R is optionally substituted C_{1-20} aliphatic as described in the present disclosure. In some embodiments, R' is R, wherein R is optionally substituted C_{1-20} heteroaliphatic as described in the present disclosure. In some embodiments, R' is R, wherein R is optionally substituted C_{6-20} aryl as described in the present disclosure. In some embodiments, R' is R, wherein R is optionally substituted C_{6-20} arylaliphatic as described in the present disclosure. In some embodiments, R' is R, wherein R is optionally substituted C_{6-20} arylheteroaliphatic as described in the present disclosure. In some embodiments, R' is R, wherein R is optionally substituted 5-20 membered heteroaryl as described in the present disclosure. In some embodiments, R' is R, wherein R is optionally substituted 3-20 membered heterocyclyl as described in the present disclosure. In some embodiments, two or more R' are R, and are optionally and independently taken together to form an optionally substituted ring as described in the present disclosure.

[00284] In some embodiments, each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-

30 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, or

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

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

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

[00285] In some embodiments, each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-30 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, or

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

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

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

[00286] In some embodiments, each R is independently –H, or an optionally substituted group selected from C_{1-20} aliphatic, C_{1-20} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-20} aryl, C_{6-20} arylaliphatic, C_{6-20} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-20 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-20 membered heterocyclyl having 1-10 heteroatoms independently selected

from oxygen, nitrogen, sulfur, phosphorus and silicon, or

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

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-20 membered monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-20 membered monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[00287] In some embodiments, each R is independently –H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-30 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[00288] In some embodiments, each R is independently –H, or an optionally substituted group selected from C_{1-20} aliphatic, C_{1-20} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-20} aryl, C_{6-20} arylaliphatic, C_{6-20} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-20 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-20 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[00289] In some embodiments, R is hydrogen. In some embodiments, R is not hydrogen. In some embodiments, R is an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, a 5-30 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and a 3-30 membered heterocyclic ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[00290] In some embodiments, R is hydrogen or an optionally substituted group selected from C_{1-20} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-7 membered

saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00291] In some embodiments, R is optionally substituted C_{1-30} aliphatic. In some embodiments, R is optionally substituted C_{1-20} aliphatic. In some embodiments, R is optionally substituted C_{1-15} aliphatic. In some embodiments, R is optionally substituted C_{1-10} aliphatic. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted hexyl, pentyl, butyl, propyl, ethyl or methyl. In some embodiments, R is optionally substituted hexyl. In some embodiments, R is optionally substituted pentyl. In some embodiments, R is optionally substituted butyl. In some embodiments, R is optionally substituted propyl. In some embodiments, R is optionally substituted ethyl. In some embodiments, R is optionally substituted methyl. In some embodiments, R is hexyl. In some embodiments, R is pentyl. In some embodiments, R is butyl. In some embodiments, R is propyl. In some embodiments, R is ethyl. In some embodiments, R is methyl. In some embodiments, R is isopropyl. In some embodiments, R is *n*-propyl. In some embodiments, R is *tert*-butyl. In some embodiments, R is *sec*-butyl. In some embodiments, R is *n*-butyl. In some embodiments, R is $-(CH_2)_2CN$.

[00292] In some embodiments, R is optionally substituted C_{3-30} cycloaliphatic. In some embodiments, R is optionally substituted C_{3-20} cycloaliphatic. In some embodiments, R is optionally substituted C_{3-10} cycloaliphatic. In some embodiments, R is optionally substituted cyclohexyl. In some embodiments, R is cyclohexyl. In some embodiments, R is optionally substituted cyclopentyl. In some embodiments, R is cyclopentyl. In some embodiments, R is optionally substituted cyclobutyl. In some embodiments, R is cyclobutyl. In some embodiments, R is optionally substituted cyclopropyl. In some embodiments, R is cyclopropyl.

[00293] In some embodiments, R is an optionally substituted 3-30 membered saturated or partially unsaturated carbocyclic ring. In some embodiments, R is an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring. In some embodiments, R is an optionally substituted 3-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, R is an optionally substituted 4-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, R is an optionally substituted 5-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, R is an optionally substituted 6-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, R is an optionally substituted 7-membered saturated or partially unsaturated carbocyclic ring. In some embodiments, R is optionally substituted cycloheptyl. In some

embodiments, R is cycloheptyl. In some embodiments, R is optionally substituted cyclohexyl. In some embodiments, R is cyclohexyl. In some embodiments, R is optionally substituted cyclopentyl. In some embodiments, R is cyclopentyl. In some embodiments, R is optionally substituted cyclobutyl. In some embodiments, R is cyclobutyl. In some embodiments, R is optionally substituted cyclopropyl. In some embodiments, R is cyclopropyl.

[00294] In some embodiments, when R is or comprises a ring structure, *e.g.*, cycloaliphatic, cycloheteroaliphatic, aryl, heteroaryl, *etc.*, the ring structure can be monocyclic, bicyclic or polycyclic. In some embodiments, R is or comprises a monocyclic structure. In some embodiments, R is or comprises a bicyclic structure. In some embodiments, R is or comprises a polycyclic structure.

[00295] In some embodiments, R is optionally substituted C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is optionally substituted C_{1-20} heteroaliphatic having 1-10 heteroatoms. In some embodiments, R is optionally substituted C_{1-20} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus or silicon, optionally including one or more oxidized forms of nitrogen, sulfur, phosphorus or selenium. In some embodiments, R is optionally substituted C_{1-30} heteroaliphatic comprising 1-10 groups independently selected from , –N=, ≡N, –S–, –S(O)–, –S(O)$_2$–, –O–, =O, , , and .

[00296] In some embodiments, R is optionally substituted C_{6-30} aryl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl. In some embodiments, R is substituted phenyl.

[00297] In some embodiments, R is an optionally substituted 8-10 membered bicyclic saturated, partially unsaturated or aryl ring. In some embodiments, R is an optionally substituted 8-10 membered bicyclic saturated ring. In some embodiments, R is an optionally substituted 8-10 membered bicyclic partially unsaturated ring. In some embodiments, R is an optionally substituted 8-10 membered bicyclic aryl ring. In some embodiments, R is optionally substituted naphthyl.

[00298] In some embodiments, R is optionally substituted 5-30 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is optionally substituted 5-30 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, R is optionally substituted 5-30 membered heteroaryl ring having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is optionally substituted 5-30 membered heteroaryl ring having 1-5 heteroatoms independently selected from oxygen, nitrogen, and

sulfur.

[00299] In some embodiments, R is an optionally substituted 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is a substituted 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an unsubstituted 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, sulfur, and oxygen. In some embodiments, R is a substituted 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an unsubstituted 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, sulfur, and oxygen.

[00300] In some embodiments, R is an optionally substituted 5-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur. In some embodiments, R is an optionally substituted 6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00301] In some embodiments, R is an optionally substituted 5-membered monocyclic heteroaryl ring having one heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R is selected from optionally substituted pyrrolyl, furanyl, or thienyl.

[00302] In some embodiments, R is an optionally substituted 5-membered heteroaryl ring having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 5-membered heteroaryl ring having one nitrogen atom, and an additional heteroatom selected from sulfur or oxygen. Example R groups include but are not limited to optionally substituted pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl or isoxazolyl.

[00303] In some embodiments, R is an optionally substituted 5-membered heteroaryl ring having three heteroatoms independently selected from nitrogen, oxygen, and sulfur. Example R groups include but are not limited to optionally substituted triazolyl, oxadiazolyl or thiadiazolyl.

[00304] In some embodiments, R is an optionally substituted 5-membered heteroaryl ring having four heteroatoms independently selected from nitrogen, oxygen, and sulfur. Example R groups include but are not limited to optionally substituted tetrazolyl, oxatriazolyl and thiatriazolyl.

[00305] In some embodiments, R is an optionally substituted 6-membered heteroaryl ring having 1–4 nitrogen atoms. In some embodiments, R is an optionally substituted 6-membered heteroaryl ring having 1–3 nitrogen atoms. In other embodiments, R is an optionally substituted 6-membered heteroaryl ring having 1–2 nitrogen atoms. In some embodiments, R is an optionally substituted 6-membered

heteroaryl ring having four nitrogen atoms. In some embodiments, R is an optionally substituted 6-membered heteroaryl ring having three nitrogen atoms. In some embodiments, R is an optionally substituted 6-membered heteroaryl ring having two nitrogen atoms. In certain embodiments, R is an optionally substituted 6-membered heteroaryl ring having one nitrogen atom. Example R groups include but are not limited to optionally substituted pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, or tetrazinyl.

[00306] 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.

[00307] In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having three heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having four heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having five heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00308] In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having

one heteroatom independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted indolyl. In some embodiments, R is optionally substituted benzofuranyl. In some embodiments, R is optionally substituted benzo[*b*]thienyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted azaindolyl. In some embodiments, R is optionally substituted benzimidazolyl. In some embodiments, R is optionally substituted benzothiazolyl. In some embodiments, R is optionally substituted benzoxazolyl. In some embodiments, R is an optionally substituted indazolyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having three heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted oxazolopyridiyl, thiazolopyridinyl or imidazopyridinyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having four heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted purinyl, oxazolopyrimidinyl, thiazolopyrimidinyl, oxazolopyrazinyl, thiazolopyrazinyl, imidazopyrazinyl, oxazolopyridazinyl, thiazolopyridazinyl or imidazopyridazinyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having five heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00309] In some embodiments, R is optionally substituted 1,4-dihydropyrrolo[3,2-*b*]pyrrolyl, 4*H*-furo[3,2-*b*]pyrrolyl, 4H-thieno[3,2-*b*]pyrrolyl, furo[3,2-*b*]furanyl, thieno[3,2-*b*]furanyl, thieno[3,2-*b*]thienyl, 1H-pyrrolo[1,2-*a*]imidazolyl, pyrrolo[2,1-b]oxazolyl or pyrrolo[2,1-b]thiazolyl. In some embodiments, R is optionally substituted dihydropyrroloimidazolyl, 1*H*-furoimidazolyl, 1*H*-thienoimidazolyl, furooxazolyl, furoisoxazolyl, 4*H*-pyrrolooxazolyl, 4*H*-pyrroloisoxazolyl, thienooxazolyl, thienoisoxazolyl, 4*H*-pyrrolothiazolyl, furothiazolyl, thienothiazolyl, 1*H*-imidazoimidazolyl, imidazooxazolyl or imidazo[5,1-b]thiazolyl.

[00310] In certain embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having 1–2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In other embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted quinolinyl. In some embodiments, R is an optionally substituted isoquinolinyl. In some embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted quinazoline or a quinoxaline.

[00311] In some embodiments, R is 3-30 membered heterocyclic ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R

is 3-30 membered heterocyclic ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, R is 3-30 membered heterocyclic ring having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is 3-30 membered heterocyclic ring having 1-5 heteroatoms independently selected from oxygen, nitrogen, and sulfur.

[00312] In some embodiments, R is an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is a substituted 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an unsubstituted 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 5–7 membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 5–6 membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 5-membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 6-membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 7-membered partially unsaturated monocyclic ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted 3-membered heterocyclic ring having one heteroatom selected from nitrogen, oxygen or sulfur. In some embodiments, R is optionally substituted 4-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted 5-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted 6-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted 7-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00313] In some embodiments, R is an optionally substituted 3-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 4-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and

sulfur. In some embodiments, R is an optionally substituted 6-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 7-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00314] In some embodiments, R is an optionally substituted 4-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is nitrogen. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is oxygen. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is sulfur. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having 2 oxygen atoms. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having 2 nitrogen atoms. In some embodiments, R is an optionally substituted 4-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is nitrogen. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is oxygen. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is sulfur. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having 2 oxygen atoms. In some embodiments, R is an optionally substituted 4-membered partially unsaturated heterocyclic ring having 2 nitrogen atoms.

[00315] In some embodiments, R is an optionally substituted 5-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and

sulfur. In some embodiments, R is an optionally substituted 5-membered partially unsaturated heterocyclic ring having 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom. In some embodiments, R is an optionally substituted 5-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is nitrogen. In some embodiments, R is an optionally substituted 5-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is oxygen. In some embodiments, R is an optionally substituted 5-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is sulfur. In some embodiments, R is an optionally substituted 5-membered partially unsaturated heterocyclic ring having 2 oxygen atoms. In some embodiments, R is an optionally substituted 5-membered partially unsaturated heterocyclic ring having 2 nitrogen atoms.

[00316] In some embodiments, R is an optionally substituted 6-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 6-membered partially unsaturated heterocyclic ring having 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 6-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom. In some embodiments, R is an optionally substituted 6-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is nitrogen. In some embodiments, R is an optionally substituted 6-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is oxygen. In some embodiments, R is an optionally substituted 6-membered partially unsaturated heterocyclic ring having no more than 1 heteroatom, wherein the heteroatom is sulfur. In some embodiments, R is an optionally substituted 6-membered partially unsaturated heterocyclic ring having 2 oxygen atoms. In some embodiments, R is an optionally substituted 6-membered partially unsaturated heterocyclic ring having 2 nitrogen atoms.

[00317] In certain embodiments, R is a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is optionally substituted oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepaneyl, aziridineyl, azetidineyl, pyrrolidinyl, piperidinyl, azepanyl, thiiranyl, thietanyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, thiepanyl, dioxolanyl, oxathiolanyl, oxazolidinyl, imidazolidinyl, thiazolidinyl, dithiolanyl, dioxanyl, morpholinyl, oxathianyl, piperazinyl, thiomorpholinyl, dithianyl, dioxepanyl, oxazepanyl, oxathiepanyl, dithiepanyl, diazepanyl, dihydrofuranonyl, tetrahydropyranonyl, oxepanonyl, pyrolidinonyl, piperidinonyl, azepanonyl,

dihydrothiophenonyl, tetrahydrothiopyranonyl, thiepanonyl, oxazolidinonyl, oxazinanonyl, oxazepanonyl, dioxolanonyl, dioxanonyl, dioxepanonyl, oxathiolinonyl, oxathianonyl, oxathiepanonyl, thiazolidinonyl, thiazinanonyl, thiazepanonyl, imidazolidinonyl, tetrahydropyrimidinonyl, diazepanonyl, imidazolidinedionyl, oxazolidinedionyl, thiazolidinedionyl, dioxolanedionyl, oxathiolanedionyl, piperazinedionyl, morpholinedionyl, thiomorpholinedionyl, tetrahydropyranyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrothiophenyl, or tetrahydrothiopyranyl.

[00318] In certain embodiments, R is an optionally substituted 5–6 membered partially unsaturated monocyclic ring having 1–2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted tetrahydropyridinyl, dihydrothiazolyl, dihydrooxazolyl, or oxazolinyl group.

[00319] In some embodiments, R is an optionally substituted 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted indolinyl. In some embodiments, R is optionally substituted isoindolinyl. In some embodiments, R is optionally substituted 1, 2, 3, 4-tetrahydroquinolinyl. In some embodiments, R is optionally substituted 1, 2, 3, 4-tetrahydroisoquinolinyl. In some embodiments, R is an optionally substituted azabicyclo[3.2.1]octanyl.

[00320] In some embodiments, R is an optionally substituted 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00321] In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted 1,4-dihydropyrrolo[3,2-*b*]pyrrolyl, 4*H*-furo[3,2-*b*]pyrrolyl, 4H-thieno[3,2-*b*]pyrrolyl, furo[3,2-*b*]furanyl, thieno[3,2-*b*]furanyl, thieno[3,2-*b*]thienyl, 1H-pyrrolo[1,2-*a*]imidazolyl, pyrrolo[2,1-b]oxazolyl or pyrrolo[2,1-b]thiazolyl. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having three heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted dihydropyrroloimidazolyl, 1*H*-furoimidazolyl, 1*H*-thienoimidazolyl, furooxazolyl, furoisoxazolyl, 4*H*-pyrrolooxazolyl, 4*H*-pyrroloisoxazolyl, thienooxazolyl, thienoisoxazolyl, 4*H*-pyrrolothiazolyl, furothiazolyl, thienothiazolyl, 1*H*-imidazoimidazolyl, imidazooxazolyl or imidazo[5,1-b]thiazolyl. In some embodiments, R is an

optionally substituted 5,6–fused heteroaryl ring having four heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having five heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00322] In some embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In other embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having 1–2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having one heteroatom independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted indolyl. In some embodiments, R is optionally substituted benzofuranyl. In some embodiments, R is optionally substituted benzo[*b*]thienyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted azaindolyl. In some embodiments, R is optionally substituted benzimidazolyl. In some embodiments, R is optionally substituted benzothiazolyl. In some embodiments, R is optionally substituted benzoxazolyl. In some embodiments, R is an optionally substituted indazolyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having three heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted oxazolopyridiyl, thiazolopyridinyl or imidazopyridinyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having four heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted purinyl, oxazolopyrimidinyl, thiazolopyrimidinyl, oxazolopyrazinyl, thiazolopyrazinyl, imidazopyrazinyl, oxazolopyridazinyl, thiazolopyridazinyl or imidazopyridazinyl. In certain embodiments, R is an optionally substituted 5,6–fused heteroaryl ring having five heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00323] In certain embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having 1–5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having 1–2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In other embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having one heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted quinolinyl. In some embodiments, R is optionally substituted isoquinolinyl. In some embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted quinazolinyl, phthalazinyl, quinoxalinyl or naphthyridinyl. In some embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having three heteroatoms independently selected from

nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted pyridopyrimidinyl, pyridopyridazinyl, pyridopyrazinyl, or benzotriazinyl. In some embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having four heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is optionally substituted pyridotriazinyl, pteridinyl, pyrazinopyrazinyl, pyrazinopyridazinyl, pyridazinopyridazinyl, pyrimidopyridazinyl or pyrimidopyrimidinyl. In some embodiments, R is an optionally substituted 6,6–fused heteroaryl ring having five heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00324] In some embodiments, R is optionally substituted C_{6-30} arylaliphatic. In some embodiments, R is optionally substituted C_{6-20} arylaliphatic. In some embodiments, R is optionally substituted C_{6-10} arylaliphatic. In some embodiments, an aryl moiety of the arylaliphatic has 6, 10, or 14 aryl carbon atoms. In some embodiments, an aryl moiety of the arylaliphatic has 6 aryl carbon atoms. In some embodiments, an aryl moiety of the arylaliphatic has 10 aryl carbon atoms. In some embodiments, an aryl moiety of the arylaliphatic has 14 aryl carbon atoms. In some embodiments, an aryl moiety is optionally substituted phenyl.

[00325] In some embodiments, R is optionally substituted C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is optionally substituted C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, R is optionally substituted C_{6-20} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is optionally substituted C_{6-20} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, R is optionally substituted C_{6-10} arylheteroaliphatic having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, R is optionally substituted C_{6-10} arylheteroaliphatic having 1-5 heteroatoms independently selected from oxygen, nitrogen, and sulfur.

[00326] In some embodiments, two R groups are optionally and independently taken together to form a covalent bond. In some embodiments, −C=O is formed. In some embodiments, −C=C− is formed. In some embodiments, —C≡C— is formed.

[00327] In some embodiments, two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-20 membered monocyclic, bicyclic or polycyclic ring having, in addition to the

atom, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-10 membered monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-6 membered monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-3 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-5 membered monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-3 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[00328] In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-20 membered monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-10 membered monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-10 membered monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-6 membered monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-3 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon. In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-5 membered monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-3 heteroatoms independently selected from oxygen, nitrogen, sulfur,

phosphorus and silicon.

[00329] In some embodiments, heteroatoms in R groups, or in the structures formed by two or more R groups taken together, are selected from oxygen, nitrogen, and sulfur. In some embodiments, a formed ring is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20-membered. In some embodiments, a formed ring is saturated. In some embodiments, a formed ring is partially saturated. In some embodiments, a formed ring is aromatic. In some embodiments, a formed ring comprises a saturated, partially saturated, or aromatic ring moiety. In some embodiments, a formed ring comprises 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 aromatic ring atoms. In some embodiments, a formed contains no more than 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 aromatic ring atoms. In some embodiments, aromatic ring atoms are selected from carbon, nitrogen, oxygen and sulfur.

[00330] In some embodiments, a ring formed by two or more R groups (or two or more groups selected from R and variables that can be R) taken together is a C_{3-30} cycloaliphatic, C_{6-30} aryl, 5-30 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, or 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, ring as described for R, but bivalent or multivalent.

[00331] In some embodiments, P^L is P(=W). In some embodiments, P^L is P. In some embodiments, P^L is $P{\rightarrow}B(R')_3$. In some embodiments, P of P^L is chiral. In some embodiments, P of P^L is *R*p. In some embodiments, P of P^L is *S*p. In some embodiments, a linkage of formula **I** is a phosphate linkage or a salt form thereof. In some embodiments, a linkage of formula **I** is a phosphorothioate linkage or a salt form thereof. In some embodiments, P^L is P*(=W), wherein P* is a chiral linkage phosphorus. In some embodiments, P^L is P*(=O), wherein P* is a chiral linkage phosphorus.

[00332] In some embodiments, W is O. In some embodiments, W is S. In some embodiments, W is Se.

[00333] Each of X, Y, Z and R^1 is independently as described in the present disclosure, for example, as described, in some embodiments, R^1 is H. In some embodiments, $-X-L-R^1$ is $-X-R^1$. In some embodiments, $-X-L-R^1$ is $-X-H$. In some embodiments, Y and Z are O, and X is S. In some embodiments, Y and Z are O and X is O. Additional embodiments of each of the variables are independently described in the present disclosure.

[00334] In some embodiments, a provided oligonucleotide has the structure of formula O-I. In some embodiments, an oligonucleotide of formula O-I comprise chemical modifications (*e.g.*, sugar modification, base modifications, modified internucleotidic linkages, *etc.*, and patterns thereof), stereochemistry (of 5'-C, chiral phosphorus, *etc.*, and patterns thereof), base sequences, *etc.*, as described in the present disclosure. In some embodiments, a provided oligonucleotide of formula O-I is one selected from in Table 1A, Table 17, *etc.*

[00335] In some embodiments, the present disclosure provides multimers of oligonucleotides. In some embodiments, at least one of the monomer is a C9orf72 oligonucleotide. In some embodiments, a multimer is a multimer of the same oligonucleotides. In some embodiments, a multimer is a multimer of structurally different oligonucleotides. In some embodiments, each oligonucleotide of a multimer performs its functions independently through its own pathways, e.g., RNA interference (RNAi), RNase H dependent, etc. In some embodiments, provided oligonucleotides exist in an oligomeric or polymeric form, in which one or more oligonucleotide moieties are linked together by linkers, e.g., L, L^M, etc., through nucleobases, sugars, and/or internucleotidic linkages of the oligonucleotide moieties. For example, in some embodiments, a provided multimer compound has the structure of $(A^c)_a$–L^M–$(A^c)_b$, wherein each variable is independently as described in the present disclosure.

[00336] In some embodiments, a provided compound, *e.g.*, an oligonucleotide of a provided composition, has the structure of:

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

or a salt thereof, wherein:

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

or a salt thereof, wherein:

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

a is 1-1000;

b is 1-1000;

L^M is a multivalent linker; and

each R^D is independently a chemical moiety.

[00337] In some embodiments, a provided compound, *e.g.*, an oligonucleotide of a provided composition, have the structure of:

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

or a salt thereof, wherein:

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

a is 1-1000;

b is 1-1000;

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

R^{CD} is an optionally substituted, linear or branched group selected from a C_{1-100} aliphatic group and a C_{1-100} heteroaliphatic group having 1-30 heteroatoms 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;

R^{LD} is an optionally substituted, linear or branched group selected from a C_{1-100} aliphatic group wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, $-C\equiv C-$, $-C(R')_2-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$, $-OP(O)(NR')O-$, $-OP(OR')O-$, $-OP(SR')O-$, $-OP(NR')O-$, $-OP(R')O-$, or $-OP(OR')[B(R')_3]O-$; and one or more carbon atoms are optionally and independently replaced with Cy^L;

R^{TD} is a targeting moiety;

each L^M is independently a covalent bond, or a bivalent or multivalent, optionally substituted, linear or branched group selected from a C_{1-100} aliphatic group and a C_{1-100} heteroaliphatic group having 1-30 heteroatoms 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, $-C\equiv C-$, $-C(R')_2-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$, $-OP(O)(NR')O-$, $-OP(OR')O-$, $-OP(SR')O-$, $-OP(NR')O-$, $-OP(R')O-$, or $-OP(OR')[B(R')_3]O-$; and one or more carbon atoms are optionally and independently replaced with Cy^L;

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

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 independently selected from oxygen, nitrogen, sulfur,

phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-30 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, or

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

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

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

[00338] In some embodiments, A^c–[–L^M–(R^D)$_a$]$_b$, [(A^c)$_a$–L^M]$_b$–R^D, or (A^c)$_a$–L^M–(R^D)$_b$ is a conjugate of a provided oligonucleotide with one or more chemical moieties, *e.g.*, targeting moieties, carbohydrate moieties, lipid moieties, *etc.*

[00339] In some embodiments, (R^D)b–L^M– is (R^D)b–L^{M1}–L^{M2} as described in the present disclosure.

[00340] In some embodiments, [H]$_a$–A^c or [H]$_b$–A^c is an oligonucleotide as described in the present disclosure. In some embodiments, [H]$_a$–A^c or [H]$_b$–A^c is of formula O-I.

[00341] In some embodiments, R^D is an additional chemical moiety as described in the present disclosure. In some embodiments, R^D is a targeting moiety as described in the present disclosure. In some embodiments, R^D is R^{TD}, which is a targeting moiety as described in the present disclosure (*e.g.*, targeting moiety described as embodiment for R^D as targeting moiety). In some embodiments, In some embodiments, R^D is R^{CD}, wherein R^{CD} is as described in the present disclosure. In some embodiments, R^{CD} comprises one or more carbohydrate moieties. In some embodiments, R^D is R^{LD}. In some embodiments, R^{LD} is a lipid moiety as described in the present disclosure.

[00342] In some embodiments, a is 1-100. In some embodiments, a is 1-50. In some embodiments, a is 1-40. In some embodiments, a is 1-30. In some embodiments, a is 1-20. In some embodiments, a is 1-15. In some embodiments, a is 1-10. In some embodiments, a is 1-9. In some embodiments, a is 1-8. In some embodiments, a is 1-7. In some embodiments, a is 1-6. In some embodiments, a is 1-5. In some embodiments, a is 1-4. In some embodiments, a is 1-3. In some embodiments, a is 1-2. In some embodiments, a is 1. In some embodiments, a is 2. In some

embodiments, a is 3. In some embodiments, a is 4. In some embodiments, a is 5. In some embodiments, a is 6. In some embodiments, a is 7. In some embodiments, a is 8. In some embodiments, a is 9. In some embodiments, a is 10. In some embodiments, a is more than 10.

[00343] In some embodiments, b is 1-100. In some embodiments, b is 1-50. In some embodiments, b is 1-40. In some embodiments, b is 1-30. In some embodiments, b is 1-20. In some embodiments, b is 1-15. In some embodiments, b is 1-10. In some embodiments, b is 1-9. In some embodiments, b is 1-8. In some embodiments, b is 1-7. In some embodiments, b is 1-6. In some embodiments, b is 1-5. In some embodiments, b is 1-4. In some embodiments, b is 1-3. In some embodiments, b is 1-2. In some embodiments, b is 1. In some embodiments, b is 2. In some embodiments, b is 3. In some embodiments, b is 4. In some embodiments, b is 5. In some embodiments, b is 6. In some embodiments, b is 7. In some embodiments, b is 8. In some embodiments, b is 9. In some embodiments, b is 10. In some embodiments, b is 1. In some embodiments, b is 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, or more.

[00344] In some embodiments, z is 1-1000. In some embodiments, z +1 is an oligonucleotide length as described in the present disclosure. In some embodiments, z is no less than 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19. In some embodiments, z is no less than 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14. In some embodiments, z is no more than 50, 60, 70, 80, 90, 100, 150, or 200. In some embodiments, z is 5-50, 10-50, 14-50, 14-45, 14-40, 14-35, 14-30, 14-25, 14-100, 14-150, 14-200, 14-250, 14-300, 15-50, 15-45, 15-40, 15-35, 15-30, 15-25, 15-100, 15-150, 15-200, 15-250, 15-300, 16-50, 16-45, 16-40, 16-35, 16-30, 16-25, 16-100, 16-150, 16-200, 16-250, 16-300, 17-50, 17-45, 17-40, 17-35, 17-30, 17-25, 17-100, 17-150, 17-200, 17-250, 17-300, 18-50, 18-45, 18-40, 18-35, 18-30, 18-25, 18-100, 18-150, 18-200, 18-250, 18-300, 19-50, 19-45, 19-40, 19-35, 19-30, 19-25, 19-100, 19-150, 19-200, 19-250, or 19-300. In some embodiments, z is 10. In some embodiments, z is 11. In some embodiments, z is 12. In some embodiments, z is 13. In some embodiments, z is 14. In some embodiments, z is 15. In some embodiments, z is 16. In some embodiments, z is 17. In some embodiments, z is 18. In some embodiments, z is 19. In some embodiments, z is 20. In some embodiments, z is 21. In some embodiments, z is 22. In some embodiments, z is 23. In some embodiments, z is 24. In some embodiments, z is 25. In some embodiments, z is 26. In some embodiments, z is 27. In some embodiments, z is 28. In some embodiments, z is 29. In some embodiments, z is 30. In some embodiments, z is 31. In some embodiments, z is 32. In some embodiments, z is 33. In some embodiments, z is 34.

[00345] In some embodiments, L^M is $-L^{M1}-L^{M2}-L^{M3}-$ as described in the present disclosure. In some embodiments, L^M is L^{M1} as described in the present disclosure. In some embodiments, L^M is L^{M2} as described in the present disclosure. In some embodiments, L^M is L^{M3} as described in the present

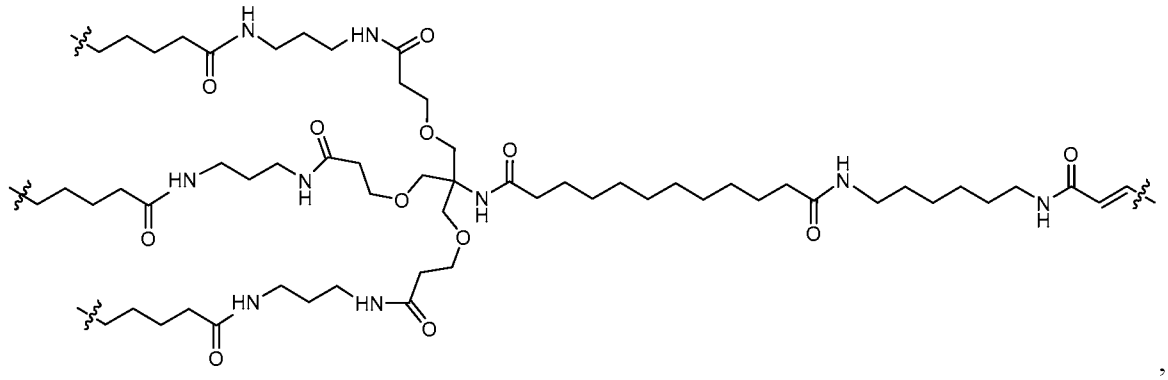
disclosure.

[00346] In some embodiments, at least one L^M is directly bound to a sugar unit of a provided oligonucleotide. In some embodiments, a L^M directly binds to a sugar unit incorporates a lipid moiety into an oligonucleotide. In some embodiments, a L^M directly binds to a sugar unit incorporates a carbohydrate moiety into an oligonucleotide. In some embodiments, a L^M directly binds to a sugar unit incorporates a R^{LD} group into an oligonucleotide. In some embodiments, a L^M directly binds to a sugar unit incorporates a R^{CD} group into an oligonucleotide. In some embodiments, L^M is directed bound through 5'-OH of an oligonucleotide chain. In some embodiments, L^M is directed bound through 3'-OH of an oligonucleotide chain.

[00347] In some embodiments, at least one L^M is directly bound to an internucleotidic linkage unit of a provided oligonucleotide. In some embodiments, a L^M directly binds to an internucleotidic linkage unit incorporates a lipid moiety into an oligonucleotide. In some embodiments, a L^M directly binds to an internucleotidic linkage unit incorporates a carbohydrate moiety into an oligonucleotide. In some embodiments, a L^M directly binds to an internucleotidic linkage unit incorporates a R^{LD} group into an oligonucleotide. In some embodiments, a L^M directly binds to an internucleotidic linkage unit incorporates a R^{CD} group into an oligonucleotide.

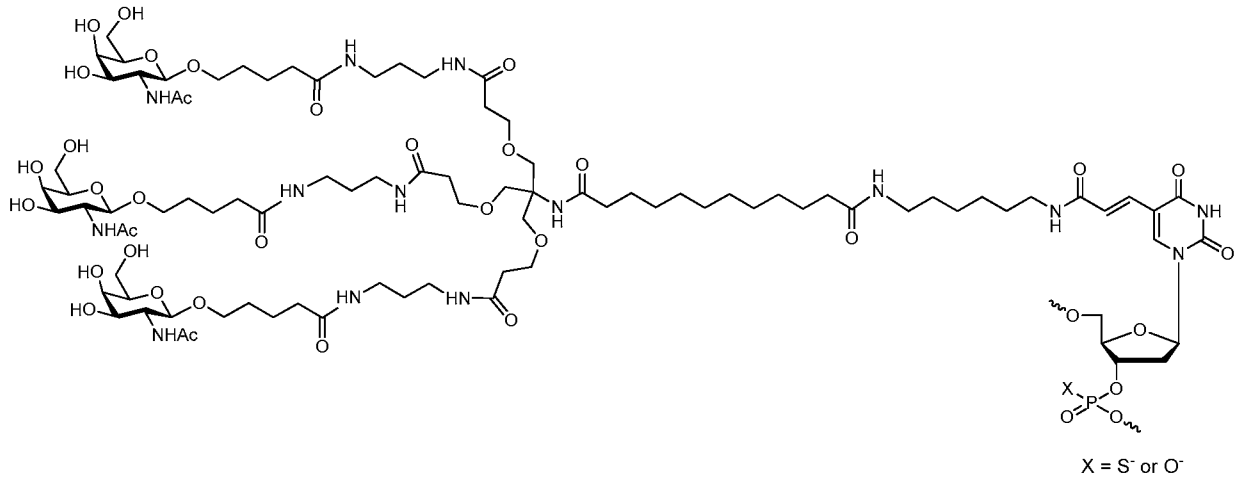
[00348] In some embodiments, at least one L^M is directly bound to a nucleobase unit of a provided oligonucleotide. In some embodiments, a L^M directly binds to a nucleobase unit incorporates a lipid moiety into an oligonucleotide. In some embodiments, a L^M directly binds to a nucleobase unit incorporates a carbohydrate moiety into an oligonucleotide. In some embodiments, a L^M directly binds to a nucleobase unit incorporates a R^{LD} group into an oligonucleotide. In some embodiments, a L^M directly binds to a nucleobase unit incorporates a R^{CD} group into an oligonucleotide.

[00349] In some embodiments, L^M is bivalent. In some embodiments, L^M is multivalent. In some embodiments, L^M is

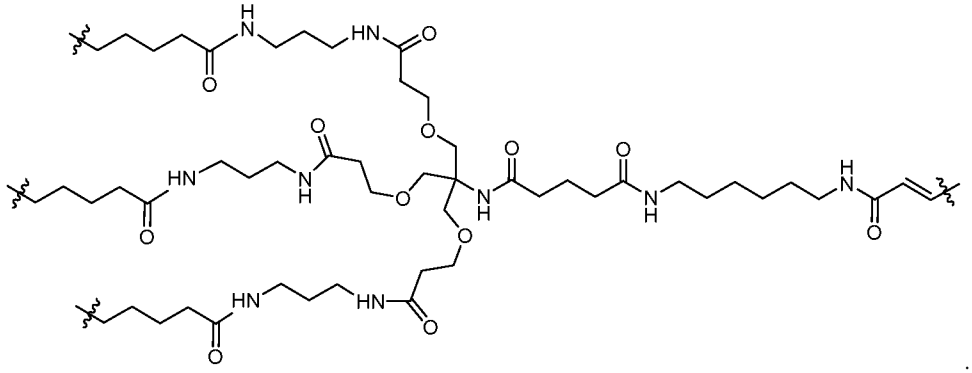


,

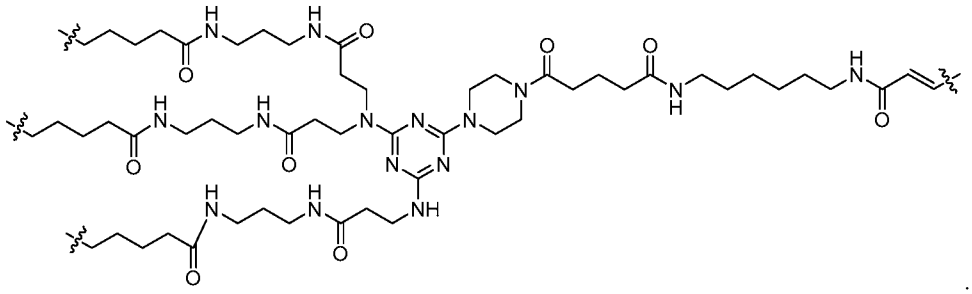
wherein L^M is directly bond to a nucleobase, for example, as in:

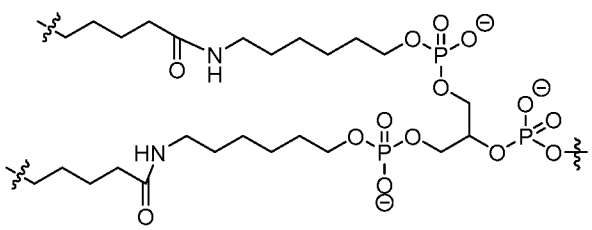


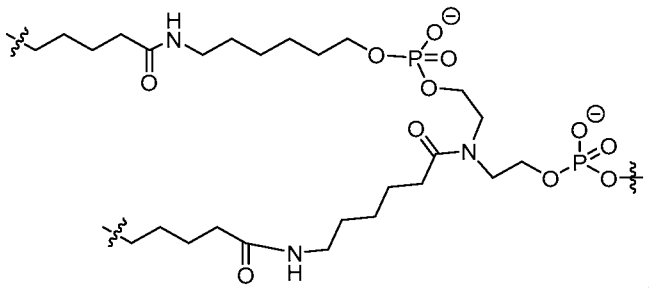
In some embodiments, L^M is



In some embodiments, L^M is



In some embodiments, L^M is  . In some embodiments,

L^M is  .

[00350] In some embodiments, R^{LD} is optionally substituted C_{10}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, or C_{25} to C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, C_{25}, C_{26}, C_{27}, C_{28}, C_{29}, C_{30}, C_{35}, C_{40}, C_{45}, C_{50}, C_{60}, C_{70}, or C_{80} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-80} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-80} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-70} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-70} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-60} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-60} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-50} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-50} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-40} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-40} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{10-30} aliphatic. In some embodiments, R^{LD} is optionally substituted C_{20-30} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, or C_{25} to C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, C_{25}, C_{26}, C_{27}, C_{28}, C_{29}, C_{30}, C_{35}, C_{40}, C_{45}, C_{50}, C_{60}, C_{70}, or C_{80} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-80} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-80} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-70} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-70} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-60} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-60} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-50} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-50} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-40} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-40} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{10-30} aliphatic. In some embodiments, R^{LD} is unsubstituted C_{20-30} aliphatic.

[00351] In some embodiments, R^{LD} is not hydrogen. In some embodiments, R^{LD} is a lipid moiety. In some embodiments, R^{LD} is a targeting moiety. In some embodiments, R^{LD} is a targeting moiety comprising a carbohydrate moiety. In some embodiments, R^{LD} is a GalNAc moiety.

[00352] In some embodiments, R^{TD} is R^{LD}, wherein R^{LD} is independently as described in the present disclosure. In some embodiments, R^{TD} is R^{CD}, wherein R^{CD} is independently as described in the present disclosure.

[00353] In some embodiments, R^{CD} is an optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently

selected from oxygen, nitrogen, sulfur, phosphorus, boron and silicon, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, –C(R')$_2$–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–; and one or more carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, R^{CD} is an optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus, boron and silicon, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, –C(R')$_2$–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–; and one or more carbon atoms are independently replaced with a monosaccharide, disaccharide or polysaccharide moiety. In some embodiments, R^{CD} is an optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus, boron and silicon, wherein one or more methylene units are optionally and independently replaced with C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, –C(R')$_2$–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–; and one or more carbon atoms are independently replaced with a GalNac moiety.

[00354] In some embodiments, the present disclosure provides salts of oligonucleotides, and pharmaceutical compositions thereof. In some embodiments, a salt is a pharmaceutically acceptable salt. In some embodiments, each hydrogen ion that may be donated to a base (e.g., under conditions of an aqueous solution, a pharmaceutical composition, etc.) is replaced by a non-H^+ cation. For example, in some embodiments, a pharmaceutically acceptable salt of an oligonucleotide is an all-metal ion salt, wherein each hydrogen ion (for example, of –OH, –SH, etc.) of each internucleotidic linkage (*e.g.*, a

natural phosphate linkage, a phosphorothioate diester linkage, etc.) is replaced by a metal ion. In some embodiments, a provided salt is an all-sodium salt. In some embodiments, a provided pharmaceutically acceptable salt is an all-sodium salt. In some embodiments, a provided salt is an all-sodium salt, wherein each internucleotidic linkage which is a natural phosphate linkage (acid form −O−P(O)(OH)−O−), if any, exists as its sodium salt form (−O−P(O)(ONa)−O−), and each internucleotidic linkage which is a phosphorothioate diester linkage (acid form −O−P(O)(SH)−O−), if any, exists as its sodium salt form (−O−P(O)(SNa)−O−).

[00355] In some embodiments, a provided compound, *e.g.*, a provided oligonucleotide, has a purity of 60%-100%. In some embodiments, a 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 purity is at least 60%. In some embodiments, a purity is at least 70%. In some embodiments, a purity is at least 80%. In some embodiments, a purity is at least 85%. In some embodiments, a purity is at least 90%. In some embodiments, a purity is at least 91%. In some embodiments, a purity is at least 92%. In some embodiments, a purity is at least 93%. In some embodiments, a purity is at least 94%. In some embodiments, a purity is at least 95%. In some embodiments, a purity is at least 96%. In some embodiments, a purity is at least 97%. In some embodiments, a purity is at least 98%. In some embodiments, a purity is at least 99%. In some embodiments, a purity is at least 99.5%.

[00356] In some embodiments, a provided compound, *e.g.*, a provided oligonucleotide, 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%.

[00357] 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.

[00358] 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.

[00359] 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.

[00360] In some embodiments, a provided compound, *e.g.*, oligonucleotide and/or compositions thereof, can modulate activities and/or functions of a C9orf72 target. In some embodiments, a C9orf72 target gene is a gene with respect to which expression and/or activity of one or more C9orf72 gene products (*e.g.*, RNA and/or protein products) are intended to be altered. In many embodiments, a C9orf72 target gene is intended to be inhibited. Thus, when a C9orf72 oligonucleotide as described herein acts on a particular C9orf72 target gene, presence and/or activity of one or more gene products of that C9orf72 gene are altered when the oligonucleotide is present as compared with when it is absent.

[00361] In some embodiments, a C9orf72 target is a specific allele (e.g., a pathological allele) with respect to which expression and/or activity of one or more products (*e.g.*, RNA and/or protein products) are intended to be altered. In many embodiments, a C9orf72 target allele is one whose presence and/or expression is associated (*e.g.*, correlated) with presence, incidence, and/or severity, of one or more diseases and/or conditions, e.g., a C9orf72-related disorder. Alternatively or additionally, in some embodiments, a C9orf72 target allele is one for which alteration of level and/or activity of one or more gene products correlates with improvement (*e.g.*, delay of onset, reduction of severity, responsiveness to

other therapy, etc) in one or more aspects of a disease and/or condition. In some such embodiments, C9orf72 oligonucleotides and methods thereof as described herein may preferentially or specifically target the pathological allele relative to the non-pathological allele, e.g., one or more less-associated/unassociated allele(s). In some embodiments, a pathological allele of C9orf72 comprises a repeat expansion, e.g., a hexanucleotide repeat expansion (HRE), e.g., a hexanucleotide repeat expansion of greater than about 30 and up to 500 or 1000 or more.

[00362] In some embodiments, a C9orf72 target sequence is a sequence to which an oligonucleotide as described herein binds. In many embodiments, a C9orf72 target sequence is identical to, or is an exact complement of, a sequence of a provided oligonucleotide, or of consecutive residues therein (*e.g.*, a provided oligonucleotide includes a target-binding sequence that is identical to, or an exact complement of, a C9orf72 target sequence). In some embodiments, a small number of differences/mismatches is tolerated between (a relevant portion of) an oligonucleotide and its target sequence. In many embodiments, a C9orf72 target sequence is present within a C9orf72 target gene. In many embodiments, a C9orf72 target sequence is present within a transcript (*e.g.*, an mRNA and/or a pre-mRNA) produced from a C9orf72 target gene. In some embodiments, a C9orf72 target sequence includes one or more allelic sites (i.e., positions within a C9orf72 target gene at which allelic variation occurs). In some such embodiments, a provided oligonucleotide binds to one allele preferentially or specifically relative to one or more other alleles.

[00363] In some embodiments, C9orf72 (chromosome 9 open reading frame 72) is a gene or its gene product, also designated as C9ORF72, C9, ALSFTD, FTDALS, FTDALS1, DENNL72; External IDs: MGI: 1920455 HomoloGene: 10137 GeneCards: C9orf72. C9orf72 is also informally designated C9. C9orf72 Orthologs: Species: Human Entrez: 203228; Ensembl: ENSG00000147894; UniProt: Q96LT7; RefSeq (mRNA): NM_145005 NM_001256054 NM_018325; RefSeq (protein): NP_001242983 NP_060795 NP_659442; Location (UCSC): Chr 9: 27.55 – 27.57 Mb; Species: Mouse Entrez: 73205; Ensembl: ENSMUSG00000028300; UniProt: Q6DFW0; RefSeq (mRNA): NM_001081343; RefSeq (protein): NP_00107481; Location (UCSC): Chr 4: 35.19 – 35.23 Mb. Nucleotides which encode C9orf72 include, without limitation, GENBANK Accession No. NM_001256054.1; GENBANK Accession No. NT_008413.18; GENBANK Accession No. BQ068108.1; GENBANK Accession No. NM_018325.3; GENBANK Accession No. DN993522.1; GENBANKAccession No. NM_145005.5; GENBANK Accession No. DB079375.1; GENBANK Accession No. BU194591.1; Sequence Identifier 4141_014_A 5; Sequence Identifier 4008_73_A; and GENBANKAccession No. NT_008413.18. C9orf72 reportedly is a 481 amino acid protein with a molecular mass of 54328 Da, which may undergo post-translational modifications of ubiquitination and phosphorylation. The expression levels of C9orf72 reportedly may be highest in the central nervous

system and the protein localizes in the cytoplasm of neurons as well as in presynaptic terminals. C9orf72 reportedly plays a role in endosomal and lysosomal trafficking regulation and has been shown to interact with RAB proteins that are involved in autophagy and endocytic transport. C9orf72 reportedly activates RAB5, a GTPase that mediates early endosomal trafficking. Mutations in C9orf72 reportedly have been associated with ALS and FTD. DeJesus-Hernandez et al. 2011 Neuron 72: 245-256; Renton et al. 2011 Neuron 72: 257-268; and Itzcovich et al. 2016. Neurobiol. Aging. Volume 40, Pages 192.e13–192.e15. A hexanucleotide repeat expansion (e.g., (GGGGCC)n) in C9orf72 reportedly may be present in subjects suffering from a neurological disease, such as a C9orf72-related disorder.

[00364] In some embodiments, C9orf72 is not capitalized and is rendered as c9orf72.

[00365] In some embodiments, a C9orf72 oligonucleotide can comprise any of various linkers, additional moieties (including but not limited to targeting moieties), and/or be chirally controlled and/or have any of various bases sequences and/or chemical structures or formats as described herein.

[00366] Various linker, carbohydrate moieties and targeting moieties, including many known in the art, can be utilized in accordance with the present disclosure. In some embodiments, a carbohydrate moiety is a targeting moiety. In some embodiments, a targeting moiety is a carbohydrate moiety.

[00367] 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. In some embodiments, oligonucleotides of the same oligonucleotide type are identical. In some embodiments, the present disclosure provides chirally controlled C9orf72 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 C9orf72 oligonucleotides 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%.

[00368] 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 of configuration *R*p. In some embodiments, a provided oligonucleotide is a stereounimer of configuration *S*p.

[00369] In some embodiments, a provided oligonucleotide is an altmer. In some embodiments, a provided oligonucleotide is a P-modification altmer. In some embodiments, a provided oligonucleotide is a stereoaltmer.

[00370] In some embodiments, a provided oligonucleotide is a blockmer. In some embodiments, a provided oligonucleotide is a P-modification blockmer. In some embodiments, a provided oligonucleotide is a stereoblockmer.

[00371] In some embodiments, a provided oligonucleotide is a gapmer.

[00372] In some embodiments, a provided oligonucleotide is a skipmer.

[00373] In some embodiments, a provided oligonucleotide is a hemimer. In some embodiments, a hemimer is an oligonucleotide wherein the 5'-end or the 3'-end region has a sequence that possesses a structure feature that the rest of the oligonucleotide does not have. In some embodiments, the 5'-end or the 3'-end region has or comprises 2 to 20 nucleotides. In some embodiments, a structural feature is a base modification. In some embodiments, a structural feature is a sugar modification. In some embodiments, a structural feature is a P-modification. In some embodiments, a structural feature is stereochemistry of the chiral internucleotidic linkage. In some embodiments, a structural feature is or comprises a base modification, a sugar modification, a P-modification, or stereochemistry of the chiral internucleotidic linkage, or combinations thereof. In some embodiments, a hemimer is an oligonucleotide in which each sugar moiety of the 5'-end region shares a common modification. In some embodiments, a hemimer is an oligonucleotide in which each sugar moiety of the 3'-end region shares a common modification. In some embodiments, a common sugar modification of the 5' or 3'-end region is not shared by any other sugar moieties in the oligonucleotide. In some embodiments, an example hemimer is an oligonucleotide comprising a sequence of substituted or unsubstituted 2'-O-alkyl sugar modified nucleosides, bicyclic sugar modified nucleosides, β-D-ribonucleosides or β-D- deoxyribonucleosides (for example 2'-MOE modified nucleosides, and LNA™ or ENA™ bicyclic sugar modified nucleosides) at one terminus region and a sequence of nucleosides with a different sugar moiety (such as a substituted or unsubstituted 2'-O-alkyl sugar modified nucleosides, bicyclic sugar modified nucleosides or natural ones) at the other terminus region. In some embodiments, a provided oligonucleotide is a combination of one or more of unimer, altmer, blockmer, gapmer, hemimer and skipmer. In some embodiments, a provided oligonucleotide is a combination of one or more of unimer, altmer, blockmer, gapmer, and skipmer. For instance, in some embodiments, a provided oligonucleotide is both an altmer and a gapmer. In some embodiments, a provided nucleotide is both a gapmer and a skipmer. One of skill in the chemical and synthetic arts will recognize that numerous other combinations of patterns are available and are limited only by the commercial availability and / or synthetic accessibility of constituent parts required to synthesize a provided oligonucleotide in accordance with methods of the present disclosure. In some embodiments, a hemimer structure provides advantageous benefits. In some embodiments, provided oligonucleotides are 5'-hemimers that comprises modified sugar moieties in a 5'-end sequence. In some embodiments, provided oligonucleotides are 5'-hemimers that comprises modified 2'-sugar moieties in a

5'-end sequence.

[00374] In some embodiments, a provided oligonucleotide comprises one or more optionally substituted nucleotides. In some embodiments, a provided oligonucleotide comprises one or more modified nucleotides. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted nucleosides. In some embodiments, a provided oligonucleotide comprises one or more modified nucleosides. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted LNAs.

[00375] In some embodiments, a provided oligonucleotide comprises one or more optionally substituted nucleobases. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted natural nucleobases. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted modified nucleobases. In some embodiments, a provided oligonucleotide comprises one or more 5-methylcytidine; 5-hydroxymethylcytidine, 5-formylcytosine, or 5-carboxylcytosine. In some embodiments, a provided oligonucleotide comprises one or more 5-methylcytidine.

[00376] In some embodiments, each nucleobase of a provided oligonucleotide, e.g., one 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–$(R^D)_b$, is independently an optionally substituted or protected nucleobase of adenine, cytosine, guanosine, thymine, or uracil. In some embodiments, each BA is independently an optionally substituted or protected nucleobase of adenine, cytosine, guanosine, thymine, or uracil. As appreciated by those skilled in the art, various protected nucleobases, including those widely known in the art, for example, those used in oligonucleotide preparation (e.g., protected nucleobases of WO/2010/064146, WO/2011/005761, WO/2013/012758, WO/2014/010250, US2013/0178612, WO/2014/012081, WO/2015/107425, WO2017/015555, and WO2017/062862, protected nucleobases of each of which are incorporated herein by reference), and can be utilized in accordance with the present disclosure.

[00377] In some embodiments, a provided oligonucleotide comprises one or more optionally substituted sugars. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted sugars found in naturally occurring DNA and RNA. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted ribose or deoxyribose. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted ribose or deoxyribose, wherein one or more hydroxyl groups of the ribose or deoxyribose moiety is optionally and independently replaced by halogen, R', –$N(R')_2$, –OR', or –SR', wherein each R' is independently described in the present disclosure. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with halogen, R', –$N(R')_2$, –OR', or –SR', wherein each R' is independently

described in the present disclosure. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with halogen. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with one or more –F. halogen. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with –OR', wherein each R' is independently described in the present disclosure. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with –OR', wherein each R' is independently an optionally substituted C_1–C_6 aliphatic. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with –OR', wherein each R' is independently an optionally substituted C_1–C_6 alkyl. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with –OMe. In some embodiments, a provided oligonucleotide comprises one or more optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally and independently substituted with –O–methoxyethyl.

[00378] In some embodiments, a provided oligonucleotide is single-stranded oligonucleotide. In some embodiments, a provided single-stranded C9orf72 oligonucleotide further comprises one or more additional strands which are partially or completely complementary to the single-stranded C9orf72 oligonucleotide.

[00379] In some embodiments, a provided oligonucleotide is a hybridized oligonucleotide strand. In certain embodiments, a provided oligonucleotide is a partially hybridized oligonucleotide strand. In certain embodiments, a provided oligonucleotide is a completely hybridized oligonucleotide strand. In certain embodiments, a provided oligonucleotide is a double-stranded oligonucleotide. In certain embodiments, a provided oligonucleotide is a triple-stranded oligonucleotide (*e.g.*, a triplex).

[00380] In some embodiments, a provided C9orf72 oligonucleotide is chimeric. For example, in some embodiments, a provided oligonucleotide (e.g., a C9orf72 oligonucleotide which has a base sequence which comprises, consists of, or comprises a portion of a base sequence of a C9orf72 oligonucleotide disclosed herein) is DNA-RNA chimera, DNA-LNA chimera, a chimera comprising any two or more of DNA, RNA, LNA, 2'-modified sugars, etc.

[00381] In some embodiments, a C9orf72 oligonucleotide can comprise a chemical structure described in WO2012/030683.

[00382] In some embodiments, a provided oligonucleotide is a therapeutic agent.

[00383] In some embodiments, a provided oligonucleotide comprises a nucleic acid analog, *e.g.*, GNA, LNA, PNA, TNA, F-HNA (F-THP or 3'-fluoro tetrahydropyran), MNA (mannitol nucleic acid, *e.g.*, Leumann 2002 Bioorg. Med. Chem. 10: 841-854), ANA (anitol nucleic acid), and Morpholino.

[00384] In some embodiments, a provided oligonucleotide is about 2-500 nucleotide units in length. In some embodiments, a provided oligonucleotide is about 5-500 nucleotide units in length. In some embodiments, a provided oligonucleotide is about 10-50 nucleotide units in length. In some embodiments, a provided oligonucleotide is about 15-50 nucleotide units in length. In some embodiments, each nucleotide unit independently comprises a heteroaryl nucleobase unit (e.g., adenine, cytosine, guanosine, thymine, and uracil, each of which is optionally and independently substituted or protected), a sugar unit comprising a 5-10 membered heterocyclyl ring, and an internucleotidic linkage having the structure of formula **I**.

[00385] In some embodiments, a provided oligonucleotide is from about 15 to about 30 nucleotide units in length. In some embodiments, a provided oligonucleotide is from about 10 to about 25 nucleotide units in length. In some embodiments, a provided oligonucleotide is from about 15 to about 22 nucleotide units in length. In some embodiments, a provided oligonucleotide is from about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotide units in length.

[00386] In some embodiments, an oligonucleotide is at least 15 nucleotide units in length. In some embodiments, an oligonucleotide is at least 16 nucleotide units in length. In some embodiments, an oligonucleotide is at least 17 nucleotide units in length. In some embodiments, an oligonucleotide is at least 18 nucleotide units in length. In some embodiments, an oligonucleotide is at least 19 nucleotide units in length. In some embodiments, an oligonucleotide is at least 20 nucleotide units in length. In some embodiments, an oligonucleotide is at least 21 nucleotide units in length. In some embodiments, an oligonucleotide is at least 22 nucleotide units in length. In some embodiments, an oligonucleotide is at least 23 nucleotide units in length. In some embodiments, an oligonucleotide is at least 24 nucleotide units in length. In some embodiments, an oligonucleotide is at least 25 nucleotide units in length. In some other embodiments, an oligonucleotide is at least 30 nucleotide units in length. In some other embodiments, an oligonucleotide is a duplex of complementary strands of at least 18 nucleotide units in length. In some other embodiments, an oligonucleotide is a duplex of complementary strands of at least 21 nucleotide units in length.

[00387] In some embodiments, oligonucleotides of an oligonucleotide type characterized by 1) a common base sequence and length, 2) a common pattern of backbone linkages, and 3) a common pattern of backbone chiral centers, have the same chemical structure. For example, they have the same base sequence, the same pattern of nucleoside modifications, the same pattern of backbone linkages (*i.e.*,

pattern of internucleotidic linkage types, for example, phosphate, phosphorothioate, etc), the same pattern of backbone chiral centers (*i.e.* pattern of linkage phosphorus stereochemistry (*R*p/*S*p)), and the same pattern of backbone phosphorus modifications (*e.g.*, pattern of "–XLR^1" groups in Formula **I**).

[00388] **Oligonucleotides**

[00389] In some embodiments, provided C9orf72 oligonucleotides can direct a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product. In some embodiments, provided C9orf72 oligonucleotides can direct a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product and has a base sequence which consists of, comprises, or comprises a portion (e.g., a span of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or more contiguous bases) of the base sequence of any C9orf72 oligonucleotide disclosed herein, and the oligonucleotide comprises at least one non-naturally-occuring modification of a base, sugar and/or internucleotidic linkage.

[00390] In some embodiments, a provided composition comprises an oligonucleotide. In some embodiments, a provided oligonucleotide comprises one or more carbohydrate moieties. In some embodiments, a provided oligonucleotide comprises one or more targeting moieties. Non-limiting examples of additional chemical moieties which can be conjugated to an oligonucleotide are shown in Example 1.

[00391] In some embodiments, provided oligonucleotides can direct a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product. In some embodiments, provided oligonucleotides can direct a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product via RNase H-mediated knockdown. In some embodiments, provided oligonucleotides can direct a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product by sterically blocking translation after binding to a C9orf72 target gene mRNA, and/or by altering or interfering with mRNA splicing. In some embodiments, a C9orf72 target gene comprises a hexanucleotide repeat expansion.

[00392] In some embodiments, C9orf72 oligonucleotides include nucleic acids (including antisense compounds), including but not limited to antisense oligonucleotides (ASOs), oligonucleotides, double- and single-stranded siRNAs; and C9orf72 oligonucleotide can be co-administered or be used as part of a treatment regiment along with aptamers, antibodies, peptides, small molecules, and/or other agents capable of inhibiting the expression of C9orf72 antisense transcript or gene and/or its expression product or gene product, or a gene or gene product which increases the expression, activity and/or level of a C9orf72 transcript comprising a repeat expansion or its gene product, or a gene or gene product which is associated with a C9orf72-related disorder.

[00393] In some embodiments, a provided oligonucleotide capable of directing a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product has a base sequence (or a

portion thereof), pattern of chemical modification (or a portion thereof), structural element or a portion thereof, or a format or portion thereof described herein. In some embodiments, a provided oligonucleotide capable of directing a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product has the base sequence (or a portion thereof), pattern of chemical modification (or a portion thereof), format of any oligonucleotide disclosed herein, *e.g.*, in Table 1A or in the Figures, or otherwise disclosed herein, or a structural element or format or portion thereof described herein.

[00394] In some embodiments, a C9orf72 oligonucleotide can hybridize to a C9orf72 nucleic acid derived from either DNA strand. In some embodiments, a C9orf72 oligonucleotide can hybridize to a C9orf72 antisense or sense transcript. In some embodiments, a C9orf72 oligonucleotide can hybridize to a C9orf72 nucleic acid in any stage of RNA processing, including but not limited to a pre-mRNA or a mature mRNA. In some embodiments, a C9orf72 oligonucleotide can hybridize to any element of a C9orf72 nucleic acid or its complement, including but not limited to: a promoter region, an enhancer region, a transcriptional stop region, a translational start signal, a translation stop signal, a coding region, a non-coding region, an exon, an intron, the 5' UTR, the 3' UTR, a repeat region, a hexanucleotide repeat expansion, a splice junction, intron/exon or exon/intron junction, an exon:exon splice junction, an exonic splicing silencer (ESS), an exonic splicing enhancer (ESE), exon 1a, exon 1b, exon 1c, exon 1d, exon 1e, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, intron 1, intron 2, intron 3, intron 4, intron 5, intron 6, intron 7, intron 8, intron 9, or intron 10 of a C9orf72 nucleic acid. The introns and exons alternate; intron 1 is between exon 1 (or 1a or 1b or 1c, etc.) and exon 2; intron 2 is between exon 2 and 3; etc. The positions of exons and introns in variant transcripts of C9orf72 are diagrammed in the literature, e.g., WO 2014/062691.

[00395] In some embodiments, a C9orf72 sequence is represented by:

CAAAGAAAAGGGGGAGGTTTTGTTAAAAAAGAGAAATGTTACATAGTGCTCTTTGAGAAAATTCATTGGC
ACTATTAAGGATCTGAGGAGCTGGTGAGTTTCAACTGGTGAGTGATGGTGGTAGATAAAATTAGAGCTGC
AGCAGGTCATTTTAGCAACTATTAGATAAAACTGGTCTCAGGTCACAACGGGCAGTTGCAGCAGCTGGAC
TTGGAGAGAATTACACTGTGGGAGCAGTGTCATTTGTCCTAAGTGCTTTTCTACCCCCTACCCCCACTAT
TTTAGTTGGGTATAAAAAGAATGACCCAATTTGTATGATCAACTTTCACAAAGCATAGAACAGTAGGAAA
AGGGTCTGTTTCTGCAGAAGGTGTAGACGTTGAGAGCCATTTTGTGTATTTATTCCTCCCTTTCTTCCTC
GGTGAATGATTAAAACGTTCTGTGTGATTTTTAGTGATGAAAAAGATTAAATGCTACTCACTGTAGTAAG
TGCCATCTCACACTTGCAGATCAAAAGGCACACAGTTTAAAAAACCTTTGTTTTTTTACACATCTGAGTG
GTGTAAATGCTACTCATCTGTAGTAAGTGGAATCTATACACCTGCAGACCAAAAGACGCAAGGTTTCAAA
AATCTTTGTGTTTTTTACACATCAAACAGAATGGTACGTTTTTCAAAAGTTAAAAAAAAACAACTCATCC
ACATATTGCAACTAGCAAAAATGACATTCCCCAGTGTGAAAATCATGCTTGAGAGAATTCTTACATGTAA
AGGCAAAATTGCGATGACTTTGCAGGGGACCGTGGGATTCCCGCCCGCAGTGCCGGAGCTGTCCCCTACC

AGGGTTTGCAGTGGAGTTTTGAATGCACTTAACAGTGTCTTACGGTAAAAACAAAATTTCATCCACCAAT
TATGTGTTGAGCGCCCACTGCCTACCAAGCACAAACAAAACCATTCAAAACCACGAAATCGTCTTCACTT
TCTCCAGATCCAGCAGCCTCCCCTATTAAGGTTCGCACACGCTATTGCGCCAACGCTCCTCCAGAGCGGG
TCTTAAGATAAAAGAACAGGACAAGTTGCCCCGCCCCATTTCGCTAGCCTCGTGAGAAAACGTCATCGCA
CATAGAAAACAGACAGACGTAACCTACGGTGTCCCGCTAGGAAAGAGAGGTGCGTCAAACAGCGACAAGT
TCCGCCCACGTAAAAGATGACGCTTGGTGTGTCAGCCGTCCCTGCTGCCCGGTTGCTTCTCTTTTGGGGG
CGGGGTCTAGCAAGAGCAGGTGTGGGTTTAGGAGGTGTGTGTTTTTGTTTTTCCCACCCTCTCTCCCCAC
TACTTGCTCTCACAGTACTCGCTGAGGGTGAACAAGAAAAGACCTGATAAAGATTAACCAGAAGAAAACA
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GCGGCGGCGGAGGCGCAGGCGGTGGCGAGTGGGTGAGTGAGGAGGCGGCATCCTGGCGGGTGGCTGTTTG
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TCCCTCTCATTTCTCTGACCGAAGCTGGGTGTCGGGCTTTCGCCTCTAGCGACTGGTGGAATTGCCTGCA
TCCGGGCCCCGGGCTTCCCGGCGGCGGCGGCGGCGGCGGCGGCGCAGGGACAAGGGATGGGGATCTGGCC
TCTTCCTTGCTTTCCCGCCCTCAGTACCCGAGCTGTCTCCTTCCCGGGGACCCGCTGGGAGCGCTGCCGC
TGCGGGCTCGAGAAAAGGGAGCCTCGGGTACTGAGAGGCCTCGCCTGGGGGAAGGCCGGAGGGTGGGCGG
CGCGCGGCTTCTGCGGACCAAGTCGGGGTTCGCTAGGAACCCGAGACGGTCCCTGCCGGCGAGGAGATCA
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TTATATACTACTTGACATATAGCTTAAGAAACTTACTGTTGTTGTCTTTTTGCTGTTATGGTCTTAACGT
TTTTATTTCTACAAACATTATAAACTCCACACTTTATTGTTTTTTAATTTTACTTATACAGTCAATTATC
TTTTAAAGATATTTAAATATAAACATTCAAAACACCCCAAT (SEQ ID NO: 1).

[00396] In some embodiments, a sequence of exon 1a is represented by nt 1137 - 1216; exon 1b, 1510 - 1572; exon 1c, 1137 - 1294; exon 1d, 1241 - 1279; and exon 1e, 1135 - 1169 of SEQ ID NO: 1. In

some embodiments, intron 1 is represented by 1217 - 7838 (if the transcript includes exon 1a), 1573 - 7838 (1b), 1295 - 7838 (1c), 1280 - 7838 (1d), or 1170 - 7838 (1e) of SEQ ID NO: 1. In some embodiments, a sequence of exon 2 is represented by nt 7839 - 8326; exon 3, 9413 - 9472; exon 4, 12527 - 12622; exon 5, 13354 - 13418; exon 6, 14704 - 14776; exon 7, 16396 - 16512; exon 8, 18207 - 18442; exon 9, 24296 - 24353; exon 10, 26337 - 26446; and exon 11, 26581 – 28458 of SEQ ID NO: 1. In some embodiments, introns lie between the exons. The portion upstream (5') of exon 1a, 1b, 1c, 1d, or 1e includes the 5'-UTR. The portion downstream (3') of exon 11 is the 3'-UTR.

[00397] In some embodiments, a C9orf72 oligonucleotide recognizes a site within a C9orf72 Intron 1 nearby the repeat expansion and is selected from: WV-6969, WV-3690, WV-6976, WV-7002, WV-6970, WV-3689, WV-6960, WV-7001, WV-6974, WV-6978, WV-6952, WV-6989, WV-3704, WV-7007, WV-7004, WV-6951, WV-6474, WV-3688, WV-7006, WV-6977, WV-6955, WV-6995, WV-6972, WV-7003, WV-6982, WV-6996, WV-7005, WV-6986, WV-6979, WV-6971, WV-6985, WV-6488, WV-6489, WV-6980, WV-6981, or any oligonucleotide having the same base sequence of any of these oligonucleotides. In some embodiments, a C9orf72 oligonucleotide recognizes a site within C9orf72 Exon 1a and is selected from: WV-3677, WV-6940, WV-3683, WV-6931, WV-3679, WV-6927, WV-6922, WV-6937, WV-6926, WV-3685, WV-6930, WV-6932, WV-6928, WV-6933, WV-6936, WV-7027, WV-3678, WV-8114, WV-8122, WV-8311, WV-8315, WV-8312, WV-8313, WV-8314, WV-8316, WV-8317, or WV-8318, or any oligonucleotide having the same base sequence of any of these oligonucleotides. In some embodiments, a C9orf72 oligonucleotide recognizes a site within C9orf72 Antisense (AS) transcript and is selected from: WV-3723, WV-3737, WV-3719, WV-3730, WV-3722, WV-3743, WV-3745, WV-3739, WV-3724, WV-3732, WV-3734, WV-3733, WV-3720, WV-3721, WV-3731, or any oligonucleotide having the same base sequence of any of these oligonucleotides. In some embodiments, a C9orf72 oligonucleotide recognizes a site within C9orf72 Exon 2 transcript and is selected from: WV-3662 and WV-7118, or any oligonucleotide having the same base sequence of any of these oligonucleotides. In some embodiments, a C9orf72 oligonucleotide can hybridize to a portion of the C9orf72 sequence represented in GENBANK Accession No. NT_008413.18 or a complement thereof. In some embodiments, a C9orf72 oligonucleotide can hybridize to a portion of the C9orf72 pre-mRNA represented by the region which begins in the region from the start site of exon 1a to the start site of exon 1b. In some embodiments, a C9orf72 oligonucleotide can hybridize to a portion of the C9orf72 pre-mRNA represented by the region which begins in the region from the end site of exon 1a to the start site of exon 1b. In some embodiments, a c9orf72 oligonucleotide recognizes a site which straddles the junction between an intron and an exon.

[00398] In some embodiments, a c9orf72 oligonucleotide straddles the junction between exon 1b and intron 1. In some embodiments, a c9orf72 oligonucleotide straddles the junction between exon 1b

and intron 1, and has a base sequence which is, comprises or comprises 15 contiguous bases of the sequence CCTCACTCACCCACTCGCCA.

[00399] Without wishing to be bound by any particular scientific theory, the present disclosure notes that the sequence CCTCACTCACCCACTCGCCA straddles the junction of exon 1b and intron 1 reported for c9orf72 mRNA Variant 2 or V2 (which lacks the hexanucleotide repeat), and that the site may be blocked by the splicing machinery from being bound by an oligonucleotide having a sequence which is, comprises or comprises 15 contiguous bases of the sequence CCTCACTCACCCACTCGCCA. This sequence exists in c9orf72 mRNA variants V1, V2 and V3, but an oligonucleotide having a sequence which is, comprises or comprises 15 contiguous bases of the sequence CCTCACTCACCCACTCGCCA is particularly efficacious in degrading disease-associated variants V1 and V3 relative to non-disease-associated V2. Without wishing to be bound by any particular theory, the present disclosure suggests that the sequence CCTCACTCACCCACTCGCCA is in the middle of an intron reported in V1 and V3; that the sequence CCTCACTCACCCACTCGCCA straddles the junction of an exon (1b) and an intron (1) reported for V2, and access to this site may be sterically blocked by the splicing machinery. In some embodiments, a C9orf72 oligonucleotide comprises a base sequence complementary to a 5' branching site at an intron-exon junction. In some embodiments, a C9orf72 oligonucleotide comprises a sequence complementary to a 5' branching site at the junction of a C9orf72 exon 1 and a C9orf72 intron 1. In some embodiments, a 5' branching site at the junction of C9orf72 exon 1 and intron 1 comprises the base sequence of GTGAGT. In some embodiments, a C9orf72 oligonucleotide comprises a base sequence complementary to GTGAGT. In some embodiments, an oligonucleotide is capable of preferentially decreasing the expression, level and/or activity of a disease-associated allele of a gene or a gene product thereof relative to that of a corresponding wild-type allele of the gene or the gene product thereof, wherein the oligonucleotide has a base sequence complementary to both the disease-associated allele and the wild-type allele, and wherein the binding site of the oligonucleotide in a mRNA or DNA of the disease-associated allele is less accessible to the oligonucleotide than the binding site of the oligonucleotide in a mRNA or DNA expressing the wild-type allele. In some embodiments, the accessibility of the oligonucleotide to a binding site in a mRNA or DNA of the disease-associated allele is decreased by binding of splicing machinery and/or other nucleic acids or proteins to the mRNA or DNA of the disease-associate allele. In some embodiments, the present disclosure pertains to: an oligonucleotide capable of preferentially decreasing (knocking down) the expression, level and/or activity of a mutant or disease-associated allele of a gene or a gene product thereof relative to that of a corresponding wild-type or non-disease-associated allele of the gene or the gene product thereof, wherein the oligonucleotide has a base sequence complementary to both the mutant or disease-associated allele and the wild-type or non-disease-associated allele, and wherein the binding site of (e.g., sequence

complementary to) the oligonucleotide in a nucleic acid (e.g., chromosomal DNA, mRNA, pre-mRNA, etc.) of the mutant or disease-associated allele is less accessible to the oligonucleotide (e.g., due to increased binding of splicing machinery and/or other nucleic acids or proteins) than the binding site of the oligonucleotide in a nucleic acid of the wild-type or non-disease-associated allele.

[00400] In some embodiments, a C9orf72 oligonucleotide can hybridize to a portion of the C9orf72 pre-mRNA represented by GENBANK Accession No. NT_008413.18, nucleosides 27535000 to 27565000 or a complement thereof.

[00401] In some embodiments, a C9orf72 oligonucleotide can hybridize to an intron. In some embodiments, a C9orf72 oligonucleotide can hybridize to an intron comprising a hexanucleotide repeat.

[00402] In some embodiments, a C9orf72 oligonucleotide hybridizes to all variants of C9orf72 derived from the sense strand. In some embodiments, the antisense oligonucleotides described herein selectively hybridize to a variant of C9orf72 derived from the sense strand, including but not limited to that comprising a hexanucleotide repeat expansion. In some embodiments, a hexanucleotide repeat expansion comprises at least 24 repeats of any hexanucleotide. In some embodiments, a hexanucleotide repeat expansion comprises at least 30 repeats of any hexanucleotide. In some embodiments, a hexanucleotide repeat expansion comprises at least 50 repeats of any of a hexanucleotide. In some embodiments, a hexanucleotide repeat expansion comprises at least 100 repeats of any of a hexanucleotide. In some embodiments, a hexanucleotide repeat expansion comprises at least 200 repeats of any hexanucleotide. In some embodiments, a hexanucleotide repeat expansion comprises at least 500 repeats of any hexanucleotide. In some embodiments, a hexanucleotide is GGGGCC, GGGGGG, GGGGGC, GGGGCG, CCCCGG, CCCCCC, GCCCCC, and/or CGCCCC. In some embodiments, a hexanucleotide GGGGCC is designated GGGGCCexp or $(GGGGCC)_n$, or is a repeat of the hexanucleotide GGGGCC.

[00403] In some embodiments, a C9orf72 target of a C9orf72 oligonucleotide is a C9orf72 RNA which is not a mRNA. In some embodiments, provided oligonucleotides in provided compositions, *e.g.*, oligonucleotides of a first plurality, comprise base modifications, sugar modifications, and/or internucleotidic linkage modifications. In some embodiments, provided oligonucleotides comprise base modifications and sugar modifications. In some embodiments, provided oligonucleotides comprise base modifications and internucleotidic linkage modifications. In some embodiments, provided oligonucleotides comprise sugar modifications and internucleotidic modifications. In some embodiments, provided compositions comprise base modifications, sugar modifications, and internucleotidic linkage modifications. Example chemical modifications, such as base modifications, sugar modifications, internucleotidic linkage modifications, etc. are widely known in the art including but not limited to those

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

[00404] In some embodiments, the present disclosure provides a stereorandom oligonucleotide having a base sequence which is, comprises or comprises a portion of the base sequence of any oligonucleotide described herein. In some embodiments, a portion of a base sequence is at least 15 contiguous bases thereof. In some embodiments, the present disclosure provides an oligonucleotide having a base sequence which is, comprises or comprises a portion of the base sequence of any oligonucleotide described herein, wherein the oligonucleotide comprises one or more stereorandom internucleotidic linkages. In some embodiments, the present disclosure provides an oligonucleotide having a base sequence which is, comprises or comprises a portion of the base sequence of any oligonucleotide described herein, wherein the oligonucleotide comprises one or more stereorandom phosphorothioate internucleotidic linkages.

[00405] In some embodiments, oligonucleotide properties can be adjusted by optimizing stereochemistry (pattern of backbone chiral centers) and chemical modifications (modifications of base, sugar, and/or internucleotidic linkage) or patterns thereof.

[00406] In some embodiments, a pattern of backbone chiral centers in a C9orf72 oligonucleotide provides increased stability. In some embodiments, a pattern of backbone chiral centers provides surprisingly increased activity. In some embodiments, a pattern of backbone chiral centers provides increased stability and activity. In some embodiments, a pattern of backbone chiral centers provides surprisingly increased binding to certain proteins. In some embodiments, a pattern of backbone chiral centers provides surprisingly enhanced delivery.

[00407] In some embodiments, the present disclosure pertains to a c9orf72 oligonucleotide wherein the oligonucleotide comprises a backbone comprising at least one chiral center. In some embodiments, the present disclosure pertains to a c9orf72 oligonucleotide wherein the oligonucleotide comprises a backbone comprising at least one chiral center which is a phosphorothioate in the Rp or Sp configuration.

[00408] In some embodiments, a C9orf72 oligonucleotide has a pattern of backbone chiral centers.

[00409] 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, (*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.

[00410] 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.

[00411] 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.

[00412] 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^o, 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-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.

[00413] In some embodiments, a common pattern of backbone chiral centers (*e.g.*, a pattern of backbone chiral centers in a C9orf72 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 of the Sp configuration, O represents a phosphodiester, and R represents a phosphorothioate of the Rp configuration.

[00414] 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.

[00415] In some embodiments, 5% or more of the internucleotidic linkages of provided oligonucleotides are modified internucleotidic linkages. In some embodiments, 10% or more of the internucleotidic linkages of provided oligonucleotides are modified internucleotidic linkages. In some embodiments, 15% or more of the internucleotidic linkages of provided oligonucleotides are modified internucleotidic linkages. In some embodiments, 20% or more of the internucleotidic linkages of provided oligonucleotides are modified internucleotidic linkages. In some embodiments, 25% or more of the internucleotidic linkages of provided oligonucleotides are modified internucleotidic linkages. In some embodiments, 30% or more of the internucleotidic linkages of provided oligonucleotides are modified internucleotidic linkages. In some embodiments, 35% or more of the internucleotidic linkages of provided oligonucleotides are modified internucleotidic linkages. In some embodiments, 40% or more of the internucleotidic linkages of provided oligonucleotides are modified internucleotidic linkages.

[00416] In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by administration of an oligonucleotide. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% total by RNase H-mediated knockdown directed by an oligonucleotide. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by administration of an oligonucleotide in a cell(s) in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by RNase H-mediated knockdown directed by an oligonucleotide in a cell(s) in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by administration of an oligonucleotide at a concentration of 25 nm or less in a cell(s) in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by administration of an oligonucleotide at a concentration of 10 nm or less in a cell(s) in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by administration of an oligonucleotide at a concentration of 5 nm or less in a cell(s) in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by RNase H-mediated knockdown directed by an oligonucleotide at a concentration of 5 nm or less in a

cell(s) in vitro. In some embodiments, a cell(s) is a mammalian cell(s). In some embodiments, a cell(s) is a human cell(s). In some embodiments, a cell(s) is a hepatic cell(s). In some embodiments, a cell(s) is a Huh7 or Hep3B cell(s). In some embodiments, a C9orf72 oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 20% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, a C9orf72 oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 30% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, a C9orf72 oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 40% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, a C9orf72 oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 50% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, a C9orf72 oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 60% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, a C9orf72 oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 70% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, a C9orf72 oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 80% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, a C9orf72 oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 90% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, an oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 20% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, an oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 30% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, an oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 40% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, an oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 50% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, an oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 60% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, an oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 70% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, an oligonucleotide is capable of decreasing expression or level of a C9orf72 target gene or its gene product by at least about 80% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, an oligonucleotide is capable of decreasing expression or level of a

C9orf72 target gene or its gene product by at least about 90% in a cell(s) in vitro at a concentration of 25 nM or less. In some embodiments, IC50 is inhibitory concentration to decrease expression or level or a C9orf72 target gene or its gene product by 50% in a cell(s) in vitro.

[00417] In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises (*S*p)m*R*p or *R*p(*S*p)m. In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises *R*p(*S*p)m. In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises (*S*p)m*R*p. In some embodiments, m is 2. In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises *R*p(*S*p)$_2$. In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises (*S*p)$_2$*R*p(*S*p)$_2$. In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises (*R*p)$_2$*R*p(*S*p)$_2$. In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises *R*p*S*p*R*p(*S*p)$_2$. In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises *S*p*R*p*R*p(*S*p)$_2$. In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises (*S*p)$_2$*R*p.

[00418] 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.

[00419] 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, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises

(*S*p)m(*R*p)n. In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises (*S*p)m(*R*p)n. 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, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises (*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 (*R*p)n(*S*p)m. 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).

[00420] In some embodiments, the present disclosure provides a C9orf72 oligonucleotide of an oligonucleotide type whose pattern of backbone chiral centers comprises (*S*p)m(*R*p)n(*S*p)t. In some embodiments, a repeating pattern is (*S*p)m(*R*p)n(*S*p)t, wherein n is 1-10, t is 1-50, 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 (*S*p)m(*R*p)n(*S*p)t. In some embodiments, a repeating pattern is (*S*p)t(*R*p)n(*S*p)m, wherein n is 1-10, t is 1-50, 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 (*S*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 (*S*p)t(*R*p)n(*S*p)m.

[00421] 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.

[00422] 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.

[00423] 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.

[00424] 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.

[00425] 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.

[00426] 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.

[00427] 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.

[00428] 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 (*S*p)t*R*p$(Sp)_5$.

In some embodiments, (*S*p)t(*R*p)n(*S*p)m is *S*p*R*p(*S*p)$_5$. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is (*S*p)$_2$*R*p(*S*p)$_5$. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is (*S*p)$_3$*R*p(*S*p)$_5$. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is (*S*p)$_4$*R*p(*S*p)$_5$. In some embodiments, (*S*p)t(*R*p)n(*S*p)m is (*S*p)$_5$*R*p(*S*p)$_5$.

[00429] In some embodiments, provided oligonucleotides are blockmers. In some embodiments, provided oligonucleotide are altmers. In some embodiments, provided oligonucleotides are altmers comprising alternating blocks. In some embodiments, a blockmer or an altmer can be defined by chemical modifications (including presence or absence), *e.g.*, base modifications, sugar modification, internucleotidic linkage modifications, stereochemistry, etc., or patterns thereof. Example chemical modifications, stereochemistry and patterns thereof for a block and/or an alternating unit include but are not limited to those described in this disclosure, such as those described for an oligonucleotide, etc. In some embodiments, a blockmer comprises a pattern of ..SS..RR..SS..RR… In some embodiments, an altmer comprises a pattern of SRSRSRSR.

[00430] In some embodiments, a provided pattern of backbone chiral centers comprises repeating (*S*p)m(*R*p)n, (*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 units. In some embodiments, a repeating unit is (*S*p)m(*R*p)n. In some embodiments, a repeating unit is *S*p*R*p. In some embodiments, a repeating unit is *S*p*S*p*R*p. In some embodiments, a repeating unit is *S*p*R*p*R*p. In some embodiments, a repeating unit is *R*p*R*p*S*p. In some embodiments, a repeating unit is (*R*p)n(*S*p)m. In some embodiments, a repeating unit is (*N*p)t(*R*p)n(*S*p)m. In some embodiments, a repeating unit is (*S*p)t(*R*p)n(*S*p)m.

[00431] In some embodiments, a provided pattern of backbone chiral centers is or comprises (Rp/Sp)x-(All Rp or All Sp)-(Rp/Sp)y. In some embodiments, a provided pattern of backbone chiral centers is or comprises (Rp/Sp)-(All Rp or All Sp)-(Rp/Sp). In some embodiments, a provided pattern of backbone chiral centers is or comprises (Rp)x-(All Sp)-(Rp)y. In some embodiments, a provided pattern of backbone chiral centers is or comprises (Rp)-(All Sp)-(Rp). In some embodiments, a provided pattern of backbone chiral centers is or comprises (Sp)x-(All Rp)-(Sp)y. In some embodiments, a provided pattern of backbone chiral centers is or comprises (Sp)-(All Rp)-(Sp). In some embodiments, a provided pattern of backbone chiral centers is or comprises (Rp/Sp)x-(repeating (Sp)m(Rp)n)-(Rp/Sp)y. In some embodiments, a provided pattern of backbone chiral centers is or comprises (Rp/Sp)-(repeating (Sp)m(Rp)n)-(Rp/Sp). In some embodiments, a provided pattern of backbone chiral centers is or comprises (Rp/Sp)x-(repeating SpSpRp)-(Rp/Sp)y. In some embodiments, a provided pattern of backbone chiral centers is or comprises (Rp/Sp)-(repeating SpSpRp)-(Rp/Sp).

[00432] In some embodiments, a provided oligonucleotide comprises any pattern of stereochemistry or any sugar modification described herein.

[00433] 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.

[00434] In some embodiments, 5% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 10% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 15% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 20% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 25% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 30% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 35% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 40% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 45% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 50% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 55% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 60% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 65% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 70% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 75% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 80% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 85% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 90% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, 95% or more of the sugar moieties of provided oligonucleotides are modified. In some embodiments, each sugar moiety of provided oligonucleotides is modified. In some embodiments, a modified sugar moiety comprises a 2'-modification. In some embodiments, a modified sugar moiety comprises a 2'-modification. In some embodiments, a 2'-modification is 2'-OR^1. In some embodiments, a 2'-modification is a 2'-OMe. In some embodiments, a 2'-modification is a 2'-MOE. In

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

[00435] 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 an *S*p chiral internucleotidic linkage. In some embodiments, a nucleoside comprising a 2'-F is followed by an *S*p chiral internucleotidic linkage. In some embodiments, a nucleoside comprising a 2'-modification is preceded by an *S*p chiral internucleotidic linkage. In some embodiments, a nucleoside comprising a 2'-F is preceded by an *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.

[00436] Provided oligonucleotides can comprise various number of natural phosphate linkages. In some embodiments, provided oligonucleotides comprise no natural phosphate linkages. In some embodiments, provided oligonucleotides comprise one natural phosphate linkage. In some embodiments, provided oligonucleotides comprise 1 to 30 or more natural phosphate linkages. In some embodiments, provided oligonucleotides comprise about 25 or more consecutive modified sugar moieties. In some embodiments, provided oligonucleotides comprise about 1 to 20 or more consecutive modified sugar moieties. In some embodiments, provided oligonucleotides comprise no more than about 5% to 90% unmodified sugar moieties. In some embodiments, each sugar moiety of the oligonucleotides of the first plurality is independently modified. In some embodiments, provided oligonucleotides are capable of

directing a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product.

[00437] In some embodiments, each oligonucleotide of the first plurality comprises one or more modified sugar moieties and modified internucleotidic linkages. In some embodiments, each oligonucleotide of the first plurality comprises two or more modified sugar moieties. In some embodiments, each oligonucleotide of the first plurality comprises three or more modified sugar moieties. In some embodiments, each oligonucleotide of the first plurality comprises four or more modified sugar moieties. In some embodiments, each oligonucleotide of the first plurality comprises five or more modified sugar moieties. In some embodiments, each oligonucleotide of the first plurality comprises ten or more modified sugar moieties. In some embodiments, each oligonucleotide of the first plurality comprises about 15 or more modified sugar moieties. In some embodiments, each oligonucleotide of the first plurality comprises about 20 or more modified sugar moieties. In some embodiments, each oligonucleotide of the first plurality comprises about 25 or more modified sugar moieties.

[00438] In some embodiments, each oligonucleotide of the first plurality comprises two or more modified internucleotidic linkages. In some embodiments, each oligonucleotide of the first plurality comprises three or more modified internucleotidic linkages. In some embodiments, each oligonucleotide of the first plurality comprises four or more modified internucleotidic linkages. In some embodiments, each oligonucleotide of the first plurality comprises five or more modified internucleotidic linkages. In some embodiments, each oligonucleotide of the first plurality comprises ten or more modified internucleotidic linkages. In some embodiments, each oligonucleotide of the first plurality comprises about 15 or more modified internucleotidic linkages. In some embodiments, each oligonucleotide of the first plurality comprises about 20 or more modified internucleotidic linkages. In some embodiments, each oligonucleotide of the first plurality comprises about 25 or more modified internucleotidic linkages.

[00439] In some embodiments, about 5% of the internucleotidic linkages in each oligonucleotide of the first plurality are modified internucleotidic linkages. In some embodiments, about 10% of the internucleotidic linkages in each oligonucleotide of the first plurality are modified internucleotidic linkages. In some embodiments, about 20% of the internucleotidic linkages in each oligonucleotide of the first plurality are modified internucleotidic linkages. In some embodiments, about 30% of the internucleotidic linkages in each oligonucleotide of the first plurality are modified internucleotidic linkages. In some embodiments, about 40% of the internucleotidic linkages in each oligonucleotide of the first plurality are modified internucleotidic linkages. In some embodiments, about 50% of the internucleotidic linkages in each oligonucleotide of the first plurality are modified internucleotidic linkages. In some embodiments, about 60% of the internucleotidic linkages in each oligonucleotide of the first plurality are modified internucleotidic linkages. In some embodiments, about 70% of the internucleotidic linkages in each oligonucleotide of the first plurality are modified internucleotidic

linkages. In some embodiments, about 80% of the internucleotidic linkages in each oligonucleotide of the first plurality are modified internucleotidic linkages. In some embodiments, about 85% of the internucleotidic linkages in each oligonucleotide of the first plurality are modified internucleotidic linkages. In some embodiments, about 90% of the internucleotidic linkages in each oligonucleotide of the first plurality are modified internucleotidic linkages. In some embodiments, about 95% of the internucleotidic linkages in each oligonucleotide of the first plurality are modified internucleotidic linkages.

[00440] In some embodiments, compared to a reference condition, provided chirally controlled C9orf72 oligonucleotide compositions are surprisingly effective. In some embodiments, desired biological effects (*e.g.*, as measured by decreased levels of undesired mRNA, proteins, etc.) can be enhanced by more than 5, 10, 15, 20, 25, 30, 40, 50, or 100 fold. In some embodiments, a change is measured by increase of a desired mRNA level compared to a reference condition. In some embodiments, a change is measured by decrease of an undesired mRNA level compared to a reference condition. In some embodiments, a reference condition is absence of oligonucleotide treatment. In some embodiments, a reference condition is a stereorandom composition of oligonucleotides having the same base sequence and chemical modifications.

[00441] In some embodiments, provided oligonucleotides contain increased levels of one or more isotopes. In some embodiments, provided oligonucleotides are labeled, *e.g.*, by one or more isotopes of one or more elements, *e.g.*, hydrogen, carbon, nitrogen, etc. In some embodiments, provided oligonucleotides in provided compositions, *e.g.*, oligonucleotides of a first plurality, comprise base modifications, sugar modifications, and/or internucleotidic linkage modifications, wherein the oligonucleotides contain an enriched level of deuterium. In some embodiments, provided oligonucleotides are labeled with deuterium (replacing $-^{1}H$ with $-^{2}H$) at one or more positions. In some embodiments, one or more ^{1}H of an oligonucleotide or any moiety conjugated to the oligonucleotide (*e.g.*, a targeting moiety, etc.) is substituted with ^{2}H. Such oligonucleotides can be used in any composition or method described herein.

[00442] In some embodiments, the present disclosure provides an oligonucleotide composition comprising a first plurality of oligonucleotides which:

1) have a common base sequence complementary to a C9orf72 target sequence in a transcript; and

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

[00443] 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.

[00444] 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**.

[00445] In some embodiments, a common base sequence and length may be referred to as a common base sequence. In some embodiments, oligonucleotides having a common base sequence may have the same pattern of nucleoside modifications, *e.g.*, sugar modifications, base modifications, etc. In some embodiments, a pattern of nucleoside modifications may be represented by a combination of locations and modifications. In some embodiments, a pattern of backbone linkages comprises locations and types (*e.g.*, phosphate, phosphorothioate, substituted phosphorothioate, etc.) of each internucleotidic linkages. A pattern of backbone chiral centers of an oligonucleotide can be designated by a combination of linkage phosphorus stereochemistry (*R*p/*S*p) from 5' to 3'. As exemplified above, locations of non-chiral linkages may be obtained, for example, from pattern of backbone linkages.

[00446] As understood by a person having ordinary skill in the art, a stereorandom or racemic preparation of oligonucleotides is prepared by non-stereoselective and/or low-stereoselective coupling of nucleotide monomers, typically without using any chiral auxiliaries, chiral modification reagents, and/or chiral catalysts. In some embodiments, in a substantially racemic (or chirally uncontrolled) preparation of oligonucleotides, all or most coupling steps are not chirally controlled in that the coupling steps are not specifically conducted to provide enhanced stereoselectivity. An example substantially racemic preparation of oligonucleotides is the preparation of phosphorothioate oligonucleotides through sulfurizing phosphite triesters from commonly used phosphoramidite oligonucleotide synthesis with either tetraethylthiuram disulfide or (TETD) or 3H-1, 2-bensodithiol-3-one 1, 1-dioxide (BDTD), a well-known process in the art. In some embodiments, substantially racemic preparation of oligonucleotides provides substantially racemic oligonucleotide compositions (or chirally uncontrolled oligonucleotide compositions). In some embodiments, at least one coupling of a nucleotide monomer has a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9, 92:8, 97:3, 98:2, or 99:1. In some embodiments, at least two couplings of a nucleotide monomer have a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9, 92:8, 97:3, 98:2, or 99:1. In some embodiments, at least three couplings of a nucleotide monomer have a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9, 92:8, 97:3, 98:2, or 99:1. In some embodiments, at least four couplings of a nucleotide monomer have a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9,

92:8, 97:3, 98:2, or 99:1. In some embodiments, at least five couplings of a nucleotide monomer have a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9, 92:8, 97:3, 98:2, or 99:1. In some embodiments, each coupling of a nucleotide monomer independently has a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9, 92:8, 97:3, 98:2, or 99:1. In some embodiments, in a stereorandom or racemic preparations, at least one internucleotidic linkage has a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9, 92:8, 97:3, 98:2, or 99:1. In some embodiments, at least two internucleotidic linkages have a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9, 92:8, 97:3, 98:2, or 99:1. In some embodiments, at least three internucleotidic linkages have a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9, 92:8, 97:3, 98:2, or 99:1. In some embodiments, at least four internucleotidic linkages have a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9, 92:8, 97:3, 98:2, or 99:1. In some embodiments, at least five internucleotidic linkages have a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9, 92:8, 97:3, 98:2, or 99:1. In some embodiments, each internucleotidic linkage independently has a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9, 92:8, 97:3, 98:2, or 99:1. In some embodiments, a diastereoselectivity is lower than about 60:40. In some embodiments, a diastereoselectivity is lower than about 70:30. In some embodiments, a diastereoselectivity is lower than about 80:20. In some embodiments, a diastereoselectivity is lower than about 90:10. In some embodiments, a diastereoselectivity is lower than about 91:9. In some embodiments, a diastereoselectivity is lower than about 92:8. In some embodiments, a diastereoselectivity is lower than about 93:7. In some embodiments, a diastereoselectivity is lower than about 94:6. In some embodiments, a diastereoselectivity is lower than about 95:5. In some embodiments, a diastereoselectivity is lower than about 96:4. In some embodiments, a diastereoselectivity is lower than about 97:3. In some embodiments, a diastereoselectivity is lower than about 98:2. In some embodiments, a diastereoselectivity is lower than about 99:1. In some embodiments, at least one coupling has a diastereoselectivity lower than about 90:10. In some embodiments, at least two couplings have a diastereoselectivity lower than about 90:10. In some embodiments, at least three couplings have a diastereoselectivity lower than about 90:10. In some embodiments, at least four couplings have a diastereoselectivity lower than about 90:10. In some embodiments, at least five couplings have a diastereoselectivity lower than about 90:10. In some embodiments, each coupling independently has a diastereoselectivity lower than about 90:10. In some embodiments, at least one internucleotidic linkage has a diastereoselectivity lower than about 90:10. In some embodiments, at least two internucleotidic linkages have a diastereoselectivity lower than about 90:10. In some embodiments, at least three internucleotidic linkages have a diastereoselectivity lower than about 90:10. In some embodiments, at least four internucleotidic linkages have a diastereoselectivity lower than about 90:10. In some

embodiments, at least five internucleotidic linkages have a diastereoselectivity lower than about 90:10. In some embodiments, each internucleotidic linkage independently has a diastereoselectivity lower than about 90:10.

[00447] In some embodiments, a chirally controlled internucleotidic linkage, such as those of oligonucleotides of chirally controlled C9orf72 oligonucleotide compositions, has a diastereoselectivity of 90:10 or more. In some embodiments, each chirally controlled internucleotidic linkage, such as those of oligonucleotides of chirally controlled C9orf72 oligonucleotide compositions, has a diastereoselectivity of 90:10 or more. In some embodiments, the selectivity is 91:9 or more. In some embodiments, the selectivity is 92:8 or more. In some embodiments, the selectivity is 97:3 or more. In some embodiments, the selectivity is 94:6 or more. In some embodiments, the selectivity is 95:5 or more. In some embodiments, the selectivity is 96:4 or more. In some embodiments, the selectivity is 97:3 or more. In some embodiments, the selectivity is 98:2 or more. In some embodiments, the selectivity is 99:1 or more.

[00448] As understood by a person having ordinary skill in the art, in some embodiments, diastereoselectivity of a coupling or a linkage can be assessed through the diastereoselectivity of a dimer formation under the same or comparable conditions, wherein the dimer has the same 5'- and 3'-nucleosides and internucleotidic linkage.

[00449] In some embodiments, the present disclosure provides chirally controlled (and/or stereochemically pure) oligonucleotide compositions comprising a first plurality of oligonucleotides defined by having:

1) a common base sequence and length;

2) a common pattern of backbone linkages; and

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

[00450] In some embodiments, the present disclosure provides chirally controlled C9orf72 oligonucleotide composition of a first plurality of oligonucleotides in that the composition is enriched, relative to a substantially racemic preparation of the same oligonucleotides, for oligonucleotides of a single oligonucleotide type. In some embodiments, the present disclosure provides chirally controlled C9orf72 oligonucleotide composition of a first plurality of oligonucleotides in that the composition is enriched, relative to a substantially racemic preparation of the same oligonucleotides, for oligonucleotides of a single oligonucleotide type that share:

1) a common base sequence and length;

2) a common pattern of backbone linkages; and

3) a common pattern of backbone chiral centers.

[00451] In some embodiments, oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of base modifications. In some embodiments, oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments, oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have identical structures.

[00452] In some embodiments, oligonucleotides of an oligonucleotide type have a common pattern of backbone phosphorus modifications and a common pattern of sugar modifications. In some embodiments, oligonucleotides of an oligonucleotide type have a common pattern of backbone phosphorus modifications and a common pattern of base modifications. In some embodiments, oligonucleotides of an oligonucleotide type have a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments, oligonucleotides of an oligonucleotide type are identical.

[00453] In some embodiments, a C9orf72 oligonucleotide 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.

[00454] In some embodiments, oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications. In some embodiments, oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments, oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of sugar modifications. In some embodiments, oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of base modifications. In some embodiments, oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments,

oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers are identical.

[00455] In some embodiments, oligonucleotides in provided compositions have a common pattern of backbone phosphorus modifications. In some embodiments, a common base sequence is a base sequence of an oligonucleotide type. In some embodiments, a provided composition is an oligonucleotide composition that is chirally controlled in that the composition contains a non-random or controlled level of a first plurality of C9orf72 oligonucleotides of an individual oligonucleotide type, 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 phosphorus modifications.

[00456] As noted above and understood in the art, in some embodiments, the base sequence of an oligonucleotide may refer to the identity and/or modification status of nucleoside residues (*e.g.*, of sugar and/or base components, relative to standard naturally occurring nucleotides such as adenine, cytosine, guanosine, thymine, and uracil) in the oligonucleotide and/or to the hybridization character (*i.e.*, the ability to hybridize with particular complementary residues) of such residues.

[00457] 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 phosphorus modifications.

Thus, in some embodiments, oligonucleotides of a particular type may share identical bases but differ in their pattern of base modifications and/or sugar modifications. In some embodiments, oligonucleotides of a particular type may share identical bases and pattern of base modifications (including, *e.g.*, absence of base modification), but differ in pattern of sugar modifications.

[00458] In some embodiments, purity of a C9orf72 oligonucleotide can be controlled by stereoselectivity of each coupling step in its preparation process. In some embodiments, a coupling step has a stereoselectivity (*e.g.*, diastereoselectivity) of 60% (60% of the new internucleotidic linkage formed from the coupling step has the intended stereochemistry). After such a coupling step, the new internucleotidic linkage formed may be referred to have a 60% purity. In some embodiments, each coupling step has a stereoselectivity of at least 60%. In some embodiments, each coupling step has a

stereoselectivity of at least 70%. In some embodiments, each coupling step has a stereoselectivity of at least 80%. In some embodiments, each coupling step has a stereoselectivity of at least 85%. In some embodiments, each coupling step has a stereoselectivity of at least 90%. In some embodiments, each coupling step has a stereoselectivity of at least 91%. In some embodiments, each coupling step has a stereoselectivity of at least 92%. In some embodiments, each coupling step has a stereoselectivity of at least 93%. In some embodiments, each coupling step has a stereoselectivity of at least 94%. In some embodiments, each coupling step has a stereoselectivity of at least 95%. In some embodiments, each coupling step has a stereoselectivity of at least 96%. In some embodiments, each coupling step has a stereoselectivity of at least 97%. In some embodiments, each coupling step has a stereoselectivity of at least 98%. In some embodiments, each coupling step has a stereoselectivity of at least 99%. In some embodiments, each coupling step has a stereoselectivity of at least 99.5%. In some embodiments, each coupling step has a stereoselectivity of virtually 100%. In some embodiments, a coupling step has a stereoselectivity of virtually 100% in that all detectable product from the coupling step by an analytical method (*e.g.*, NMR, HPLC, etc) has the intended stereoselectivity.

[00459] Among other things, the present disclosure recognizes that combinations of oligonucleotide structural elements (*e.g.*, patterns of chemical modifications, backbone linkages, backbone chiral centers, and/or backbone phosphorus modifications) can provide surprisingly improved properties such as bioactivities.

[00460] In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of oligonucleotides that include one or more modified backbone linkages, bases, and/or sugars.

[00461] In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of oligonucleotides having a common base sequence of at least 15 bases. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of oligonucleotides having a common base sequence of at least 16 bases. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of oligonucleotides having a common base sequence of at least 17 bases. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of oligonucleotides having a common base sequence of at least 18 bases. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of oligonucleotides having a common base sequence of at least 19 bases. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of oligonucleotides having a common base sequence of at least 20 bases. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of oligonucleotides having a common base sequence of at least 21 bases. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations

are of oligonucleotides having a common base sequence of at least 22 bases. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of oligonucleotides having a common base sequence of at least 23 bases. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of oligonucleotides having a common base sequence of at least 24 bases. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of oligonucleotides having a common base sequence of at least 25 bases. In some embodiments, provided chirally controlled (and/or stereochemically pure) preparations are of oligonucleotides having a common base sequence of at least 30, 35, 40, 45, 50, 55, 60, 65, 70, or 75 bases.

[00462] In some embodiments, provided compositions comprise oligonucleotides containing one or more residues which are modified at the sugar moiety. In some embodiments, provided compositions comprise oligonucleotides containing one or more residues which are modified at the 2' position of the sugar moiety (referred to herein as a "2'-modification"). Examples of such modifications are described above and herein and include, but are not limited to, 2'-OMe, 2'-MOE, 2'-LNA, 2'-F, FRNA, FANA, 5'-vinyl, Morpholino, *S*-cEt, etc. In some embodiments, provided compositions comprise oligonucleotides containing one or more residues which are 2'-modified. For example, in some embodiments, provided oligonucleotides contain one or more residues which are 2'-O-methoxyethyl (2'-MOE)-modified residues. In some embodiments, provided compositions comprise oligonucleotides which do not contain any 2'-modifications. In some embodiments, provided compositions are oligonucleotides which do not contain any 2'-MOE residues. That is, in some embodiments, provided oligonucleotides are not MOE-modified. Additional example sugar modifications are described in the present disclosure.

[00463] In some embodiments, one or more is one. In some embodiments, one or more is two. In some embodiments, one or more is three. In some embodiments, one or more is four. In some embodiments, one or more is five. In some embodiments, one or more is six. In some embodiments, one or more is seven. In some embodiments, one or more is eight. In some embodiments, one or more is nine. In some embodiments, one or more is ten. In some embodiments, one or more is at least one. In some embodiments, one or more is at least two. In some embodiments, one or more is at least three. In some embodiments, one or more is at least four. In some embodiments, one or more is at least five. In some embodiments, one or more is at least six. In some embodiments, one or more is at least seven. In some embodiments, one or more is at least eight. In some embodiments, one or more is at least nine. In some embodiments, one or more is at least ten.

[00464] As a person having ordinary skill in the art understands, provided oligonucleotide compositions and methods have various uses as known by a person having ordinary skill in the art. Methods for assessing provided compositions, and properties and uses thereof, are also widely known and practiced by a person having ordinary skill in the art. Example properties, uses, and/or methods include

but are not limited to those described in WO/2014/012081 and WO/2015/107425.

[00465] In some embodiments, a chiral internucleotidic linkage has the structure of Formula **I**. 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**. In some embodiments, each chiral internucleotidic linkage in a single oligonucleotide of a provided composition is a phosphorothioate.

[00466] In some embodiments, oligonucleotides of the present disclosure comprise one or more modified sugar moieties. In some embodiments, C9orf72 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.

[00467] In some embodiments, a sugar modification is a 2'-modification. Commonly used 2'-modifications include but are not limited to 2'–OR^1, wherein R^1 is not hydrogen. In some embodiments, a modification is 2'–OR, wherein R is optionally substituted aliphatic. In some embodiments, a modification is 2'–OMe. In some embodiments, a modification is 2'-*O*-MOE. In some embodiments, the present disclosure demonstrates that inclusion and/or location of particular chirally pure internucleotidic linkages can provide stability improvements comparable to or better than those achieved through use of modified backbone linkages, bases, and/or sugars. In some embodiments, a provided single oligonucleotide of a provided composition has no modifications on the sugars. In some embodiments, a provided single oligonucleotide of a provided composition has no modifications on 2'-positions of the sugars (*i.e.*, the two groups at the 2'-position are either –H/–H or –H/–OH). In some embodiments, a provided single oligonucleotide of a provided composition does not have any 2'-MOE modifications.

[00468] In some embodiments, a 2'-modification is –O–L– or –L– which connects the 2'-carbon of a sugar moiety to another carbon of a sugar moiety. In some embodiments, a 2'-modification is –O–L– or –L– which connects the 2'-carbon of a sugar moiety to the 4'-carbon of a sugar moiety. In some embodiments, a 2'-modification is *S*-cEt. In some embodiments, a modified sugar moiety is an LNA moiety.

[00469] In some embodiments, a 2'-modification is –F. In some embodiments, a 2'-modification is FANA. In some embodiments, a 2'-modification is FRNA.

[00470] In some embodiments, a sugar modification is a 5'-modification, *e.g.*, *R*-5'-Me, *S*-5'-Me, etc.

[00471] 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.

[00472] 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.

[00473] In some embodiments, a single oligonucleotide 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 *S*p configuration.

[00474] In some embodiments, a C9orf72 oligonucleotide is or comprises a C9orf72 oligonucleotide selected from the group consisting of: WV-3536, WV-3537, WV-3538, WV-3539, WV-3540, WV-3541, WV-3542, WV-3561, WV-3562, WV-3563, WV-3564, WV-3565, WV-3566, WV-3567, WV-3568, WV-3569, WV-3570, WV-3571, WV-3572, WV-3573, WV-3574, WV-3575, WV-3576, WV-3577, WV-3578, WV-3579, WV-3580, WV-3581, WV-3582, WV-3583, WV-3584, WV-3585, WV-3586, WV-3587, WV-3588, WV-3589, WV-3590, WV-3591, WV-3592, WV-3593, WV-3594, WV-3595, WV-3596, WV-3597, WV-3598, WV-3599, WV-3600, WV-3601, WV-3602, WV-3603, WV-3604, WV-3605, WV-3606, WV-3607, WV-3608, WV-3609, WV-3610, WV-3611, WV-

3612, WV-3613, WV-3614, WV-3615, WV-3616, WV-3617, WV-3618, WV-3619, WV-3620, WV-3621, WV-3622, WV-3623, WV-3624, WV-3625, WV-3626, WV-3627, WV-3628, WV-3629, WV-3630, WV-3631, WV-3632, WV-3633, WV-3634, WV-3635, WV-3636, WV-3637, WV-3638, WV-3639, WV-3640, WV-3641, WV-3642, WV-3643, WV-3644, WV-3645, WV-3646, WV-3647, WV-3648, WV-3649, WV-3650, WV-3651, WV-3652, WV-3653, WV-3654, WV-3655, WV-3656, WV-3657, WV-3658, WV-3659, WV-3660, WV-3661, WV-3662, WV-3663, WV-3664, WV-3665, WV-3666, WV-3667, WV-3668, WV-3669, WV-3670, WV-3671, WV-3672, WV-3673, WV-3674, WV-3675, WV-3676, WV-3677, WV-3678, WV-3679, WV-3680, WV-3681, WV-3682, WV-3683, WV-3684, WV-3685, WV-3686, WV-3687, WV-3688, WV-3689, WV-3690, WV-3691, WV-3692, WV-3693, WV-3694, WV-3695, WV-3696, WV-3697, WV-3698, WV-3699, WV-3700, WV-3701, WV-3702, WV-3703, WV-3704, WV-3705, WV-3706, WV-3707, WV-3708, WV-3709, WV-3710, WV-3711, WV-3712, WV-3713, WV-3714, WV-3715, WV-3716, WV-3717, WV-3718, WV-3719, WV-3720, WV-3721, WV-3722, WV-3723, WV-3724, WV-3725, WV-3726, WV-3727, WV-3728, WV-3729, WV-3730, WV-3731, WV-3732, WV-3733, WV-3734, WV-3735, WV-3736, WV-3737, WV-3738, WV-3739, WV-3740, WV-3741, WV-3742, WV-3743, WV-3744, WV-3745, WV-3746, WV-3747, WV-3748, WV-3749, WV-3750, WV-3751, WV-3752, WV-5905, WV-5906, WV-5907, WV-5908, WV-5909, WV-5910, WV-5911, WV-5912, WV-5913, WV-5914, WV-5915, WV-5916, WV-5917, WV-5918, WV-5919, WV-5920, WV-5921, WV-5922, WV-5923, WV-5924, WV-5925, WV-5926, WV-5927, WV-5928, WV-5929, WV-5930, WV-5931, WV-5932, WV-5933, WV-5934, WV-5935, WV-5936, WV-5937, WV-5938, WV-5939, WV-5940, WV-5941, WV-5942, WV-5943, WV-5944, WV-5945, WV-5946, WV-5947, WV-5948, WV-5949, WV-5950, WV-5951, WV-5952, WV-5953, WV-5954, WV-5955, WV-5956, WV-5957, WV-5958, WV-5959, WV-5960, WV-5961, WV-5962, WV-5963, WV-5964, WV-5965, WV-5966, WV-5967, WV-5968, WV-5969, WV-5970, WV-5971, WV-5972, WV-5973, WV-5974, WV-5975, WV-5976, WV-5977, WV-5978, WV-5979, WV-5980, WV-5981, WV-5982, WV-5983, WV-5984, WV-5985, WV-5986, WV-5987, WV-5988, WV-5989, WV-5990, WV-5991, WV-5992, WV-5993, WV-5994, WV-5995, WV-5996, WV-5997, WV-5998, WV-5999, WV-6000, WV-6408, WV-6471, WV-6472, WV-6473, WV-6474, WV-6475, WV-6476, WV-6477, WV-6478, WV-6479, WV-6480, WV-6481, WV-6482, WV-6483, WV-6484, WV-6485, WV-6486, WV-6487, WV-6488, WV-6489, WV-6490, WV-6491, WV-6492, WV-6831, WV-6832, WV-6833, WV-6834, WV-6835, WV-6836, WV-6837, WV-6838, WV-6839, WV-6840, WV-6841, WV-6842, WV-6843, WV-6844, WV-6845, WV-6846, WV-6847, WV-6848, WV-6849, WV-6850, WV-6851, WV-6852, WV-6853, WV-6854, WV-6855, WV-6856, WV-6857, WV-6858, WV-6859, WV-6860, WV-6861, WV-6862, WV-6863, WV-6864, WV-6865, WV-6866, WV-6867, WV-6868, WV-6869, WV-6870, WV-6871, WV-6872, WV-6873, WV-6874, WV-6875, WV-6876, WV-

6877, WV-6878, WV-6879, WV-6880, WV-6881, WV-6882, WV-6883, WV-6884, WV-6885, WV-6886, WV-6887, WV-6888, WV-6889, WV-6890, WV-6891, WV-6892, WV-6893, WV-6894, WV-6895, WV-6896, WV-6897, WV-6898, WV-6899, WV-6900, WV-6901, WV-6902, WV-6903, WV-6904, WV-6905, WV-6906, WV-6907, WV-6908, WV-6909, WV-6910, WV-6911, WV-6912, WV-6913, WV-6914, WV-6915, WV-6916, WV-6917, WV-6918, WV-6919, WV-6920, WV-6921, WV-6922, WV-6923, WV-6924, WV-6925, WV-6926, WV-6927, WV-6928, WV-6929, WV-6930, WV-6931, WV-6932, WV-6933, WV-6934, WV-6935, WV-6936, WV-6937, WV-6938, WV-6939, WV-6940, WV-6941, WV-6942, WV-6943, WV-6944, WV-6945, WV-6946, WV-6947, WV-6948, WV-6949, WV-6950, WV-6951, WV-6952, WV-6953, WV-6954, WV-6955, WV-6956, WV-6957, WV-6958, WV-6959, WV-6960, WV-6961, WV-6962, WV-6963, WV-6964, WV-6965, WV-6966, WV-6967, WV-6968, WV-6969, WV-6970, WV-6971, WV-6972, WV-6973, WV-6974, WV-6975, WV-6976, WV-6977, WV-6978, WV-6979, WV-6980, WV-6981, WV-6982, WV-6983, WV-6984, WV-6985, WV-6986, WV-6987, WV-6988, WV-6989, WV-6990, WV-6991, WV-6992, WV-6993, WV-6994, WV-6995, WV-6996, WV-6997, WV-6998, WV-6999, WV-7000, WV-7001, WV-7002, WV-7003, WV-7004, WV-7005, WV-7006, WV-7007, WV-7008, WV-7009, WV-7010, WV-7011, WV-7012, WV-7013, WV-7014, WV-7015, WV-7016, WV-7017, WV-7018, WV-7019, WV-7020, WV-7021, WV-7022, WV-7023, WV-7024, WV-7025, WV-7026, WV-7027, WV-7028, WV-7029, WV-7030, WV-7031, WV-7032, WV-7033, WV-7034, WV-7035, WV-7036, WV-7037, WV-7038, WV-7039, WV-7040, WV-7041, WV-7042, WV-7043, WV-7044, WV-7045, WV-7046, WV-7047, WV-7048, WV-7049, WV-7050, WV-7051, WV-7052, WV-7053, WV-7054, WV-7055, WV-7056, WV-7057, WV-7058, WV-7059, WV-7060, WV-7061, WV-7062, WV-7063, WV-7064, WV-7065, WV-7066, WV-7067, WV-7068, WV-7069, WV-7070, WV-7071, WV-7072, WV-7073, WV-7074, WV-7075, WV-7076, WV-7077, WV-7078, WV-7079, WV-7080, WV-7081, WV-7082, WV-7083, WV-7084, WV-7085, WV-7086, WV-7087, WV-7088, WV-7089, WV-7090, WV-7091, WV-7092, WV-7093, WV-7094, WV-7095, WV-7096, WV-7097, WV-7098, WV-7099, WV-7100, WV-7101, WV-7102, WV-7103, WV-7117, WV-7118, WV-7119, WV-7120, WV-7121, WV-7122, WV-7123, WV-7124, WV-7125, WV-7126, WV-7127, WV-7128, WV-7129, WV-7130, WV-7131, WV-7132, WV-7405, WV-7434, WV-7435, WV-7601, WV-7602, WV-7603, WV-7604, WV-7605, WV-7606, WV-7657, WV-7658, WV-7659, WV-7773, WV-7774, WV-7775, WV-7866, WV-8005, WV-8006, WV-8007, WV-8008, WV-8009, WV-8010, WV-8011, WV-8012, WV-8114, WV-8115, WV-8116, WV-8117, WV-8118, WV-8119, WV-8120, WV-8121, WV-8122, WV-8123, WV-8124, WV-8125, WV-8126, WV-8127, WV-8128, WV-8129, WV-8311, WV-8312, WV-8313, WV-8314, WV-8315, WV-8316, WV-8317, WV-8318, WV-8319, WV-8320, WV-8321, WV-8322, WV-8329, WV-8444, WV-8445, WV-8446, WV-8447, WV-8452, WV-8453, WV-8454, WV-8455, WV-8456, WV-8457, WV-

8458, WV-8459, WV-8460, WV-8461, WV-8462, WV-8463, WV-8464, WV-8465, WV-8466, WV-8467, WV-8468, WV-8469, WV-8470, WV-8471, WV-8472, WV-8473, WV-8474, WV-8475, WV-8476, WV-8477, WV-8547, WV-8548, WV-8549, WV-8550, WV-8551, WV-8568, WV-8569, WV-8594, WV-8595, WV-8691, WV-8692, WV-8693, WV-8694, WV-8695, WV-8696, WV-9062, WV-9063, WV-9228, WV-9285, WV-9286, WV-9380, WV-9381, WV-9394, WV-9395, WV-9396, WV-9397, WV-9398, WV-9399, and WV-9421, and any C9orf72 oligonucleotide described herein.

[00475] Those skilled in the art, reading the present specification, will appreciate that the present disclosure specifically does not exclude the possibility that any C9orf72 or other oligonucleotide described herein which is labeled as an antisense oligonucleotide (ASO) may also or alternatively operate through another mechanism (e.g., as a ssRNAi utilizing RISC); the disclosure also notes that various oligonucleotides may operate via different mechanisms (utilizing RNase H, sterically blocking translation or other post-transcriptional processes, changing the conformation of a C9orf72 target nucleic acid, etc.).

Chirally Controlled Oligonucleotides and Chirally Controlled Oligonucleotide Compositions

[00476] In some embodiments, provided C9orf72 oligonucleotides are capable of directing a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product. In some embodiments, provided C9orf72 oligonucleotides are capable of directing a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product by sterically blocking translation after annealing to a C9orf72 target gene mRNA, and/or by altering or interfering with mRNA splicing. In some embodiments, a C9orf72 target gene comprises a repeat expansion. In some embodiments, provided C9orf72 oligonucleotides are chirally controlled.

[00477] The present disclosure provides chirally controlled C9orf72 oligonucleotides, and chirally controlled C9orf72 oligonucleotide compositions which are of high crude purity and of high diastereomeric purity. In some embodiments, the present disclosure provides chirally controlled C9orf72 oligonucleotides, and chirally controlled C9orf72 oligonucleotide compositions which are of high crude purity. In some embodiments, the present disclosure provides chirally controlled C9orf72 oligonucleotides, and chirally controlled C9orf72 oligonucleotide compositions which are of high diastereomeric purity.

[00478] In some embodiments, a C9orf72 oligonucleotide is a substantially pure preparation of a C9orf72 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.

[00479] In some embodiments, the present disclosure provides C9orf72 oligonucleotides comprising one or more diastereomerically pure internucleotidic linkages with respect to the chiral linkage phosphorus. In some embodiments, the present disclosure provides C9orf72 oligonucleotides

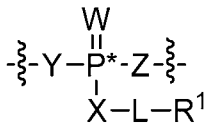
comprising one or more diastereomerically pure internucleotidic linkages having the structure of Formula **I**. In some embodiments, the present disclosure provides C9orf72 oligonucleotides comprising one or more diastereomerically pure internucleotidic linkages with respect to the chiral linkage phosphorus, and one or more phosphate diester linkages. In some embodiments, the present disclosure provides C9orf72 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 C9orf72 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 below.

[00480] **Internucleotidic linkages**

[00481] In some embodiments, provided C9orf72 oligonucleotides are capable of directing a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product. In some embodiments, provided C9orf72 oligonucleotides comprise any internucleotidic linkage described herein or known in the art.

[00482] 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 a C9orf72 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.

[00483] In certain embodiments, a internucleotidic linkage has the structure of Formula **I**:



(I)

wherein each variable is as defined and described below. In some embodiments, a linkage of Formula **I** is

chiral. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide comprising one or more modified internucleotidic linkages of Formula **I**. In some embodiments, the present disclosure provides a chirally controlled C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 oligonucleotide is a C9orf72 oligonucleotide in a provided composition that is of the particular oligonucleotide type. In some embodiments, a chirally controlled C9orf72 oligonucleotide is a C9orf72 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 C9orf72 oligonucleotide is a C9orf72 oligonucleotide in a chirally controlled composition that is of the particular oligonucleotide type, and the chirally controlled C9orf72 oligonucleotide is of the type. In some embodiments, a chirally controlled C9orf72 oligonucleotide is a C9orf72 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 C9orf72 oligonucleotide shares the common base sequence, the common pattern of backbone linkages, and the common pattern of backbone chiral centers.

[00484] In some embodiments, the present disclosure provides a chirally controlled C9orf72 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 C9orf72 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 C9orf72 oligonucleotide is characterized by a repeating pattern of alternating stereochemisty.

[00485] In some embodiments, the present disclosure provides a chirally controlled C9orf72

oligonucleotide, 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**, disclosed herein.

[00486] In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide, wherein at least two of the individual internucleotidic linkages within the oligonucleotide have different stereochemistry and/or different P-modifications relative to one another and the oligonucleotide has a structure represented by the following formula:

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

wherein:

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

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

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

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

[00487] In some such embodiments, each n has the same value; in some embodiments, each even n has the same value as each other even n; in some embodiments, each odd n has the same value each other odd n; in some embodiments, at least two even ns have different values from one another; in some embodiments, at least two odd ns have different values from one another.

[00488] In some embodiments, at least two adjacent ns are equal to one another, so that a provided C9orf72 oligonucleotide includes adjacent blocks of S stereochemistry linkages and R stereochemistry linkages of equal lengths. In some embodiments, provided C9orf72 oligonucleotides include repeating blocks of S and R stereochemistry linkages of equal lengths. In some embodiments, provided C9orf72 oligonucleotides include repeating blocks of S and R stereochemistry linkages, where at least two such blocks are of different lengths from one another; in some such embodiments each S

stereochemistry block is of the same length, and is of a different length from each R stereochemistry length, which may optionally be of the same length as one another.

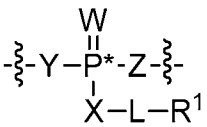
[00489] In some embodiments, at least two skip-adjacent ns are equal to one another, so that a provided C9orf72 oligonucleotide includes at least two blocks of linkages of a first stereochemistry that are equal in length to one another and are separated by a block of linkages of the other stereochemistry, which separating block may be of the same length or a different length from the blocks of first stereochemistry.

[00490] In some embodiments, ns associated with linkage blocks at the ends of a provided C9orf72 oligonucleotide are of the same length. In some embodiments, provided C9orf72 oligonucleotides have terminal blocks of the same linkage stereochemistry. In some such embodiments, the terminal blocks are separated from one another by a middle block of the other linkage stereochemistry.

[00491] In some embodiments, a provided C9orf72 oligonucleotide of formula [$S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny$] is a stereoblockmer. In some embodiments, a provided C9orf72 oligonucleotide of formula [$S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny$] is a stereoskipmer. In some embodiments, a provided C9orf72 oligonucleotide of formula [$S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny$] is a stereoaltmer. In some embodiments, a provided C9orf72 oligonucleotide of formula [$S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny$] is a gapmer.

[00492] In some embodiments, a provided C9orf72 oligonucleotide of formula [$S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny$] is of any of the above described patterns and further comprises patterns of P-modifications. For instance, in some embodiments, a provided C9orf72 oligonucleotide of formula [$S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny$] and is a stereoskipmer and P-modification skipmer. In some embodiments, a provided C9orf72 oligonucleotide of formula [$S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny$] and is a stereoblockmer and P-modification altmer. In some embodiments, a provided C9orf72 oligonucleotide of formula [$S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny$] and is a stereoaltmer and P-modification blockmer.

[00493] In some embodiments, a provided C9orf72 oligonucleotide of formula [$S^Bn1R^Bn2S^Bn3R^Bn4...S^BnxR^Bny$] is a chirally controlled C9orf72 oligonucleotide comprising one or more modified internucleotidic linkages independently having 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)$_2$N(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)$_2$N(R′)–, –N(R′)S(O)$_2$– –SC(O)–, –C(O)S–, –OC(O)–, and –C(O)O–

each R′ is independently –R, -C(O)R, -CO_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 —§— independently represents a connection to a nucleoside.

[00494] In some embodiments, L is a covalent bond or an optionally substituted, linear or branched C_1–C_{10} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–;

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

each R′ is independently –R, -C(O)R, -CO_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

[00495] each $-\!\!\!

[00497] 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.

[00498] In some embodiments, a chirally controlled C9orf72 oligonucleotide is linked to a solid support. In some embodiments, a chirally controlled C9orf72 oligonucleotide is cleaved from a solid support.

[00499] In some embodiments, a chirally controlled C9orf72 oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least two consecutive modified internucleotidic linkages. In some embodiments, a chirally controlled C9orf72 oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least two consecutive phosphorothioate triester internucleotidic linkages.

[00500] In some embodiments, a provided C9orf72 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, OXOX, OXOX, OXXO, XOOX, XXOOXX, XOXOXOXX, OXOXOXOO, XXX, XXXX, XXXXX, XXXXXX, XXXXXXX, XXXXXXXX, XXXXXXXXX, XXXXXXXXXX, OOOOOOOOOOOOOOOO, OOOOOOOOOOOOOOOOO, OOOOOOOOOOOOOOOOO, OOOOOOOOOOOOOOOOO, OOOOOOOOOOOOOOOOOO, OOOOOOOOOOOOOOOOOO, XOXOXOXOOOXOOXXXXXO, XOXOXOXOXOXOOOOOOOXX, XOXOXOXOXOXOOOOOOXX, XOXOXOXOXOXOOOOOXXX, XOXOXOXOXOXOOOOOOXX, XOXOXOXOXOXOXXXXXX, XOXOXOXOXOXOXXXXXXO, XOXOXOXOXOXOXXXXXXX, XOXOXOXOXOXOXXXXXXXXXXO, XOXOXOXOXOXOXXXXXXXXXXX, XXOXOXOXOOOXOOXXXXXO, XXOXOXOXOXOXOOOOOOOXX, XXOXOXOXOXOXOOOOOOXX, XXOXOXOXOXOXOOOOOXXX, XXOXOXOXOXOXOOOOOOXX, XXOXOXOXOXOXOXXXXXX, XXOXOXOXOXOXOXXXXXXO, XXOXOXOXOXOXOXXXXXXX, XXOXOXOXOXOXOXXXXXXXXXXO, XXOXOXOXOXOXOXXXXXXXXXXX, XXOXOXXXOOOXOOXXXXXO, XXOXOXXXOXOXOOOOOOXX, XXOXOXXXOXOXOOOOOOXX, XXOXOXXXOXOXOOOOOOXX,

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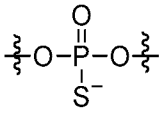
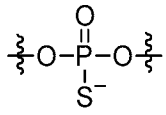
or any span of at least 5 consecutive internucleotidic linkages thereof, wherein O indicates a phosphodiester, and X indicates an internucleotidic linkage or modified internucleotidic linkage which is not phosphodiester; in some embodiments, a modified internucleotidic linkage is a phosphorothioate; in some embodiments, a modified internucleotidic linkage is chirally controlled; in some embodiments, a modified internucleotidic linkage is a chirally controlled phosphorothioate.

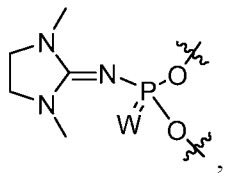
[00501] In some embodiments, a C9orf72 oligonucleotide can comprise any internucleotidic linkage described herein or known in the art.

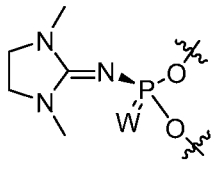
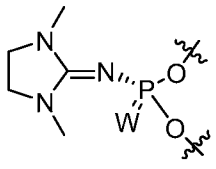
[00502] In some embodiments, the present disclosure provides C9orf72 oligonucleotides comprising one or more modified internucleotidic linkages independently having the structure of Formula **I**, disclosed herein. In some embodiments, a modified internucleotidic linkage is phosphorothioate. Examples of internucleotidic linkages having the structure of Formula **I** are widely known in the art.

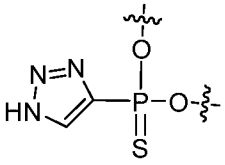
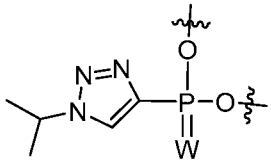
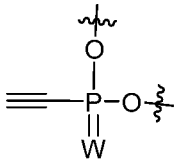
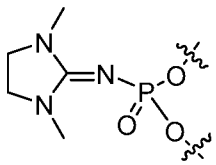
[00503] In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein at least one

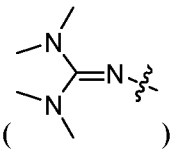
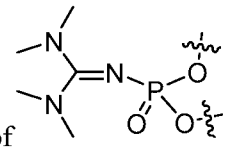
internucleotidic linkage has a chiral linkage phosphorus. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein at least one internucleotidic linkage has the structure of Formula **I**. In some embodiments, the present disclosure provides a chirally controlled C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein each internucleotidic linkage is  .

[00504] 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

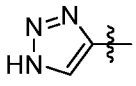
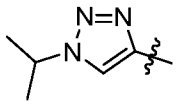
comprises an optionally substituted cyclic guanidine moiety and has the structure of:  ,

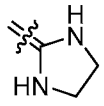
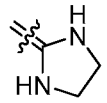
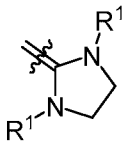
 , or  , wherein W is O or S. In some embodiments, W is O. In some embodiments, W is S. In some embodiments, a non-negatively charged internucleotidic linkage is stereochemically controlled.

[00505] 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.

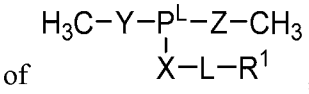
[00506] In some embodiments, a C9orf72 oligonucleotide comprises a lipid moiety In some embodiments, an internucleotidic linkage comprises a Tmg group (). In some embodiments, an internucleotidic linkage comprises a Tmg group and has the structure of  (the "Tmg internucleotidic linkage"). In some embodiments, neutral internucleotidic linkages include internucleotidic linkages of PNA and PMO, and an Tmg internucleotidic linkage.

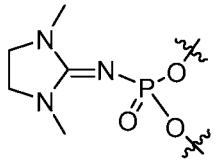
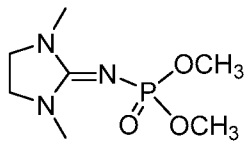
[00507] In some embodiments, a non-negatively charged internucleotidic linkage has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **II**, **II-a-1**, **II-a-2, II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., or a salt form thereof. 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.

[00508] 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.,  .

[00509] 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.

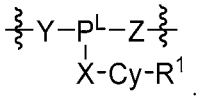
[00510] In some embodiments, a modified internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, comprises a triazole or alkyne moiety, each of which is optionally substituted. In some embodiments, a modified internucleotidic linkage comprises a triazole moiety. In some embodiments, 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.

[00511] 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.

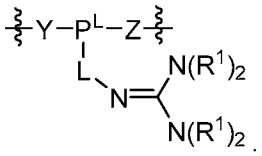
[00512] In some embodiments, a non-negatively charged internucleotidic linkage has the structure of formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **II**, **II-a-1**, **II-a-2, II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or a salt form thereof (not 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

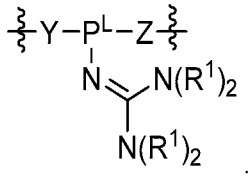
[00513] In some embodiments, X is a covalent bond and $-X-Cy-R^1$ is $-Cy-R^1$. In some embodiments, $-Cy-$ is an optionally substituted bivalent group selected from a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms. In some embodiments, $-Cy-$ 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.

[00514] 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

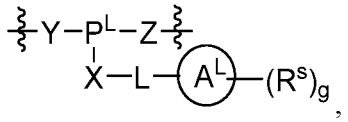
[00515] In some embodiments, R^1 is R'. In some embodiments, L is a covalent bond. In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, has the structure of formula **I-n-3** or a salt form thereof:



I-n-3

[00516] 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 $-CH_3$.

[00517] 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 $-S(O)_2R$;

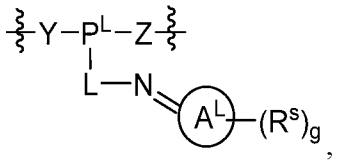
each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered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

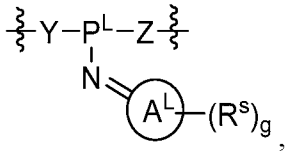
[00518] In some embodiments, a internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II**, has the structure of formula **II-a-1** or a salt form thereof:



II-a-1

or a salt form thereof.

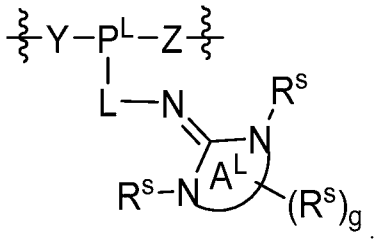
[00519] In some embodiments, a internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II**, has the structure of formula **II-a-2** or a salt form thereof:



II-a-2

or a salt form thereof.

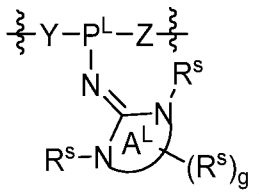
[00520] In some embodiments, A^L is bonded to –N= or L through a carbon atom. In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II** or **II-a-1**, **II-a-2**, has the structure of formula **II-b-1** or a salt form thereof:



II-b-1

[00521] 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**.

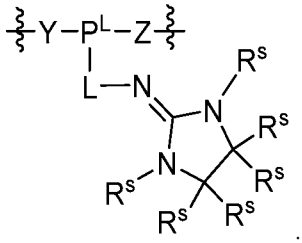
[00522] In some embodiments, A^L is bonded to –N= or L through a carbon atom. In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II** or **II-a-1**, **II-a-2**, has the structure of formula **II-b-2** or a salt form thereof:



II-b-2

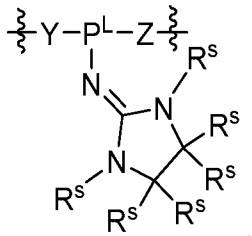
[00523] In some embodiments, Ring A^L is an optionally substituted 3-20 membered monocyclic ring having 0-10 heteroatoms (in addition to the two nitrogen atoms for formula **II-b**). In some embodiments, Ring A^L is an optionally substituted 5- membered monocyclic saturated ring.

[00524] 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:



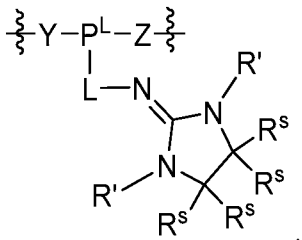
II-c-1

[00525] 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:



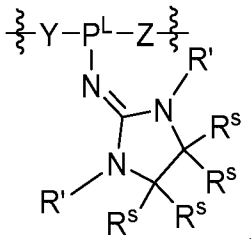
II-c-2

[00526] 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

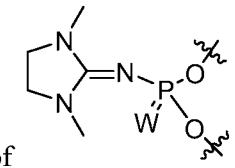
[00527] In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage of formula **II**, **II-a**, **II-b**, or **II-c** has the structure of formula **II-d-2** or a salt form thereof:



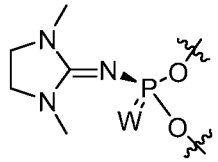
II-d-2

[00528] 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 $-H$.

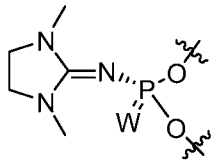
[00529] In some embodiments, a non-negatively charged internucleotidic linkage has the structure



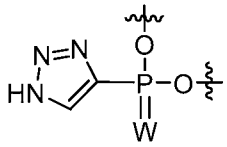
of . In some embodiments, a non-negatively charged internucleotidic linkage has the



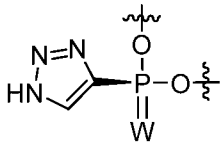
structure of . In some embodiments, a non-negatively charged internucleotidic linkage



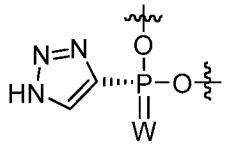
has the structure of . In some embodiments, a non-negatively charged internucleotidic



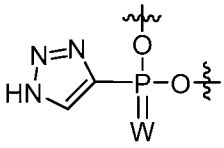
linkage has the structure of . In some embodiments, a non-negatively charged



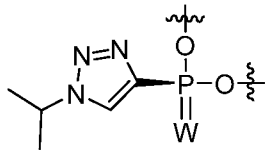
internucleotidic linkage has the structure of . In some embodiments, a non-negatively



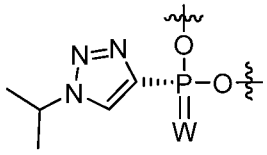
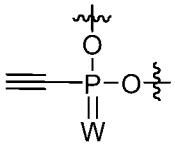
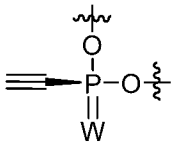
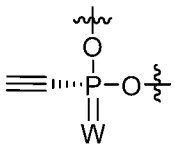
charged internucleotidic linkage has the structure of . In some embodiments, a non-



negatively charged internucleotidic linkage has the structure of . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of

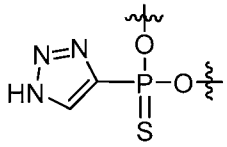
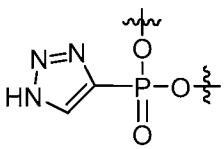


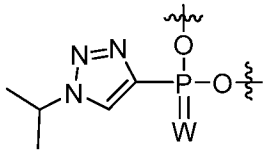
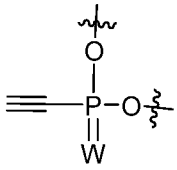
. In some embodiments, a non-negatively charged internucleotidic linkage has the

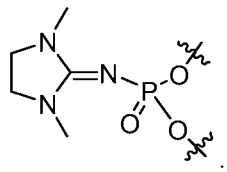
structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, W is O. In some embodiments, W is S.

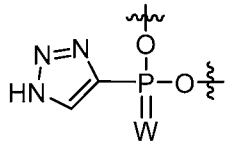
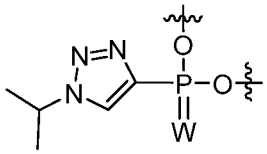
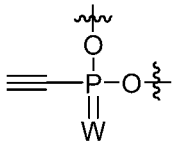
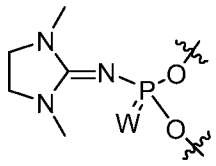
[00530] In some embodiments, each L^P independently has the structure of formula I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1, II-d-2, or a salt form thereof.

[00531] 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.

[00532] 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.

[00533] 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.

[00534] 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.

[00535] In some embodiments, an oligonucleotide comprises a neutral internucleotidic linkage and a chirally controlled internucleotidic linkage. In some embodiments, an oligonucleotide comprises a

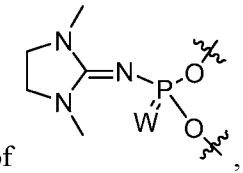
neutral internucleotidic linkage and a chirally controlled internucleotidic linkage which is a phosphorothioate in the Rp or Sp configuration. In some embodiments, the present disclosure provides an oligonucleotide comprising one or more non-negatively charged internucleotidic linkages and one or more 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.

[00536] 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.

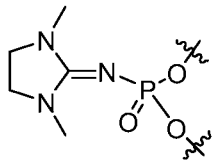
[00537] Without wishing to be bound by any particular theory, the present disclosure notes that incorporation of one or more non-negatively charged internucleotidic linkages, e.g., neutral internucleotidic linkages, into an oligonucleotide may be able to increase the oligonucleotide's ability to mediate 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.

[00538] 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.

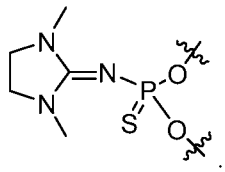
[00539] In some embodiments, a provided oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more non-negatively charged internucleotidic linkages. In some embodiments, a provided oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more neutral internucleotidic linkages. In some embodiments, 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



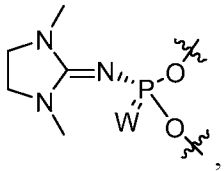
of , wherein W is O or S. In some embodiments, at least one non-negatively charged



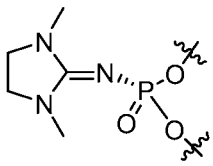
internucleotidic linkage/neutral internucleotidic linkage has the structure of . In some embodiments, at least one non-negatively charged internucleotidic linkage/neutral internucleotidic linkage



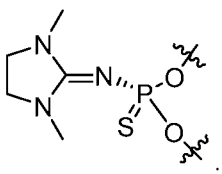
has the structure of . In some embodiments, at least one non-negatively charged



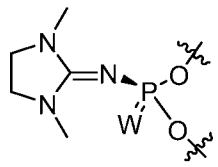
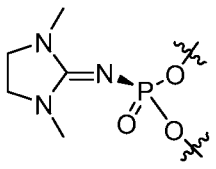
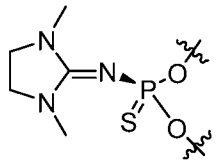
internucleotidic linkage/neutral internucleotidic linkage has the structure of , wherein W is O or S. In some embodiments, at least one non-negatively charged internucleotidic linkage/neutral



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.

[00540] In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein at least one linkage phosphorus is *R*p. It is understood by a person of ordinary skill in the art that in certain embodiments wherein the chirally controlled C9orf72 oligonucleotide comprises a base sequence, each T is independently and optionally replaced with U. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein each linkage phosphorus is *R*p. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein at least one linkage phosphorus is *S*p. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein each linkage phosphorus is *S*p. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein the oligonucleotide is a blockmer. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein the oligonucleotide is a stereoblockmer. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein the oligonucleotide is a P-modification blockmer. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein the oligonucleotide is a linkage blockmer. In some embodiments, the present disclosure

provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein the oligonucleotide is an altmer. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein the oligonucleotide is a stereoaltmer. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein the oligonucleotide is a P-modification altmer. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein the oligonucleotide is a linkage altmer. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein the oligonucleotide is a unimer. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein the oligonucleotide is a stereounimer. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein the oligonucleotide is a P-modification unimer. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein the oligonucleotide is a linkage unimer. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein the oligonucleotide is a gapmer. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein the oligonucleotide is a skipmer.

[00541] In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein each cytosine is optionally and independently replaced by 5-methylcytosine. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein at least one cytosine is optionally and independently replaced by 5-methylcytosine. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein, wherein each cytosine is optionally and independently replaced by 5-methylcytosine.

[00542] In some embodiments, a chirally controlled C9orf72 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.

[00543] In some embodiments, a chirally controlled C9orf72 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.

[00544] **Base sequence of an C9orf72 oligonucleotide**

[00545] In some embodiments, provided C9orf72 oligonucleotides are capable of directing a decrease in the expression, level and/or activity of a C9orf72 gene or its gene product. In some embodiments, a C9orf72 target gene comprises a repeat expansion. In some embodiments, provided C9orf72 oligonucleotides can comprise any base sequence described herein, or portion thereof, wherein a portion is a span of at least 15 contiguous bases, or a span of at least 15 contiguous bases with 1-5 mismatches.

[00546] In some embodiments, the base sequence of a C9orf72 oligonucleotide has a sufficient length and identity to a C9orf72 transcript target to mediate target-specific knockdown. In some embodiments, the C9orf72 oligonucleotide is complementary to a portion of a transcript target sequence.

[00547] In some embodiments, the base sequence of a C9orf72 oligonucleotide is complementary to that of a C9orf72 target transcript. As used herein, "target transcript sequence," "target sequence", "target gene", and the like, refer to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a C9orf72 gene, including mRNA that is a product of RNA processing of a primary transcription product.

[00548] The terms "complementary," "fully complementary" and "substantially complementary" herein may be used with respect to the base matching between a C9orf72 oligonucleotide and a C9orf72 target sequence, as will be understood from the context of their use. In some embodiments, the base sequence of a C9orf72 oligonucleotide is complementary to that of a C9orf72 target sequence when each

base of the oligonucleotide is capable of base-pairing with a sequential base on the target strand, when maximally aligned. As a non-limiting example, if a target sequence has, for example, a base sequence of 5'-GCAUAGCGAGCGAGGGAAAAC-3', an oligonucleotide with a base sequence of 5'GUUUUCCCUCGCUCGCUAUGC-3' is complementary or fully complementary to such a target sequence. It is noted, of course, that substitution of T for U, or vice versa, does not alter the amount of complementarity.

[00549] As used herein, a polynucleotide that is "substantially complementary" to a C9orf72 target sequence is largely or mostly complementary but not 100% complementary. In some embodiments, a sequence (e.g., a C9orf72 oligonucleotide) which is substantially complementary has 1, 2, 3, 4 or 5 mismatches from a sequence which is 100% complementary to the target sequence.

[00550] The present disclosure presents, in Table 1A and elsewhere, various oligonucleotides, each of which has a defined base sequence. In some embodiments, the disclosure encompasses any oligonucleotide having a base sequence which is, comprises, or comprises a portion of the base sequence of any of oligonucleotide disclosed herein. In some embodiments, the disclosure encompasses any oligonucleotide having a base sequence which is, comprises, or comprises a portion of the base sequence of any oligonucleotide disclosed herein, which has any chemical modification, stereochemistry, format, structural feature (e.g., any structure or pattern of modification or portion thereof), and/or any other modification described herein (e.g., conjugation with another moiety, such as a targeting moiety, carbohydrate moiety, etc.; and/or multimerization). In some embodiments, a "portion" (e.g., of a base sequence or a pattern of modifications), is at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 long. In some embodiments, a "portion" of a base sequence is at least 5 nt long. In some embodiments, a "portion" of a base sequence is at least 10 nt long. In some embodiments, a "portion" of a base sequence is at least 15 nt long. In some embodiments, a "portion" of a base sequence is at least 20 nt long.

[00551] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCCACACCTGCTCTTGCTAG.

[00552] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCGGGCAGCAGGGACGGCTG.

[00553] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCGGTTGCGGTGCCTGCGCC.

[00554] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCGGTTGTTTCCCTCCTTGT.

[00555] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTTGTTCACCCTCAGCGAGT.

[00556] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which

is, comprises or comprises a portion of: ACCCCCATCTCATCCCGCAT.

[00557] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGACCCGCTGGGAGCGCTGC.

[00558] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TGCCGCCTCCTCACTCACCC.

[00559] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCTCTCTTTCCTAGCGGGAC.

[00560] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TCCCCATTCCAGTTTCCATC.

[00561] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGCCTCTCAGTACCCGAGGC.

[00562] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGATGCCGCCTCCTCACTCA.

[00563] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGCAGCAGGGACGGCTGACA.

[00564] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TACCCGCGCCTCTTCCCGGC.

[00565] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ACAGGCTGCGGTTGTTTCCC.

[00566] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTCTTCCCGGCAGCCGAACC.

[00567] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGGAGGTCCTGCACTTTCCC.

[00568] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCTGGGTGTCGGGCTTTCGC.

[00569] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTTCCTTGCTTTCCCGCCCT.

[00570] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CGCTTCTACCCGCGCCTCTT.

[00571] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTTCTACCCGCGCCTCTTCC.

[00572] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCAGGCGGTGGCGAGTGGGT.

[00573] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCCGCCTCCTCACTCACCCA.

[00574] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ACATCCCCTCACAGGCTCTT.

[00575] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCCTCCTTGTTTTCTTCTGG.

[00576] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTGGCTCTCCAGAAGGCTGT.

[00577] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: AGGCTGTCAGCTCGGATCTC.

[00578] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CGCCTCCTCACTCACCCACT.

[00579] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTCTTTCCTAGCGGGACACC.

[00580] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CACCCACTCGCCACCGCCTG.

[00581] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TACAGGCTGCGGTTGTTTCC.

[00582] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CGCACCTCTCTTTCCTAGCG.

[00583] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TGGCGAGTGGGTGAGTGAGGAGGCGGCATC.

[00584] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCCACCCGCCAGGATGCCGC.

[00585] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GATGCACCTGACATCCCCTC.

[00586] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCTTGCTACAGGCTGCGGTT.

[00587] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTCACTCACCCACTCGCCAC.

[00588] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTCCTCACTCACCCACTCGC.

[00589] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which

is, comprises or comprises a portion of: GGGAAGGCCGGAGGGTGGGC.

[00590] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGGCAGCAGGGACGGCTGAC.

[00591] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCGCAGGCGGTGGCGAGTGGGTGAGTGAGG.

[00592] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGCTGCGGTTGTTTCCCTCC.

[00593] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TCTCAGTACCCGAGGCTCCC.

[00594] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCTTGGTGTGTCAGCCGTCC.

[00595] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTGTTCTGTCTTTGGAGCCC.

[00596] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CGCATAGAATCCAGTACCAT.

[00597] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: AGCGCGCGACTCCTGAGTTC.

[00598] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: AGGCTGCGGTTGTTTCCCTC.

[00599] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTCAGTACCCGAGGCTCCCT.

[00600] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTTCCCGGCAGCCGAACCCC.

[00601] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CACCCGCCAGGATGCCGCCT.

[00602] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ACCTCTCTTTCCTAGCGGGA.

[00603] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCTACAGGCTGCGGTTGTTT.

[00604] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCGCGACTCCTGAGTTCCAG.

[00605] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TCCCGGCAGCCGAACCCCAA.

[00606] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCCAGATCCCCATCCCTTGT.

[00607] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTCACCCACTCGCCACCGCC.

[00608] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: AGCAACCGGGCAGCAGGGAC.

[00609] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCTGCGGTTGTTTCCCTCCT.

[00610] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: AACCGGGCAGCAGGGACGGC.

[00611] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGTTGTTTCCCTCCTTGTTT.

[00612] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTTGGTGTGTCAGCCGTCCC.

[00613] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCTGGAGATGGCGGTGGGCA.

[00614] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCCGCGCCTCTTCCCGGCAG.

[00615] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTTGCTAGACCCCGCCCCCA.

[00616] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGCTCTCCAGAAGGCTGTCA.

[00617] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TCCTCACTCACCCACTCGCC.

[00618] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CAGGATGCCGCCTCCTCACT.

[00619] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCTGGTTGCTTCACAGCTCC.

[00620] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CGGGCAGCAGGGACGGCTGA.

[00621] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTGCTGCGATCCCCATTCCA.

[00622] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which

is, comprises or comprises a portion of: CCCGCCAGGATGCCGCCTCC.

[00623] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GATCCCCATCCCTTGTCCCT.

[00624] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCCTTACTCTAGGACCAAGA.

[00625] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ACCGGGCAGCAGGGACGGCT.

[00626] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TGCCAGGCTGGTTATGACTC.

[00627] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCATCCTGGCGGGTGGCTGT.

[00628] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCTCTTCCCGGCAGCCGAAC.

[00629] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCCCAAACAGCCACCCGCCA.

[00630] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTTGCGGTGCCTGCGCCCGC.

[00631] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCCAAACAGCCACCCGCCAG.

[00632] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ACCCGCCAGGATGCCGCCTC.

[00633] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TCTTCCCGGCAGCCGAACCC.

[00634] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCTCCGGCCTTCCCCCAGGC.

[00635] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCATCCGGGCCCCGGGCTTC.

[00636] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CACCCCCATCTCATCCCGCA.

[00637] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CAGAGCTTGCTACAGGCTGC.

[00638] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCGCTTCTACCCGCGCCTCT.

[00639] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTGCAGGCGTCTCCACACCC.

[00640] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ACTCACCCACTCGCCACCGC.

[00641] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCAGGCGTCTCCACACCCCC.

[00642] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCTGAGTTCCAGAGCTTGCT.

[00643] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GAGAGCCCCCGCTTCTACCC.

[00644] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TCCTGAGTTCCAGAGCTTGC.

[00645] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: AGCTTGCTACAGGCTGCGGT.

[00646] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCAAACAGCCACCCGCCAGG.

[00647] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCGCAGGCGGTGGCGAGTGGGTGAGTGAGGAGGCGGCATC.

[00648] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTGCGGTTGTTTCCCTCCTT.

[00649] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: AGCCGTCCCTGCTGCCCGGT.

[00650] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCCTCCTCACTCACCCACTC.

[00651] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TGCTACAGGCTGCGGTTGTT.

[00652] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCAGGGACGGCTGACACACC.

[00653] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: AGGATGCCGCCTCCTCACTC.

[00654] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGTCTTTTCTTGTTCACCCT.

[00655] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCTGCTCTTGCTAGACCCCG.

[00656] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTTCACCCTCAGCGAGTACT.

[00657] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCTAGCGGGACACCGTAGGT.

[00658] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCCCTCAGTACCCGAGCTGT.

[00659] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTACCCGCGCCTCTTCCCGG.

[00660] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTCTTTTCTTGTTCACCCTC.

[00661] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGGTGTCGGGCTTTCGCCTC.

[00662] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CGGTTGTTTCCCTCCTTGTT.

[00663] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCACCCTCCGGCCTTCCCCC.

[00664] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCCTCTCAGTACCCGAGGCT.

[00665] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCTCACTCACCCACTCGCCA.

[00666] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GAGCTTGCTACAGGCTGCGG.

[00667] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTGACATCCCCTCACAGGCT.

[00668] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCTGTTTGACGCACCTCTCT.

[00669] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TGGAATGGGGATCGCAGCAC.

[00670] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCGCCTCCTCACTCACCCAC.

[00671] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which

is, comprises or comprises a portion of: CCTCTGCCAAGGCCTGCCAC.

[00672] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCGACTTGCATTGCTGCCCT.

[00673] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TCACCCTCAGCGAGTACTGT.

[00674] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCGCGCCTCTTCCCGGCAGC.

[00675] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CGCCTCTTCCCGGCAGCCGA.

[00676] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TTGCTACAGGCTGCGGTTGT.

[00677] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCCGGGAAGAGGCGCGGGTAG.

[00678] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCAACCGGGCAGCAGGGACG.

[00679] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TCTTGCTAGACCCCGCCCCC.

[00680] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCTAGACCCCGCCCCCAAAA.

[00681] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCTGCGATCCCCATTCCAGT.

[00682] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCCACTCGCCACCGCCTGCG.

[00683] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTGGCAGGCCTTGGCAGAGG.

[00684] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ACGCACCTCTCTTTCCTAGC.

[00685] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: AGGGCCACCCCTCCTGGGAA.

[00686] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCAGGATGCCGCCTCCTCAC.

[00687] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ACCCGCGCCTCTTCCCGGCA.

[00688] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ACCCGAGCTGTCTCCTTCCC.

[00689] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCCTCTTCCCGGCAGCCGAA.

[00690] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ACTCCTGAGTTCCAGAGCTT.

[00691] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ATTGCCTGCATCCGGGCCCC.

[00692] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TTCTACCCGCGCCTCTTCCC.

[00693] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTACCCGAGGCTCCCTTTTC.

[00694] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCTGCTGCCCGGTTGCTTCT.

[00695] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCGCGCGACTCCTGAGTTCC.

[00696] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTCGGTGTGCTCCCCATTCT.

[00697] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ACCCACTCGCCACCGCCTGC.

[00698] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GACATCCCCTCACAGGCTCT.

[00699] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GAGCTGCCCAGGACCACTTC.

[00700] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCGGCATCCTGGCGGGTGGC.

[00701] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTCCGTGTGCTCATTGGGTC.

[00702] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TGGAATGGGGATCGCAGCACA.

[00703] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGCGGAGGCGCAGGCGGTGG.

[00704] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which

is, comprises or comprises a portion of: GCCAGGATGCCGCCTCCTCA.

[00705] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCACTCGCCACCGCCTGCGC.

[00706] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TGCCTGCATCCGGGCCCCGG.

[00707] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TTGCTAGACCCCGCCCCCAA.

[00708] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CAGGCTGCGGTTGTTTCCCT.

[00709] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCCGTCCCTGCTGCCCGGTT.

[00710] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TTTCCCCACACCACTGAGCT.

[00711] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TTCCAGAGCTTGCTACAGGC.

[00712] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCCGGCAGCCGAACCCCAAA.

[00713] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TGTGCTGCGATCCCCATTCC.

[00714] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GAGGCCAGATCCCCATCCCT.

[00715] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTCGCTGTTTGACGCACCTC.

[00716] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTCTTGCTAGACCCCGCCCC.

[00717] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCGCCAGGATGCCGCCTCCT.

[00718] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCTCCTCACTCACCCACTCG.

[00719] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ATCCCCTCACAGGCTCTTGT.

[00720] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCTCTTGCTAGACCCCGCCC.

[00721] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGTCCCTGCCGGCGAGGAGA.

[00722] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCTTCCCTGAAGGTTCCTCC.

[00723] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TCCCCTCACAGGCTCTTGTG.

[00724] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TGCTCTTGCTAGACCCCGCC.

[00725] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TTCCCGGCAGCCGAACCCCA.

[00726] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTCCCTGCTGCCCGGTTGCT.

[00727] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCTTCTACCCGCGCCTCTTC.

[00728] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTTTCCTAGCGGGACACCGT.

[00729] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTGCAGGACCTCCCTCCTGT.

[00730] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTGCTCCCCATTCTGTGGGA.

[00731] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TCCAGAGCTTGCTACAGGCT.

[00732] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCCCTCACAGGCTCTTGTGA.

[00733] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TGCTAGACCCCGCCCCCAAA.

[00734] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TCACCCACTCGCCACCGCCT.

[00735] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CTGCTCTTGCTAGACCCCGC.

[00736] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TGCGGTTGTTTCCCTCCTTG.

[00737] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which

is, comprises or comprises a portion of: GTTGTTTCCCTCCTTGTTTT.

[00738] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGCGTCTCCACACCCCCATC.

[00739] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGGCTCTCCTCAGAGCTCGA.

[00740] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ACCCTCCGGCCTTCCCCCAG.

[00741] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCGCAGCCTGTAGCAAGCTC.

[00742] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: AACCCACACCTGCTCTTGCT.

[00743] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: AGTGGTCCTGGGCAGCTCCT.

[00744] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TCCTTGCTTTCCCGCCCTCA.

[00745] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GAGCTCTGAGGAGAGCCCCC.

[00746] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCACCTCTCTTTCCTAGCGG.

[00747] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CGCCAGGATGCCGCCTCCTC.

[00748] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: AACAGCCACCCGCCAGGATG.

[00749] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CAGGGTGGCATCTGCTTCAC.

[00750] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CACTCACCCACTCGCCACCG.

[00751] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCACCCGCCAGGATGCCGCC.

[00752] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ACCCACACCTGCTCTTGCTA.

[00753] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ATGCCGCCTCCTCACTCACC.

[00754] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CACCTCTCTTTCCTAGCGGG.

[00755] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GATCCCCATTCCAGTTTCCA.

[00756] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GTCAGCCGTCCCTGCTGCCC.

[00757] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: TCACTCACCCACTCGCCACC.

[00758] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGCTCCCTTTTCTCGAGCCC.

[00759] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCAGGACCTCCCTCCTGTTT.

[00760] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCTTTCCCGCCCTCAGTACC.

[00761] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GATGCCGCCTCCTCACTCAC.

[00762] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: ACCCCAAACAGCCACCCGCC.

[00763] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCTCCTTGTTTTCTTCTGGT.

[00764] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GGCCTTGGCAGAGGTGGTGA.

[00765] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GCTCTGAGGAGAGCCCCCGC.

[00766] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: GACAGGGTGGCATCTGCTTC.

[00767] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CGCGCGACTCCTGAGTTCCA.

[00768] In some embodiments, an oligonucleotide targets C9orf72 and has a base sequence which is, comprises or comprises a portion of: CCACACCTGCTCTTGCTAGA.

[00769] In some embodiments, a portion of a base sequence is a span of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or more contiguous (consecutive) bases.

[00770] In some embodiments, the present disclosure discloses a C9orf72 oligonucleotide of a

sequence recited herein. In some embodiments, the present disclosure discloses a C9orf72 oligonucleotide of a sequence recited herein, wherein the oligonucleotide is capable of directing a decrease in the expression, level and/or activity of a C9orf72 gene or its gene product. In some embodiments, a C9orf72 oligonucleotide of a recited sequence comprises any structure described herein. In various sequences, U can be replaced by T or vice versa, or a sequence can comprise a mixture of U and T. In some embodiments, a C9orf72 oligonucleotide has a length of no more than about 49, 45, 40, 30, 35, 25, 23 total nucleotides. In some embodiments, a portion is a span of at least 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 total nucleotides with 0-3 mismatches. In some embodiments, a portion is a span of at least 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 total nucleotides with 0-3 mismatches, wherein a span with 0 mismatches is complementary and a span with 1 or more mismatches is a non-limiting example of substantial complementarity. In some embodiments, wherein the sequence recited above starts with a U at the 5'-end, the U can be deleted and/or replaced by another base. In some embodiments, the disclosure encompasses any oligonucleotide having a base sequence which is or comprises or comprises a portion of the base sequence of any oligonucleotide disclosed herein, which has a format or a portion of a format disclosed herein.

[00771] In some embodiments, a C9orf72 oligonucleotide can comprise any base sequence described herein. In some embodiments, a C9orf72 oligonucleotide can comprise any base sequence or portion thereof, described herein. In some embodiments, a C9orf72 oligonucleotide can comprise any base sequence or portion thereof, described herein, wherein a portion is a span of 15 contiguous bases, or a span of 15 contiguous bases with 1-5 mismatches. In some embodiments, a C9orf72 oligonucleotide can comprise any base sequence or portion thereof described herein in combination with any other structural element or modification described herein.

[00772] Non-limiting examples of C9orf72 oligonucleotides having various base sequences and modifications are disclosed in Table 1A, below.

Table 1A. C9orf72 oligonucleotides.

WAVE ID	Modified Sequence	Base Sequence	Stereochemistry / Internucleotidic Linkages
WV-3536	Teo * Aeo * m5Ceo * Aeo * Geo * G * m5C * T * G * m5C * G * G * T * T * G * Teo * Teo * Teo * m5Ceo * m5Ceo	TACAGGCTGCGGTTGTTTCC	XXXXXXXXXXXXXXXXXXX
WV-3537	Geo * m5Ceo * m5Ceo * Teo * Teo * A * m5C * T * m5C * T * A * G * G * A * m5C * m5Ceo * Aeo * Aeo * Geo * Aeo	GCCTTACTCTAGGACCAAGA	XXXXXXXXXXXXXXXXXXX
WV-3538	m5Ceo * Geo * m5Ceo * Aeo * Teo * A * G * A * A * T * m5C * m5C * A * G * T * Aeo * m5Ceo * m5Ceo * Aeo * Teo	CGCATAGAATCCAGTACCAT	XXXXXXXXXXXXXXXXXXX
WV-3539	mU * mA * mC * mA * mG * G * C * T * G * C * G * G * T * T * G * mU * mU * mU * mC * mC	UACAGGCTGCGGTTGUUUCC	XXXXXXXXXXXXXXXXXXX
WV-3540	mG * mC * mC * mU * mU * A * C * T * C * T * A * G * G * A * C * mC * mA * mA * mG * mA	GCCUUACTCTAGGACCAAGA	XXXXXXXXXXXXXXXXXXX
WV-3541	mC * mG * mC * mA * mU * A * G * A * A * T * C * C * A * G * T * mA * mC * mC * mA * mU	CGCAUAGAATCCAGTACCAU	XXXXXXXXXXXXXXXXXXX
WV-3542	m5Ceo * m5Ceo * Teo * Teo * m5Ceo * m5C * m5C * T * G * A * A * G * G * T * T * m5Ceo * m5Ceo * Teo * m5Ceo * m5Ceo	CCTTCCCTGAAGGTTCCTCC	XXXXXXXXXXXXXXXXXXX
WV-3561	mG * mC * mU * mG * mG * A * G * A * T * G * G * C * G * G * T * mG * mG * mG * mC * mA	GCUGGAGATGGCGGTGGGCA	XXXXXXXXXXXXXXXXXXX
WV-3562	mC * mU * mG * mU * mU * C * T * G * T * C * T * T * T * G * G * mA * mG * mC * mC * mC	CUGUUCTGTCTTTGGAGCCC	XXXXXXXXXXXXXXXXXXX
WV-3563	mU * mC * mC * mC * mC * A * T * T * C * C * A * G * T * T * T * mC * mC * mA * mU * mC	UCCCCATTCCAGTTTCCAUC	XXXXXXXXXXXXXXXXXXX
WV-3564	mG * mA * mU * mC * mC * C * C * A * T * T * C * C * A * G * T * mU * mU * mC * mC *	GAUCCCCATTCCAGTUUCCA	XXXXXXXXXXXXXXXXXXX

	mA		
WV-3565	mG * mC * mU * mG * mC * G * A * T * C * C * C * A * T * T * mC * mC * mA * mG * mU	GCUGCGATCCCCATTCCAGU	XXXXXXXXXXXXXXXXXXX
WV-3566	mG * mU * mG * mC * mU * G * C * G * A * T * C * C * C * C * A * mU * mU * mC * mC * mC * mA	GUGCUGCGATCCCCAUUCCA	XXXXXXXXXXXXXXXXXXXX
WV-3567	mU * mG * mU * mG * mC * T * G * C * G * A * T * C * C * C * C * mA * mU * mU * mC * mC	UGUGCTGCGATCCCCAUUCC	XXXXXXXXXXXXXXXXXXXX
WV-3568	mC * mA * mG * mG * mG * T * G * G * C * A * T * C * T * G * C * mU * mU * mC * mA * mC	CAGGGTGGCATCTGCUUCAC	XXXXXXXXXXXXXXXXXXXX
WV-3569	mG * mA * mC * mA * mG * G * G * T * G * G * C * A * T * C * T * mG * mC * mU * mU * mC	GACAGGGTGGCATCTGCUUC	XXXXXXXXXXXXXXXXXXXX
WV-3570	mA * mG * mG * mC * mU * G * T * C * A * G * C * T * C * G * G * mA * mU * mC * mU * mC	AGGCUGTCAGCTCGGAUCUC	XXXXXXXXXXXXXXXXXXXX
WV-3571	mG * mG * mC * mU * mC * T * C * C * A * G * A * A * G * G * C * mU * mG * mU * mC * mA	GGCUCTCCAGAAGGCUGUCA	XXXXXXXXXXXXXXXXXXXX
WV-3572	mG * mU * mG * mG * mC * T * C * T * C * C * A * G * A * A * G * mG * mC * mU * mG * mU	GUGGCTCTCCAGAAGGCUGU	XXXXXXXXXXXXXXXXXXXX
WV-3573	mU * mU * mU * mC * mC * C * C * A * C * A * C * C * A * C * T * mG * mA * mG * mC * mU	UUUCCCCACACCACTGAGCU	XXXXXXXXXXXXXXXXXXXX
WV-3574	mC * mC * mC * mC * mU * C * A * C * A * G * G * C * T * C * T * mU * mG * mU * mG * mA	CCCCUCACAGGCTCTUGUGA	XXXXXXXXXXXXXXXXXXXX
WV-3575	mU * mC * mC * mC * mC * T * C * A * C * A * G * G * C * T * C * mU * mU * mG * mU * mG	UCCCCTCACAGGCTCUUGUG	XXXXXXXXXXXXXXXXXXXX
WV-3576	mA * mU * mC * mC * mC * C * T * C * A * C * A * G * G * C * T * mC * mU * mU * mG *	AUCCCCTCACAGGCTCUUGU	XXXXXXXXXXXXXXXXXXXX

	mU		
WV-3577	mA * mC * mA * mU * mC * C * C * C * T * C * A * C * A * G * G * mC * mU * mC * mU * mU	ACAUCCCCTCACAGGCUCUU	XXXXXXXXXXXXXXXXXXXX
WV-3578	mG * mA * mC * mA * mU * C * C * C * C * T * C * A * C * A * G * mG * mC * mU * mC * mU	GACAUCCCCTCACAGGCUCU	XXXXXXXXXXXXXXXXXXX
WV-3579	mC * mU * mG * mA * mC * A * T * C * C * C * C * T * C * A * C * mA * mG * mG * mC * mU	CUGACATCCCCTCACAGGCU	XXXXXXXXXXXXXXXXXXX
WV-3580	mG * mA * mU * mG * mC * A * C * C * C * T * G * A * C * A * T * C * mC * mC * mC * mU * mC	GAUGCACCTGACATCCCCUC	XXXXXXXXXXXXXXXXXXX
WV-3581	mG * mC * mA * mC * mC * T * C * T * C * T * T * T * C * C * T * mA * mG * mC * mG * mG	GCACCTCTCTTTCCTAGCGG	XXXXXXXXXXXXXXXXXXX
WV-3582	mG * mG * mG * mC * mA * G * C * A * G * G * G * A * C * G * G * mC * mU * mG * mA * mC	GGGCAGCAGGGACGGCUGAC	XXXXXXXXXXXXXXXXXXX
WV-3583	mU * mG * mC * mU * mA * G * A * C * C * C * C * G * C * C * C * C * mC * mC * mA * mA * mA	UGCUAGACCCCGCCCCCAAA	XXXXXXXXXXXXXXXXXXX
WV-3584	mU * mC * mU * mU * mG * C * T * A * G * A * C * C * C * C * C * G * mC * mC * mC * mC * mC	UCUUGCTAGACCCCGCCCCC	XXXXXXXXXXXXXXXXXXX
WV-3585	mG * mC * mU * mC * mU * T * G * C * T * A * G * A * C * C * C * C * mC * mG * mC * mC * mC	GCUCUTGCTAGACCCCGCCC	XXXXXXXXXXXXXXXXXXX
WV-3586	mC * mU * mG * mC * mU * C * T * T * G * C * T * A * G * A * C * mC * mC * mC * mG * mC	CUGCUCTTGCTAGACCCCGC	XXXXXXXXXXXXXXXXXXX
WV-3587	mG * mC * mG * mG * mU * T * G * T * T * T * C * C * C * T * C * mC * mU * mU * mG * mU	GCGGUTGTTTCCCTCCUUGU	XXXXXXXXXXXXXXXXXXX
WV-3588	mG * mC * mU * mG * mC * G * G * T * T * T * G * T * T * T * C * C * mC * mU * mC * mC *	GCUGCGGTTGTTTCCCUCCU	XXXXXXXXXXXXXXXXXXX

	mU		
WV-3589	mG * mG * mC * mU * mG * C * G * G * T * T * G * T * T * C * mC * mC * mU * mC * mC	GGCUGCGGTTGTTTCCCUCC	XXXXXXXXXXXXXXXXXXX
WV-3590	mC * mA * mG * mG * mC * T * G * C * G * G * T * T * G * T * T * mU * mC * mC * mC * mU	CAGGCTGCGGTTGTTUCCCU	XXXXXXXXXXXXXXXXXXX
WV-3591	mU * mC * mA * mC * mU * C * A * C * C * C * A * C * T * C * G * mC * mC * mA * mC * mC	UCACUCACCCACTCGCCACC	XXXXXXXXXXXXXXXXXXX
WV-3592	mC * mC * mU * mC * mA * C * T * C * A * C * C * C * A * C * T * mC * mG * mC * mC * mA	CCUCACTCACCCACTCGCCA	XXXXXXXXXXXXXXXXXXX
WV-3593	mG * mG * mA * mU * mG * C * C * G * C * C * T * C * C * T * C * mA * mC * mU * mC * mA	GGAUGCCGCCTCCTCACUCA	XXXXXXXXXXXXXXXXXXX
WV-3594	mG * mC * mC * mA * mG * G * A * T * G * C * C * G * C * C * T * mC * mC * mU * mC * mA	GCCAGGATGCCGCCTCCUCA	XXXXXXXXXXXXXXXXXXX
WV-3595	mC * mC * mC * mC * mA * A * A * C * C * A * G * C * C * A * C * C * mC * mG * mC * mC * mA	CCCCAAACAGCCACCCGCCA	XXXXXXXXXXXXXXXXXXX
WV-3596	mG * mA * mG * mA * mG * C * C * C * C * C * C * G * C * C * T * T * C * mU * mA * mC * mC * mC	GAGAGCCCCCGCTTCUACCC	XXXXXXXXXXXXXXXXXXX
WV-3597	mG * mC * mU * mC * mU * G * A * G * G * A * G * A * G * C * C * C * mC * mC * mC * mG * mC	GCUCUGAGGAGAGCCCCGC	XXXXXXXXXXXXXXXXXXX
WV-3598	mG * mA * mG * mC * mU * C * T * G * A * G * G * A * G * A * G * mC * mC * mC * mC * mC	GAGCUCTGAGGAGAGCCCCC	XXXXXXXXXXXXXXXXXXX
WV-3599	mG * mA * mU * mC * mC * C * C * A * T * C * C * C * T * T * G * mU * mC * mC * mC * mU	GAUCCCCATCCCTTGUCCCU	XXXXXXXXXXXXXXXXXXX
WV-3600	mG * mC * mC * mA * mG * A * T * C * C * C * C * A * T * C * C * mC * mU * mU * mG *	GCCAGATCCCCATCCCUUGU	XXXXXXXXXXXXXXXXXXX

	mU		
WV-3601	mG * mA * mG * mG * mC * C * A * G * A * T * C * C * C * A * mU * mC * mC * mC * mU	GAGGCCAGATCCCCATCCCU	XXXXXXXXXXXXXXXXXXXX
WV-3602	mG * mG * mC * mU * mC * C * C * T * T * T * T * C * T * C * G * mA * mG * mC * mC * mC	GGCUCCCTTTTCTCGAGCCC	XXXXXXXXXXXXXXXXXXXX
WV-3603	mG * mU * mA * mC * mC * C * G * A * G * G * C * T * C * C * C * mU * mU * mU * mU * mC	GUACCCGAGGCTCCCUUUUC	XXXXXXXXXXXXXXXXXXXX
WV-3604	mC * mU * mC * mA * mG * T * A * C * C * C * C * G * A * G * G * C * mU * mC * mC * mC * mU	CUCAGTACCCGAGGCUCCCU	XXXXXXXXXXXXXXXXXXXX
WV-3605	mU * mC * mU * mC * mA * G * T * A * C * C * C * G * A * G * G * C * mU * mC * mC * mC	UCUCAGTACCCGAGGCUCCC	XXXXXXXXXXXXXXXXXXXX
WV-3606	mG * mC * mC * mU * mC * T * C * A * G * T * A * C * C * C * G * mA * mG * mG * mC * mU	GCCUCTCAGTACCCGAGGCU	XXXXXXXXXXXXXXXXXXXX
WV-3607	mG * mG * mC * mC * mU * C * C * T * C * A * G * T * A * C * C * C * mG * mA * mG * mG * mC	GGCCUCTCAGTACCCGAGGC	XXXXXXXXXXXXXXXXXXXX
WV-3608	mC * mC * mU * mC * mC * G * G * C * C * C * T * C * C * C * C * C * mC * mA * mG * mG * mC	CCUCCGGCCTTCCCCCAGGC	XXXXXXXXXXXXXXXXXXXX
WV-3609	mA * mC * mC * mC * mU * C * C * G * G * C * C * T * T * C * C * mC * mC * mA * mG	ACCCUCCGGCCTTCCCCCAG	XXXXXXXXXXXXXXXXXXXX
WV-3610	mC * mC * mA * mC * mC * C * T * C * C * G * G * C * C * T * T * mC * mC * mC * mC	CCACCCTCCGGCCTTCCCCC	XXXXXXXXXXXXXXXXXXXX
WV-3611	mA * mC * mC * mC * mC * C * A * T * C * T * C * C * A * T * C * C * C * mC * mG * mC * mA * mU	ACCCCCATCTCATCCCGCAU	XXXXXXXXXXXXXXXXXXXX
WV-3612	mC * mA * mC * mC * mC * C * C * A * T * C * T * C * A * T * C * C * mC * mG * mC *	CACCCCCATCTCATCCCGCA	XXXXXXXXXXXXXXXXXXXX

	mA		
WV-3613	mG * mG * mC * mG * mU * C * T * C * C * A * C * A * C * C * C * mC * mC * mA * mU * mC	GGCGUCTCCACACCCCCAUC	XXXXXXXXXXXXXXXXXXX
WV-3614	mG * mC * mA * mG * mG * C * G * T * C * T * C * C * A * C * A * mC * mC * mC * mC * mC	GCAGGCGTCTCCACACCCCC	XXXXXXXXXXXXXXXXXXX
WV-3615	mG * mU * mG * mC * mA * G * G * C * G * T * C * T * C * C * A * mC * mA * mC * mC * mC	GUGCAGGCGTCTCCACACCC	XXXXXXXXXXXXXXXXXXX
WV-3616	mC * mC * mG * mA * mC * T * T * G * C * A * T * T * G * C * T * mG * mC * mC * mC * mU	CCGACTTGCATTGCTGCCCU	XXXXXXXXXXXXXXXXXXX
WV-3617	mG * mC * mA * mG * mG * A * C * C * T * C * C * C * T * C * C * mU * mG * mU * mU * mU	GCAGGACCTCCCTCCUGUUU	XXXXXXXXXXXXXXXXXXX
WV-3618	mG * mU * mG * mC * mA * G * G * A * C * C * T * C * C * C * T * mC * mC * mU * mG * mU	GUGCAGGACCTCCCTCCUGU	XXXXXXXXXXXXXXXXXXX
WV-3619	mA * mG * mG * mG * mC * C * C * A * C * C * C * C * C * T * C * C * T * mG * mG * mG * mA * mA	AGGGCCACCCCTCCTGGGAA	XXXXXXXXXXXXXXXXXXX
WV-3620	mG * mG * mC * mC * mC * mU * T * G * G * C * A * G * A * G * G * T * mG * mG * mU * mG * mA	GGCCUTGGCAGAGGTGGUGA	XXXXXXXXXXXXXXXXXXX
WV-3621	mG * mU * mG * mG * mC * A * G * G * C * C * T * T * T * G * G * C * mA * mG * mA * mG * mG	GUGGCAGGCCTTGGCAGAGG	XXXXXXXXXXXXXXXXXXX
WV-3622	mG * mA * mG * mC * mU * G * C * C * C * C * A * G * G * A * C * C * C * mA * mC * mU * mU * mC	GAGCUGCCCAGGACCACUUC	XXXXXXXXXXXXXXXXXXX
WV-3623	mG * mC * mU * mU * mG * G * T * G * T * G * T * T * C * A * G * C * mC * mG * mU * mC * mC	GCUUGGTGTGTCAGCCGUCC	XXXXXXXXXXXXXXXXXXX
WV-3624	mC * mU * mU * mG * mG * T * G * T * G * T * C * C * A * G * C * C * C * mG * mU * mC * mC *	CUUGGTGTGTCAGCCGUCCC	XXXXXXXXXXXXXXXXXXX

	mC		
WV-3625	mG * mU * mC * mA * mG * C * C * G * T * C * C * C * T * G * C * mU * mG * mC * mC * mC	GUCAGCCGTCCCTGCUGCCC	XXXXXXXXXXXXXXXXXXX
WV-3626	mG * mC * mC * mG * mU * C * C * C * T * G * C * T * G * C * C * mC * mG * mG * mU * mU	GCCGUCCCTGCTGCCCGGUU	XXXXXXXXXXXXXXXXXXX
WV-3627	mG * mU * mC * mC * mC * T * G * C * T * G * C * C * C * C * G * G * mU * mU * mG * mC * mU	GUCCCTGCTGCCCGGUUGCU	XXXXXXXXXXXXXXXXXXX
WV-3628	mC * mC * mU * mG * mC * T * G * C * C * C * C * G * G * T * T * G * mC * mU * mU * mC * mU	CCUGCTGCCCGGTTGCUUCU	XXXXXXXXXXXXXXXXXXX
WV-3629	mC * mC * mG * mC * mA * G * C * C * C * T * G * T * A * G * C * A * mA * mG * mC * mU * mC	CCGCAGCCTGTAGCAAGCUC	XXXXXXXXXXXXXXXXXXX
WV-3630	mG * mC * mG * mG * mU * T * G * C * C * G * G * T * G * C * C * C * T * mG * mC * mG * mC * mC	GCGGUTGCGGTGCCTGCGCC	XXXXXXXXXXXXXXXXXXX
WV-3631	mG * mU * mU * mG * mC * G * G * T * T * G * C * C * T * G * C * C * G * mC * mC * mC * mG * mC	GUUGCGGTGCCTGCGCCCGC	XXXXXXXXXXXXXXXXXXX
WV-3632	mG * mG * mC * mG * mG * A * G * G * C * G * C * A * G * G * C * mG * mG * mU * mG * mG	GGCGGAGGCGCAGGCGGUGG	XXXXXXXXXXXXXXXXXXX
WV-3633	mG * mC * mA * mG * mG * C * G * G * T * G * G * C * G * A * G * mU * mG * mG * mG * mU	GCAGGCGGTGGCGAGUGGGU	XXXXXXXXXXXXXXXXXXX
WV-3634	mG * mC * mG * mG * mC * A * T * C * C * T * G * G * C * G * G * mG * mU * mG * mG * mC	GCGGCATCCTGGCGGGUGGC	XXXXXXXXXXXXXXXXXXX
WV-3635	mG * mC * mA * mU * mC * C * T * G * G * C * G * G * G * T * G * mG * mC * mU * mG * mU	GCAUCCTGGCGGGTGGCUGU	XXXXXXXXXXXXXXXXXXX
WV-3636	mG * mG * mG * mC * mU * C * T * C * C * T * C * A * G * A * G * mC * mU * mC * mG *	GGGCUCTCCTCAGAGCUCGA	XXXXXXXXXXXXXXXXXXX

	mA		
WV-3637	mG * mC * mU * mG * mG * G * T * G * T * C * G * G * C * T * mU * mU * mC * mG * mC	GCUGGGTGTCGGGCTUUCGC	XXXXXXXXXXXXXXXXXXXX
WV-3638	mG * mG * mG * mU * mG * T * C * G * G * G * C * T * T * T * C * mG * mC * mC * mU * mC	GGGUGTCGGGCTTTCGCCUC	XXXXXXXXXXXXXXXXXXXX
WV-3639	mA * mU * mU * mG * mC * C * T * G * C * A * T * C * C * G * G * mG * mC * mC * mC * mC	AUUGCCTGCATCCGGGCCCC	XXXXXXXXXXXXXXXXXXXX
WV-3640	mU * mG * mC * mC * mU * G * C * A * T * C * C * G * G * G * C * mC * mC * mC * mG * mG	UGCCUGCATCCGGGCCCCGG	XXXXXXXXXXXXXXXXXXXX
WV-3641	mG * mC * mA * mU * mC * C * G * G * G * C * C * C * C * G * G * mG * mC * mU * mU * mC	GCAUCCGGGCCCCGGGCUUC	XXXXXXXXXXXXXXXXXXXX
WV-3642	mC * mU * mU * mC * mC * T * T * G * C * T * T * C * C * C * mG * mC * mC * mC * mU	CUUCCTTGCTTTCCCGCCCU	XXXXXXXXXXXXXXXXXXXX
WV-3643	mU * mC * mC * mU * mU * G * C * T * T * T * T * C * C * C * G * C * mC * mU * mC * mA	UCCUUGCTTTCCCGCCCUCA	XXXXXXXXXXXXXXXXXXXX
WV-3644	mG * mC * mU * mU * mU * C * C * C * G * C * C * C * T * C * A * mG * mU * mA * mC * mC	GCUUUCCCGCCCTCAGUACC	XXXXXXXXXXXXXXXXXXXX
WV-3645	mG * mC * mC * mC * mU * C * A * G * T * A * C * C * C * G * A * mG * mC * mU * mG * mU	GCCCUCAGTACCCGAGCUGU	XXXXXXXXXXXXXXXXXXXX
WV-3646	mA * mC * mC * mC * mG * A * G * C * T * G * T * C * T * C * C * mU * mU * mC * mC * mC	ACCCGAGCTGTCTCCUUCCC	XXXXXXXXXXXXXXXXXXXX
WV-3647	mG * mG * mA * mC * mC * C * G * C * T * G * G * G * A * G * C * mG * mC * mU * mG * mC	GGACCCGCTGGGAGCGCUGC	XXXXXXXXXXXXXXXXXXXX
WV-3648	mG * mG * mG * mA * mA * G * G * C * C * C * G * G * A * G * G * mU * mG * mG * mG	GGGAAGGCCGGAGGGUGGGC	XXXXXXXXXXXXXXXXXXXX

	* mC		
WV-3649	mG * mG * mU * mC * mC * C * T * G * C * C * G * G * C * G * A * mG * mG * mA * mG * mA	GGUCCCTGCCGGCGAGGAGA	XXXXXXXXXXXXXXXXXXX
WV-3650	mG * mU * mC * mG * mG * T * G * T * G * C * T * C * C * C * C * mA * mU * mU * mU * mC * mU	GUCGGTGTGCTCCCCAUUCU	XXXXXXXXXXXXXXXXXXX
WV-3651	mG * mU * mG * mC * mU * C * C * C * C * A * T * T * C * T * G * mU * mG * mG * mG * mA	GUGCUCCCCATTCTGUGGGA	XXXXXXXXXXXXXXXXXXX
WV-3652	mC * mC * mU * mG * mG * T * T * G * C * C * T * C * C * A * C * A * mG * mC * mU * mC * mC	CCUGGTTGCTTCACAGCUCC	XXXXXXXXXXXXXXXXXXX
WV-3653	mG * mU * mC * mC * mC * mG * T * G * T * G * C * T * C * C * A * T * T * mG * mG * mG * mU * mC	GUCCGTGTGCTCATTGGGUC	XXXXXXXXXXXXXXXXXXX
WV-3654	mG * mG * mG * mG * mA * mG * G * T * C * C * C * T * G * C * C * A * C * T * mU * mU * mC * mC * mC	GGGAGGTCCTGCACTUUCCC	XXXXXXXXXXXXXXXXXXX
WV-3655	mC * mC * mU * mC * mU * G * C * C * C * A * A * G * G * C * C * C * T * mG * mC * mC * mA * mC	CCUCUGCCAAGGCCTGCCAC	XXXXXXXXXXXXXXXXXXX
WV-3656	mA * mG * mU * mG * mG * T * C * C * C * T * G * G * C * A * G * mC * mU * mC * mC * mU	AGUGGTCCTGGGCAGCUCCU	XXXXXXXXXXXXXXXXXXX
WV-3657	mG * mCmUmGmG * A * G * A * T * G * G * C * G * G * T * mGmGmGmC * mA	GCUGGAGATGGCGGTGGGCA	X0O0XXXXXXXXXXXX0O0X
WV-3658	mC * mUmGmUmU * C * T * G * T * C * T * mC * T * T * G * G * mAmGmCmC * mC	CUGUUCTGTCTTTGGAGCCC	X0O0XXXXXXXXXXXX0O0X
WV-3659	mU * mCmCmCmC * A * T * T * C * C * C * A * G * T * T * T * mCmCmAmU * mC	UCCCCATTCCAGTTTCCAUC	X0O0XXXXXXXXXXXX0O0X
WV-3660	mG * mAmUmCmC * C * C * A * T * T * C * C * A * G * T * mUmUmCmC * mA	GAUCCCCATTCCAGTUUCCA	X0O0XXXXXXXXXXXX0O0X
WV-3661	mG * mCmUmGmC * G * A * T * C * C * C * C * A * T * T * mCmCmAmG * mU	GCUGCGATCCCCATTCCAGU	X0O0XXXXXXXXXXXX0O0X
WV-	mG * mUmGmCmU * G * C * G * A * T * C *	GUGCUGCGATCCCCAUUCCA	X0O0XXXXXXXXXXXX0O0X

3662	C * C * C * A * mUmUmCmC * mA		
WV-3663	mU * mGmUmGmC * T * G * C * G * A * T * C * C * C * mAmUmUmC * mC	UGUGCTGCGATCCCCAUUCC	X0O0XXXXXXXXXX0O0X
WV-3664	mC * mAmGmGmG * T * G * G * C * A * T * C * T * G * C * mUmUmCmA * mC	CAGGGTGGCATCTGCUUCAC	X0O0XXXXXXXXXXX0O0X
WV-3665	mG * mAmCmAmG * G * G * T * G * G * C * A * T * C * T * mGmCmUmU * mC	GACAGGGTGGCATCTGCUUC	X0O0XXXXXXXXXXX0O0X
WV-3666	mA * mGmGmCmU * G * T * C * A * G * C * T * C * G * G * mAmUmCmU * mC	AGGCUGTCAGCTCGGAUCUC	X0O0XXXXXXXXXXX0O0X
WV-3667	mG * mGmCmUmC * T * C * C * A * G * A * A * G * C * mUmGmUmC * mA	GGCUCTCCAGAAGGCUGUCA	X0O0XXXXXXXXXXX0O0X
WV-3668	mG * mUmGmGmC * T * C * T * C * C * A * G * A * A * G * mGmCmUmG * mU	GUGGCTCTCCAGAAGGCUGU	X0O0XXXXXXXXXXX0O0X
WV-3669	mU * mUmUmCmC * C * C * A * C * A * C * C * A * C * T * mGmAmGmC * mU	UUUCCCCACACCACTGAGCU	X0O0XXXXXXXXXXX0O0X
WV-3670	mC * mCmCmCmU * C * A * C * A * G * G * G * C * T * C * T * mUmGmUmG * mA	CCCCUCACAGGCTCTUGUGA	X0O0XXXXXXXXXXX0O0X
WV-3671	mU * mCmCmCmC * T * C * A * C * A * G * G * C * T * C * mUmUmGmU * mG	UCCCCTCACAGGCTCUUGUG	X0O0XXXXXXXXXXX0O0X
WV-3672	mA * mUmCmCmC * C * T * C * A * C * A * G * G * C * T * mCmUmUmG * mU	AUCCCCTCACAGGCTCUUGU	X0O0XXXXXXXXXXX0O0X
WV-3673	mA * mCmAmUmC * C * C * C * T * C * A * C * A * G * G * mCmUmUmC * mU	ACAUCCCCTCACAGGCUCUU	X0O0XXXXXXXXXXX0O0X
WV-3674	mG * mAmCmAmU * C * C * C * C * T * C * A * C * A * G * mGmCmUmC * mU	GACAUCCCCTCACAGGCUCU	X0O0XXXXXXXXXXX0O0X
WV-3675	mC * mUmGmAmC * A * T * C * C * C * C * T * C * A * C * mAmGmGmC * mU	CUGACATCCCCTCACAGGCU	X0O0XXXXXXXXXXX0O0X
WV-3676	mG * mAmUmGmC * A * C * C * T * G * A * C * A * T * C * mCmCmCmU * mC	GAUGCACCTGACATCCCCUC	X0O0XXXXXXXXXXX0O0X
WV-3677	mG * mCmAmCmC * T * C * T * C * T * T * T * C * C * T * mAmGmCmG * mG	GCACCTCTCTTTCCTAGCGG	X0O0XXXXXXXXXXX0O0X
WV-3678	mG * mGmGmCmA * G * C * A * G * G * G * A * C * G * G * mCmUmGmA * mC	GGGCAGCAGGGACGGCUGAC	X0O0XXXXXXXXXXX0O0X
WV-3679	mU * mGmCmUmA * G * A * C * C * C * C * G * C * C * C * mCmCmAmA * mA	UGCUAGACCCCGCCCCCAAA	X0O0XXXXXXXXXXX0O0X
WV-	mU * mCmUmUmG * C * T * A * G * A * C *	UCUUGCTAGACCCCGCCCCC	X0O0XXXXXXXXXXX0O0X

3680	C * C * C * G * mCmCmCmC * mC		
WV-3681	mG * mCmUmCmU * T * G * C * T * A * G * A * C * C * mCmGmCmC * mC	GCUCUTGCTAGACCCCGCCC	X0O0XXXXXXXXXX0O0X
WV-3682	mC * mUmGmCmU * C * T * T * G * C * T * A * G * A * C * mCmCmCmG * mC	CUGCUCTTGCTAGACCCCGC	X0O0XXXXXXXXXX0O0X
WV-3683	mG * mCmGmGmU * T * G * T * T * T * C * C * C * T * C * mCmUmUmG * mU	GCGGUTGTTTCCCTCCUUGU	X0O0XXXXXXXXXX0O0X
WV-3684	mG * mCmUmGmC * G * G * T * T * G * T * T * T * C * C * C * mCmUmCmC * mU	GCUGCGGTTGTTTCCCUCCU	X0O0XXXXXXXXXX0O0X
WV-3685	mG * mGmCmUmG * C * G * G * T * T * G * T * T * T * C * C * mCmCmUmC * mC	GGCUGCGGTTGTTTCCCUCC	X0O0XXXXXXXXXX0O0X
WV-3686	mC * mAmGmGmC * T * G * C * G * G * T * T * G * T * T * T * mUmCmCmC * mU	CAGGCTGCGGTTGTTUCCCU	X0O0XXXXXXXXXX0O0X
WV-3687	mU * mCmAmCmU * C * A * C * C * C * A * C * T * C * G * G * mCmCmAmC * mC	UCACUCACCCACTCGCCACC	X0O0XXXXXXXXXX0O0X
WV-3688	mC * mCmUmCmA * C * T * C * A * C * C * C * A * C * T * mCmGmCmC * mA	CCUCACTCACCCACTCGCCA	X0O0XXXXXXXXXX0O0X
WV-3689	mG * mGmAmUmG * C * C * G * C * C * T * C * C * T * C * mAmCmUmC * mA	GGAUGCCGCCTCCTCACUCA	X0O0XXXXXXXXXX0O0X
WV-3690	mG * mCmCmAmG * G * A * T * G * C * C * C * G * C * C * T * mCmCmUmC * mA	GCCAGGATGCCGCCTCCUCA	X0O0XXXXXXXXXX0O0X
WV-3691	mC * mCmCmCmA * A * A * C * A * G * C * C * A * C * C * mCmGmCmC * mA	CCCCAAACAGCCACCCGCCA	X0O0XXXXXXXXXX0O0X
WV-3692	mG * mAmGmAmG * C * C * C * C * C * G * C * T * T * C * mUmAmCmC * mC	GAGAGCCCCCGCTTCUACCC	X0O0XXXXXXXXXX0O0X
WV-3693	mG * mCmUmCmU * G * A * G * G * A * G * A * G * C * C * mCmCmCmG * mC	GCUCUGAGGAGAGCCCCCGC	X0O0XXXXXXXXXX0O0X
WV-3694	mG * mAmGmCmU * C * T * G * A * G * G * A * G * G * mCmCmCmC * mC	GAGCUCTGAGGAGAGCCCCC	X0O0XXXXXXXXXX0O0X
WV-3695	mG * mAmUmCmC * C * C * A * T * C * C * C * T * T * G * mUmCmCmC * mU	GAUCCCCATCCCTTGUCCCU	X0O0XXXXXXXXXX0O0X
WV-3696	mG * mCmCmAmG * A * T * C * C * C * C * C * A * T * C * C * mCmUmUmG * mU	GCCAGATCCCCATCCCUUGU	X0O0XXXXXXXXXX0O0X
WV-3697	mG * mAmGmGmC * C * A * G * A * T * C * C * C * C * A * mUmCmCmC * mU	GAGGCCAGATCCCCAUCCCU	X0O0XXXXXXXXXX0O0X
WV-	mG * mGmCmUmC * C * C * T * T * T * C	GGCUCCCTTTTCTCGAGCCC	X0O0XXXXXXXXXX0O0X

3698	* T * C * G * mAmGmCmC * mC		
WV-3699	mG * mUmAmCmC * C * G * A * G * G * C * T * C * C * C * mUmUmUmU * mC	GUACCCGAGGCTCCCUUUUC	X0O0XXXXXXXXXX0O0X
WV-3700	mC * mUmCmAmG * T * A * C * C * C * G * A * G * G * C * mUmCmCmC * mU	CUCAGTACCCGAGGCUCCCU	X0O0XXXXXXXXXXX0O0X
WV-3701	mU * mCmUmCmA * G * T * A * C * C * C * C * G * A * G * G * mCmUmCmC * mC	UCUCAGTACCCGAGGCUCCC	X0O0XXXXXXXXXXX0O0X
WV-3702	mG * mCmCmUmC * T * C * A * G * T * A * C * C * C * G * mAmGmGmC * mU	GCCUCTCAGTACCCGAGGCU	X0O0XXXXXXXXXXX0O0X
WV-3703	mG * mGmCmCmU * C * T * C * A * G * T * A * C * C * C * mGmAmGmG * mC	GGCCUCTCAGTACCCGAGGC	X0O0XXXXXXXXXXX0O0X
WV-3704	mC * mCmUmCmC * G * G * C * C * T * T * C * C * C * C * mCmAmGmG * mC	CCUCCGGCCTTCCCCCAGGC	X0O0XXXXXXXXXXX0O0X
WV-3705	mA * mCmCmCmU * C * C * G * G * G * C * C * T * T * C * C * mCmCmCmA * mG	ACCCUCCGGCCTTCCCCCAG	X0O0XXXXXXXXXXX0O0X
WV-3706	mC * mCmAmCmC * C * T * C * C * G * G * C * C * C * T * T * mCmCmCmC * mC	CCACCCTCCGGCCTTCCCCC	X0O0XXXXXXXXXXX0O0X
WV-3707	mA * mCmCmCmC * C * A * T * C * T * C * A * T * C * C * mCmGmCmA * mU	ACCCCCATCTCATCCCGCAU	X0O0XXXXXXXXXXX0O0X
WV-3708	mC * mAmCmCmC * C * C * A * T * C * T * C * A * T * T * C * mCmCmGmC * mA	CACCCCCATCTCATCCCGCA	X0O0XXXXXXXXXXX0O0X
WV-3709	mG * mGmCmCmGmU * C * T * C * C * A * C * A * C * C * C * mCmCmAmU * mC	GGCGUCTCCACACCCCCAUC	X0O0XXXXXXXXXXX0O0X
WV-3710	mG * mCmAmGmG * C * G * T * C * T * C * C * A * C * A * mCmCmCmC * mC	GCAGGCGTCTCCACACCCCC	X0O0XXXXXXXXXXX0O0X
WV-3711	mG * mUmGmCmA * G * G * C * G * T * C * T * C * C * A * mCmAmCmC * mC	GUGCAGGCGTCTCCACACCC	X0O0XXXXXXXXXXX0O0X
WV-3712	mC * mCmGmAmC * T * T * G * C * A * T * T * G * C * T * mGmCmCmC * mU	CCGACTTGCATTGCTGCCCU	X0O0XXXXXXXXXXX0O0X
WV-3713	mG * mCmAmGmG * A * C * C * T * C * C * C * T * C * C * mUmGmUmU * mU	GCAGGACCTCCCTCCTGUUU	X0O0XXXXXXXXXXX0O0X
WV-3714	mG * mUmGmCmA * G * G * A * C * C * T * C * C * C * T * mCmCmUmG * mU	GUGCAGGACCTCCCTCCTGU	X0O0XXXXXXXXXXX0O0X
WV-3715	mA * mGmGmGmC * C * A * C * C * C * C * T * C * C * T * mGmGmGmA * mA	AGGGCCACCCCTCCTGGGAA	X0O0XXXXXXXXXXX0O0X
WV-	mG * mGmCmCmU * T * G * G * C * A * G *	GGCCUTGGCAGAGGTGGUGA	X0O0XXXXXXXXXXX0O0X

3716	A * G * G * T * mGmGmUmG * mA		
WV-3717	mG * mUmGmGmC * A * G * G * C * C * T * T * G * G * C * mAmGmAmG * mG	GUGGCAGGCCTTGGCAGAGG	X0O0XXXXXXXXXX0O0X
WV-3718	mG * mAmGmCmU * G * C * C * C * A * G * G * A * C * C * mAmCmUmU * mC	GAGCUGCCCAGGACCACUUC	X0O0XXXXXXXXXXXX0O0X
WV-3719	mG * mCmUmUmUmG * G * T * G * T * G * T * C * A * G * C * mCmGmUmC * mC	GCUUGGTGTGTCAGCCGUCC	X0O0XXXXXXXXXXXX0O0X
WV-3720	mC * mUmUmGmG * T * G * T * G * T * C * A * G * C * C * mGmUmCmC * mC	CUUGGTGTGTCAGCCGUCCC	X0O0XXXXXXXXXXXX0O0X
WV-3721	mG * mUmCmAmG * C * C * G * T * C * C * C * T * G * C * mUmGmCmC * mC	GUCAGCCGTCCCTGCUGCCC	X0O0XXXXXXXXXXXX0O0X
WV-3722	mG * mCmCmGmU * C * C * C * T * G * G * C * T * G * C * C * mCmGmGmU * mU	GCCGUCCCTGCTGCCCGGUU	X0O0XXXXXXXXXXXX0O0X
WV-3723	mG * mUmCmCmC * T * G * C * T * G * C * C * C * G * G * mUmUmGmC * mU	GUCCCTGCTGCCCGGUUGCU	X0O0XXXXXXXXXXXX0O0X
WV-3724	mC * mCmUmGmC * T * G * C * C * C * C * G * G * T * T * G * mCmUmUmC * mU	CCUGCTGCCCGGTTGCUUCU	X0O0XXXXXXXXXXXX0O0X
WV-3725	mC * mCmGmCmA * G * C * C * T * G * T * A * G * C * A * mAmGmCmU * mC	CCGCAGCCTGTAGCAAGCUC	X0O0XXXXXXXXXXXX0O0X
WV-3726	mG * mCmGmGmU * T * G * C * G * G * T * G * C * C * T * mGmCmGmC * mC	GCGGUTGCGGTGCCTGCGCC	X0O0XXXXXXXXXXXX0O0X
WV-3727	mG * mUmUmGmC * G * G * T * G * C * C * T * G * C * G * mCmCmCmG * mC	GUUGCGGTGCCTGCGCCCGC	X0O0XXXXXXXXXXXX0O0X
WV-3728	mG * mGmCmGmG * A * G * G * C * G * C * A * G * G * C * mGmGmUmG * mG	GGCGGAGGCGCAGGCGGUGG	X0O0XXXXXXXXXXXX0O0X
WV-3729	mG * mCmAmGmG * C * G * G * T * G * G * C * G * A * G * mUmGmGmG * mU	GCAGGCGGTGGCGAGUGGGU	X0O0XXXXXXXXXXXX0O0X
WV-3730	mG * mCmGmGmC * A * T * C * C * T * G * G * C * G * G * mGmUmGmG * mC	GCGGCATCCTGGCGGGUGGC	X0O0XXXXXXXXXXXX0O0X
WV-3731	mG * mCmAmUmC * C * T * G * G * C * G * G * T * G * mGmCmUmG * mU	GCAUCCTGGCGGGTGGCUGU	X0O0XXXXXXXXXXXX0O0X
WV-3732	mG * mGmGmCmU * C * T * C * C * T * C * A * G * A * G * mCmUmUmCmG * mA	GGGCUCTCCTCAGAGCUCGA	X0O0XXXXXXXXXXXX0O0X
WV-3733	mG * mCmUmGmG * G * T * G * T * C * G * G * G * C * T * mUmUmUmCmG * mC	GCUGGGTGTCGGGCTTUCGC	X0O0XXXXXXXXXXXX0O0X
WV-	mG * mGmGmUmG * T * C * G * G * G * C *	GGGUGTCGGGCTTTCGCCUC	X0O0XXXXXXXXXXXX0O0X

3734	T * T * T * C * mGmCmCmU * mC		
WV-3735	mA * mUmUmGmC * C * T * G * C * A * T * C * C * G * G * mGmCmCmC * mC	AUUGCCTGCATCCGGGCCCC	X0O0XXXXXXXXXXX0O0X
WV-3736	mU * mGmCmCmU * G * C * A * T * C * C * G * G * G * C * mCmCmCmG * mG	UGCCUGCATCCGGGCCCCGG	X0O0XXXXXXXXXXXX0O0X
WV-3737	mG * mCmAmUmC * C * G * G * G * C * C * C * C * G * G * mGmCmUmU * mC	GCAUCCGGGCCCCGGGCUUC	X0O0XXXXXXXXXXXX0O0X
WV-3738	mC * mUmUmCmC * T * T * G * C * T * T * T * T * C * C * C * mGmCmCmC * mU	CUUCCTTGCTTTCCCGCCCU	X0O0XXXXXXXXXXXX0O0X
WV-3739	mU * mCmCmUmU * G * C * T * T * T * C * C * C * G * C * mCmCmUmC * mA	UCCUUGCTTTCCCGCCCUCA	X0O0XXXXXXXXXXXX0O0X
WV-3740	mG * mCmUmUmU * C * C * C * G * C * C * C * T * C * A * mGmUmAmC * mC	GCUUUCCCGCCCTCAGUACC	X0O0XXXXXXXXXXXX0O0X
WV-3741	mG * mCmCmCmU * C * A * G * T * A * C * C * C * G * A * mGmCmUmG * mU	GCCCUCAGTACCCGAGCUGU	X0O0XXXXXXXXXXXX0O0X
WV-3742	mA * mCmCmCmG * A * G * C * T * G * T * C * T * C * C * mUmUmCmC * mC	ACCCGAGCTGTCTCCUUCCC	X0O0XXXXXXXXXXXX0O0X
WV-3743	mG * mGmAmCmC * C * G * C * T * G * G * G * A * G * C * mGmCmUmG * mC	GGACCCGCTGGGAGCGCUGC	X0O0XXXXXXXXXXXX0O0X
WV-3744	mG * mGmGmAmA * G * G * C * C * G * G * A * G * G * G * mUmGmGmG * mC	GGGAAGGCCGGAGGGUGGGC	X0O0XXXXXXXXXXXX0O0X
WV-3745	mG * mGmUmCmC * C * T * G * C * C * C * G * G * C * G * A * mGmGmAmG * mA	GGUCCCTGCCGGCGAGGAGA	X0O0XXXXXXXXXXXX0O0X
WV-3746	mG * mUmCmGmG * T * G * T * G * C * T * C * C * C * C * mAmUmUmC * mU	GUCGGTGTGCTCCCCAUUCU	X0O0XXXXXXXXXXXX0O0X
WV-3747	mG * mUmGmCmU * C * C * C * C * C * A * T * T * C * T * G * mUmGmGmG * mA	GUGCUCCCCCATTCTGUGGGA	X0O0XXXXXXXXXXXX0O0X
WV-3748	mC * mCmUmGmG * T * T * G * C * C * T * T * T * C * A * C * A * mGmCmUmC * mC	CCUGGTTGCTTCACAGCUCC	X0O0XXXXXXXXXXXX0O0X
WV-3749	mG * mUmCmCmG * T * G * T * G * C * C * T * C * A * T * T * T * mGmGmGmU * mC	GUCCGTGTGCTCATTGGGUC	X0O0XXXXXXXXXXXX0O0X
WV-3750	mG * mGmGmAmG * G * T * C * C * T * T * G * C * A * C * T * mUmUmUmCmC * mC	GGGAGGTCCTGCACTUUCCC	X0O0XXXXXXXXXXXX0O0X
WV-3751	mC * mCmUmCmU * G * C * C * A * A * G * G * C * C * T * mGmGmCmCmA * mC	CCUCUGCCAAGGCCTGCCAC	X0O0XXXXXXXXXXXX0O0X
WV-	mA * mGmUmGmG * T * C * C * T * G * G *	AGUGGTCCTGGGCAGCUCCU	X0O0XXXXXXXXXXXX0O0X

3752	G * C * A * G * mCmUmCmC * mU		
WV-5905	Geo * m5Ceo * Teo * Geo * Geo * A * G * A * T * G * G * C * G * G * T * Geo * Geo * Geo * m5Ceo * Aeo	GCTGGAGATGGCGGTGGGCA	XXXXXXXXXXXXXXXXXXXX
WV-5906	m5Ceo * Teo * Geo * Teo * Teo * C * T * G * T * C * T * T * T * G * G * Aeo * Geo * m5Ceo * m5Ceo * m5Ceo	CTGTTCTGTCTTTGGAGCCC	XXXXXXXXXXXXXXXXXXXX
WV-5907	Teo * m5Ceo * m5Ceo * m5Ceo * m5Ceo * A * T * T * C * C * A * G * T * T * T * m5Ceo * m5Ceo * Aeo * Teo * m5Ceo	TCCCCATTCCAGTTTCCATC	XXXXXXXXXXXXXXXXXXXX
WV-5908	Geo * Aeo * Teo * m5Ceo * m5Ceo * C * C * A * T * T * C * C * A * G * T * Teo * Teo * m5Ceo * m5Ceo * Aeo	GATCCCCATTCCAGTTTCCA	XXXXXXXXXXXXXXXXXXXX
WV-5909	Geo * m5Ceo * Teo * Geo * m5Ceo * G * A * T * C * C * C * C * A * T * T * m5Ceo * m5Ceo * Aeo * Geo * Teo	GCTGCGATCCCCATTCCAGT	XXXXXXXXXXXXXXXXXXXX
WV-5910	Geo * Teo * Geo * m5Ceo * Teo * G * C * G * A * T * C * C * C * C * A * Teo * Teo * m5Ceo * m5Ceo * Aeo	GTGCTGCGATCCCCATTCCA	XXXXXXXXXXXXXXXXXXXX
WV-5911	Teo * Geo * Teo * Geo * m5Ceo * T * G * C * G * A * T * C * C * C * C * Aeo * Teo * Teo * m5Ceo * m5Ceo	TGTGCTGCGATCCCCATTCC	XXXXXXXXXXXXXXXXXXXX
WV-5912	m5Ceo * Aeo * Geo * Geo * Geo * T * G * G * C * A * T * C * T * G * C * Teo * Teo * m5Ceo * Aeo * m5Ceo	CAGGGTGGCATCTGCTTCAC	XXXXXXXXXXXXXXXXXXXX
WV-5913	Geo * Aeo * m5Ceo * Aeo * Geo * G * G * T * G * G * C * A * T * C * T * Geo * m5Ceo * Teo * Teo * m5Ceo	GACAGGGTGGCATCTGCTTC	XXXXXXXXXXXXXXXXXXXX
WV-5914	Aeo * Geo * Geo * m5Ceo * Teo * G * T * C * A * G * C * T * C * G * G * Aeo * Teo * m5Ceo * Teo * m5Ceo	AGGCTGTCAGCTCGGATCTC	XXXXXXXXXXXXXXXXXXXX
WV-5915	Geo * Geo * m5Ceo * Teo * m5Ceo * T * C * C * A * G * A * A * G * G * C * Teo * Geo * Teo * m5Ceo * Aeo	GGCTCTCCAGAAGGCTGTCA	XXXXXXXXXXXXXXXXXXXX
WV-5916	Geo * Teo * Geo * Geo * m5Ceo * T * C * T * C * C * A * G * A * A * G * Geo * m5Ceo *	GTGGCTCTCCAGAAGGCTGT	XXXXXXXXXXXXXXXXXXXX

	Teo * Geo * Teo		
WV-5917	Teo * Teo * Teo * m5Ceo * m5Ceo * C * C * A * C * A * C * C * A * C * T * Geo * Aeo * Geo * m5Ceo * Teo	TTTCCCCACACCACTGAGCT	XXXXXXXXXXXXXXXXXXX
WV-5918	m5Ceo * m5Ceo * m5Ceo * m5Ceo * m5Ceo * Teo * C * A * C * A * G * G * C * T * C * T * Teo * Geo * Teo * Geo * Aeo	CCCCTCACAGGCTCTTGTGA	XXXXXXXXXXXXXXXXXXX
WV-5919	Teo * m5Ceo * m5Ceo * m5Ceo * m5Ceo * m5Ceo * T * C * A * C * A * G * G * C * T * C * Teo * Teo * Geo * Teo * Geo	TCCCCTCACAGGCTCTTGTG	XXXXXXXXXXXXXXXXXXX
WV-5920	Aeo * Teo * m5Ceo * m5Ceo * m5Ceo * C * T * C * A * C * A * G * G * C * T * m5Ceo * Teo * Teo * Geo * Teo	ATCCCCTCACAGGCTCTTGT	XXXXXXXXXXXXXXXXXXX
WV-5921	Aeo * m5Ceo * Aeo * Teo * m5Ceo * C * C * C * C * T * C * A * C * A * G * G * m5Ceo * Teo * m5Ceo * Teo * Teo	ACATCCCCTCACAGGCTCTT	XXXXXXXXXXXXXXXXXXX
WV-5922	Geo * Aeo * m5Ceo * Aeo * Teo * C * C * C * C * T * C * A * C * A * G * Geo * m5Ceo * Teo * m5Ceo * Teo	GACATCCCCTCACAGGCTCT	XXXXXXXXXXXXXXXXXXX
WV-5923	m5Ceo * Teo * Geo * Aeo * m5Ceo * A * T * C * C * C * C * T * C * A * C * Aeo * Geo * Geo * m5Ceo * Teo	CTGACATCCCCTCACAGGCT	XXXXXXXXXXXXXXXXXXX
WV-5924	Geo * Aeo * Teo * Geo * m5Ceo * A * C * C * T * G * A * C * A * T * C * m5Ceo * m5Ceo * m5Ceo * Teo * m5Ceo	GATGCACCTGACATCCCCTC	XXXXXXXXXXXXXXXXXXX
WV-5925	Geo * m5Ceo * Aeo * m5Ceo * m5Ceo * T * C * T * C * T * T * T * C * C * T * Aeo * Geo * m5Ceo * Geo * Geo	GCACCTCTCTTTCCTAGCGG	XXXXXXXXXXXXXXXXXXX
WV-5926	Geo * Geo * Geo * m5Ceo * Aeo * G * C * A * G * G * G * A * C * G * G * m5Ceo * Teo * Geo * Aeo * m5Ceo	GGGCAGCAGGGACGGCTGAC	XXXXXXXXXXXXXXXXXXX
WV-5927	Teo * Geo * m5Ceo * Teo * Aeo * G * A * C * C * C * C * G * C * C * C * m5Ceo * m5Ceo * Aeo * Aeo * Aeo	TGCTAGACCCCGCCCCCAAA	XXXXXXXXXXXXXXXXXXX
WV-5928	Teo * m5Ceo * Teo * Teo * Geo * C * T * A * G * A * C * C * C * C * G * m5Ceo * m5Ceo *	TCTTGCTAGACCCCGCCCCC	XXXXXXXXXXXXXXXXXXX

	m5Ceo * m5Ceo * m5Ceo		
WV-5929	Geo * m5Ceo * Teo * m5Ceo * Teo * T * G * C * T * A * G * A * C * C * C * m5Ceo * Geo * m5Ceo * m5Ceo * m5Ceo	GCTCTTGCTAGACCCCGCCC	XXXXXXXXXXXXXXXXXXX
WV-5930	m5Ceo * Teo * Geo * m5Ceo * Teo * C * T * T * G * C * T * A * G * A * C * m5Ceo * m5Ceo * m5Ceo * Geo * m5Ceo	CTGCTCTTGCTAGACCCCGC	XXXXXXXXXXXXXXXXXXX
WV-5931	Geo * m5Ceo * Geo * Geo * Teo * T * G * T * T * T * C * C * C * T * C * m5Ceo * Teo * Teo * Geo * Teo	GCGGTTGTTTCCCTCCTTGT	XXXXXXXXXXXXXXXXXXXX
WV-5932	Geo * m5Ceo * Teo * Geo * m5Ceo * G * G * T * T * G * T * T * T * T * C * C * m5Ceo * Teo * m5Ceo * m5Ceo * m5Ceo * Teo	GCTGCGGTTGTTTCCCTCCT	XXXXXXXXXXXXXXXXXXXX
WV-5933	Geo * Geo * m5Ceo * Teo * Geo * C * G * G * T * T * G * T * T * T * T * C * m5Ceo * m5Ceo * Teo * m5Ceo * m5Ceo * m5Ceo	GGCTGCGGTTGTTTCCCTCC	XXXXXXXXXXXXXXXXXXXX
WV-5934	m5Ceo * Aeo * Geo * Geo * m5Ceo * T * G * C * G * G * T * T * T * G * T * T * T * Teo * m5Ceo * m5Ceo * m5Ceo * m5Ceo * Teo	CAGGCTGCGGTTGTTTCCCT	XXXXXXXXXXXXXXXXXXXX
WV-5935	Teo * m5Ceo * Aeo * m5Ceo * Teo * C * A * C * C * C * A * C * T * C * G * m5Ceo * m5Ceo * Aeo * m5Ceo * m5Ceo	TCACTCACCCACTCGCCACC	XXXXXXXXXXXXXXXXXXXX
WV-5936	m5Ceo * m5Ceo * Teo * m5Ceo * Aeo * C * T * C * A * C * C * C * A * C * T * m5Ceo * Geo * m5Ceo * m5Ceo * m5Ceo * Aeo	CCTCACTCACCCACTCGCCA	XXXXXXXXXXXXXXXXXXXX
WV-5937	Geo * Geo * Aeo * Teo * Geo * C * C * G * C * C * T * C * C * T * C * Aeo * m5Ceo * Teo * m5Ceo * Aeo	GGATGCCGCCTCCTCACTCA	XXXXXXXXXXXXXXXXXXXX
WV-5938	Geo * m5Ceo * m5Ceo * Aeo * Geo * G * A * T * G * C * C * G * C * C * T * m5Ceo * m5Ceo * Teo * m5Ceo * Aeo	GCCAGGATGCCGCCTCCTCA	XXXXXXXXXXXXXXXXXXXX
WV-5939	m5Ceo * m5Ceo * m5Ceo * m5Ceo * Aeo * A * A * C * A * G * C * C * A * C * C * m5Ceo * Geo * m5Ceo * m5Ceo * Aeo	CCCCAAACAGCCACCCGCCA	XXXXXXXXXXXXXXXXXXXX
WV-5940	Geo * Aeo * Geo * Aeo * Geo * C * C * C * C * C * G * C * T * T * C * Teo * Aeo * m5Ceo *	GAGAGCCCCCGCTTCTACCC	XXXXXXXXXXXXXXXXXXXX

	m5Ceo * m5Ceo		
WV-5941	Geo * m5Ceo * Teo * m5Ceo * Teo * G * A * G * G * A * G * A * G * C * C * m5Ceo * m5Ceo * m5Ceo * Geo * m5Ceo	GCTCTGAGGAGAGCCCCCGC	XXXXXXXXXXXXXXXXXX
WV-5942	Geo * Aeo * Geo * m5Ceo * Teo * C * T * G * A * G * G * A * G * A * G * m5Ceo * m5Ceo * m5Ceo * m5Ceo * m5Ceo	GAGCTCTGAGGAGAGCCCCC	XXXXXXXXXXXXXXXXXXX
WV-5943	Geo * Aeo * Teo * m5Ceo * m5Ceo * C * C * A * T * C * C * C * T * T * G * Teo * m5Ceo * m5Ceo * m5Ceo * Teo	GATCCCCATCCCTTGTCCCT	XXXXXXXXXXXXXXXXXXX
WV-5944	Geo * m5Ceo * m5Ceo * Aeo * Geo * A * T * C * C * C * C * A * T * C * C * m5Ceo * Teo * Teo * Geo * Teo	GCCAGATCCCCATCCCTTGT	XXXXXXXXXXXXXXXXXXX
WV-5945	Geo * Aeo * Geo * Geo * m5Ceo * C * A * G * A * T * C * C * C * C * A * Teo * m5Ceo * m5Ceo * m5Ceo * m5Ceo * Teo	GAGGCCAGATCCCCATCCCT	XXXXXXXXXXXXXXXXXXX
WV-5946	Geo * Geo * m5Ceo * Teo * m5Ceo * C * C * T * T * T * T * C * T * C * G * Aeo * Geo * m5Ceo * m5Ceo * m5Ceo * m5Ceo	GGCTCCCTTTTCTCGAGCCC	XXXXXXXXXXXXXXXXXXX
WV-5947	Geo * Teo * Aeo * m5Ceo * m5Ceo * C * G * A * G * G * C * T * C * C * C * Teo * Teo * Teo * Teo * m5Ceo	GTACCCGAGGCTCCCTTTTC	XXXXXXXXXXXXXXXXXXX
WV-5948	m5Ceo * Teo * m5Ceo * Aeo * Geo * T * A * C * C * C * C * G * A * G * G * C * Teo * m5Ceo * m5Ceo * m5Ceo * m5Ceo * Teo	CTCAGTACCCGAGGCTCCCT	XXXXXXXXXXXXXXXXXXX
WV-5949	Teo * m5Ceo * Teo * m5Ceo * Aeo * G * T * A * C * C * C * C * G * A * G * G * m5Ceo * Teo * m5Ceo * m5Ceo * m5Ceo * m5Ceo	TCTCAGTACCCGAGGCTCCC	XXXXXXXXXXXXXXXXXXX
WV-5950	Geo * m5Ceo * m5Ceo * Teo * m5Ceo * T * C * A * G * T * A * C * C * C * G * Aeo * Geo * Geo * m5Ceo * Teo	GCCTCTCAGTACCCGAGGCT	XXXXXXXXXXXXXXXXXXX
WV-5951	Geo * Geo * m5Ceo * m5Ceo * Teo * C * T * C * A * G * T * A * C * C * C * Geo * Aeo * Geo * Geo * m5Ceo	GGCCTCTCAGTACCCGAGGC	XXXXXXXXXXXXXXXXXXX
WV-5952	m5Ceo * m5Ceo * Teo * m5Ceo * m5Ceo * G * G * C * C * T * T * C * C * C * C * m5Ceo *	CCTCCGGCCTTCCCCCAGGC	XXXXXXXXXXXXXXXXXXX

	Aeo * Geo * Geo * m5Ceo		
WV-5953	Aeo * m5Ceo * m5Ceo * m5Ceo * Teo * C * C * G * G * C * C * T * T * C * C * m5Ceo * m5Ceo * m5Ceo * Aeo * Geo	ACCCTCCGGCCTTCCCCCAG	XXXXXXXXXXXXXXXXXXX
WV-5954	m5Ceo * m5Ceo * Aeo * m5Ceo * m5Ceo * C * T * C * C * G * G * C * C * T * T * m5Ceo * m5Ceo * m5Ceo * m5Ceo * m5Ceo	CCACCCTCCGGCCTTCCCCC	XXXXXXXXXXXXXXXXXXX
WV-5955	Aeo * m5Ceo * m5Ceo * m5Ceo * m5Ceo * C * A * T * C * T * C * A * T * C * C * m5Ceo * Geo * m5Ceo * Aeo * Teo	ACCCCCATCTCATCCCGCAT	XXXXXXXXXXXXXXXXXXX
WV-5956	m5Ceo * Aeo * m5Ceo * m5Ceo * m5Ceo * C * C * A * T * C * T * C * A * T * C * m5Ceo * m5Ceo * Geo * m5Ceo * Aeo	CACCCCCATCTCATCCCGCA	XXXXXXXXXXXXXXXXXXX
WV-5957	Geo * Geo * m5Ceo * Geo * Teo * C * T * C * C * A * C * A * C * C * C * m5Ceo * m5Ceo * m5Ceo * Aeo * Teo * m5Ceo	GGCGTCTCCACACCCCCATC	XXXXXXXXXXXXXXXXXXX
WV-5958	Geo * m5Ceo * Aeo * Geo * Geo * C * G * T * C * T * C * C * A * C * A * m5Ceo * m5Ceo * m5Ceo * m5Ceo * m5Ceo * m5Ceo	GCAGGCGTCTCCACACCCCC	XXXXXXXXXXXXXXXXXXX
WV-5959	Geo * Teo * Geo * m5Ceo * Aeo * G * G * C * G * T * C * T * C * C * C * A * m5Ceo * Aeo * m5Ceo * m5Ceo * m5Ceo * m5Ceo	GTGCAGGCGTCTCCACACCC	XXXXXXXXXXXXXXXXXXX
WV-5960	m5Ceo * m5Ceo * Geo * Aeo * m5Ceo * T * T * G * C * A * T * T * T * G * C * T * Geo * m5Ceo * m5Ceo * m5Ceo * m5Ceo * Teo	CCGACTTGCATTGCTGCCCT	XXXXXXXXXXXXXXXXXXX
WV-5961	Geo * m5Ceo * Aeo * Geo * Geo * A * C * C * T * C * C * C * T * C * C * Teo * Geo * Teo * Teo * Teo	GCAGGACCTCCCTCCTGTTT	XXXXXXXXXXXXXXXXXXX
WV-5962	Geo * Teo * Geo * m5Ceo * Aeo * G * G * A * C * C * T * C * C * C * T * m5Ceo * m5Ceo * Teo * Geo * Teo	GTGCAGGACCTCCCTCCTGT	XXXXXXXXXXXXXXXXXXX
WV-5963	Aeo * Geo * Geo * Geo * m5Ceo * C * A * C * C * C * C * T * C * C * T * Geo * Geo * Geo * Aeo * Aeo	AGGGCCACCCCTCCTGGGAA	XXXXXXXXXXXXXXXXXXX
WV-5964	Geo * Geo * m5Ceo * m5Ceo * Teo * T * G * G * C * A * G * A * G * T * Geo * Geo * Teo	GGCCTTGGCAGAGGTGGTGA	XXXXXXXXXXXXXXXXXXX

	* Geo * Aeo		
WV-5965	Geo * Teo * Geo * Geo * m5Ceo * A * G * G * C * C * T * T * G * G * C * Aeo * Geo * Aeo * Geo * Geo	GTGGCAGGCCTTGGCAGAGG	XXXXXXXXXXXXXXXXXXX
WV-5966	Geo * Aeo * Geo * m5Ceo * Teo * G * C * C * C * A * G * G * A * C * C * Aeo * m5Ceo * Teo * Teo * m5Ceo	GAGCTGCCCAGGACCACTTC	XXXXXXXXXXXXXXXXXXX
WV-5967	Geo * m5Ceo * Teo * Teo * Geo * G * T * G * T * G * T * C * A * G * C * m5Ceo * Geo * Teo * m5Ceo * m5Ceo	GCTTGGTGTGTCAGCCGTCC	XXXXXXXXXXXXXXXXXXX
WV-5968	m5Ceo * Teo * Teo * Geo * Geo * T * G * T * G * T * C * A * G * C * C * Geo * Teo * m5Ceo * m5Ceo * m5Ceo	CTTGGTGTGTCAGCCGTCCC	XXXXXXXXXXXXXXXXXXX
WV-5969	Geo * Teo * m5Ceo * Aeo * Geo * C * C * G * T * C * C * C * T * G * C * Teo * Geo * m5Ceo * m5Ceo * m5Ceo	GTCAGCCGTCCCTGCTGCCC	XXXXXXXXXXXXXXXXXXX
WV-5970	Geo * m5Ceo * m5Ceo * Geo * Teo * C * C * C * T * G * C * T * G * C * C * m5Ceo * Geo * Geo * Teo * Teo	GCCGTCCCTGCTGCCCGGTT	XXXXXXXXXXXXXXXXXXX
WV-5971	Geo * Teo * m5Ceo * m5Ceo * m5Ceo * T * G * C * T * G * C * C * C * G * G * Teo * Teo * Geo * m5Ceo * Teo	GTCCCTGCTGCCCGGTTGCT	XXXXXXXXXXXXXXXXXXX
WV-5972	m5Ceo * m5Ceo * Teo * Geo * m5Ceo * T * G * C * C * C * C * G * G * T * T * T * G * m5Ceo * Teo * Teo * m5Ceo * Teo	CCTGCTGCCCGGTTGCTTCT	XXXXXXXXXXXXXXXXXXX
WV-5973	m5Ceo * m5Ceo * Geo * m5Ceo * Aeo * G * C * C * C * T * G * T * A * G * C * A * Aeo * Geo * m5Ceo * Teo * m5Ceo	CCGCAGCCTGTAGCAAGCTC	XXXXXXXXXXXXXXXXXXX
WV-5974	Geo * m5Ceo * Geo * Geo * Teo * T * G * C * G * G * T * G * C * C * C * T * Geo * m5Ceo * Geo * m5Ceo * m5Ceo	GCGGTTGCGGTGCCTGCGCC	XXXXXXXXXXXXXXXXXXX
WV-5975	Geo * Teo * Teo * Geo * m5Ceo * G * G * T * G * C * C * T * G * C * G * m5Ceo * m5Ceo * m5Ceo * Geo * Geo * m5Ceo	GTTGCGGTGCCTGCGCCCGC	XXXXXXXXXXXXXXXXXXX
WV-5976	Geo * Geo * m5Ceo * Geo * Geo * A * G * G * C * G * C * A * G * G * C * Geo * Geo * Teo *	GGCGGAGGCGCAGGCGGTGG	XXXXXXXXXXXXXXXXXXX

	Geo * Geo		
WV-5977	Geo * m5Ceo * Aeo * Geo * Geo * C * G * G * T * G * G * C * G * A * G * Teo * Geo * Geo * Geo * Teo	GCAGGCGGTGGCGAGTGGGT	XXXXXXXXXXXXXXXXXXX
WV-5978	Geo * m5Ceo * Geo * Geo * m5Ceo * A * T * C * C * T * G * G * C * G * G * Geo * Teo * Geo * Geo * m5Ceo	GCGGCATCCTGGCGGGTGGC	XXXXXXXXXXXXXXXXXXX
WV-5979	Geo * m5Ceo * Aeo * Teo * m5Ceo * C * T * G * G * C * G * G * G * T * G * Geo * m5Ceo * Teo * Geo * Teo	GCATCCTGGCGGGTGGCTGT	XXXXXXXXXXXXXXXXXXX
WV-5980	Geo * Geo * Geo * m5Ceo * Teo * C * T * C * C * T * C * A * G * A * G * m5Ceo * Teo * m5Ceo * Geo * Aeo	GGGCTCTCCTCAGAGCTCGA	XXXXXXXXXXXXXXXXXXX
WV-5981	Geo * m5Ceo * Teo * Geo * Geo * G * T * G * T * C * G * G * G * C * T * Teo * Teo * m5Ceo * Geo * m5Ceo	GCTGGGTGTCGGGCTTTCGC	XXXXXXXXXXXXXXXXXXX
WV-5982	Geo * Geo * Geo * Teo * Geo * T * C * G * G * G * C * T * T * T * C * Geo * m5Ceo * m5Ceo * Teo * m5Ceo	GGGTGTCGGGCTTTCGCCTC	XXXXXXXXXXXXXXXXXXX
WV-5983	Aeo * Teo * Teo * Geo * m5Ceo * C * T * G * C * A * T * C * C * G * G * Geo * m5Ceo * m5Ceo * m5Ceo * m5Ceo	ATTGCCTGCATCCGGGCCCC	XXXXXXXXXXXXXXXXXXX
WV-5984	Teo * Geo * m5Ceo * m5Ceo * Teo * G * C * A * T * C * C * C * G * G * G * C * m5Ceo * m5Ceo * m5Ceo * Geo * Geo	TGCCTGCATCCGGGCCCCGG	XXXXXXXXXXXXXXXXXXX
WV-5985	Geo * m5Ceo * Aeo * Teo * m5Ceo * C * G * G * G * C * C * C * C * C * G * G * Geo * m5Ceo * Teo * Teo * m5Ceo	GCATCCGGGCCCCGGGCTTC	XXXXXXXXXXXXXXXXXXX
WV-5986	m5Ceo * Teo * Teo * m5Ceo * m5Ceo * T * T * G * C * T * T * T * C * C * C * Geo * m5Ceo * m5Ceo * m5Ceo * Teo	CTTCCTTGCTTTCCCGCCCT	XXXXXXXXXXXXXXXXXXX
WV-5987	Teo * m5Ceo * m5Ceo * Teo * Teo * G * C * T * T * T * C * C * C * G * C * m5Ceo * m5Ceo * Teo * m5Ceo * Aeo	TCCTTGCTTTCCCGCCCTCA	XXXXXXXXXXXXXXXXXXX
WV-5988	Geo * m5Ceo * Teo * Teo * Teo * C * C * C * G * C * C * C * T * C * A * Geo * Teo * Aeo *	GCTTTCCCGCCCTCAGTACC	XXXXXXXXXXXXXXXXXXX

	m5Ceo * m5Ceo		
WV-5989	Geo * m5Ceo * m5Ceo * m5Ceo * Teo * C * A * G * T * A * C * C * C * G * A * Geo * m5Ceo * Teo * Geo * Teo	GCCCTCAGTACCCGAGCTGT	XXXXXXXXXXXXXXXXXXX
WV-5990	Aeo * m5Ceo * m5Ceo * m5Ceo * Geo * A * G * C * T * G * T * C * T * C * C * Teo * Teo * m5Ceo * m5Ceo * m5Ceo * m5Ceo	ACCCGAGCTGTCTCCTTCCC	XXXXXXXXXXXXXXXXXXX
WV-5991	Geo * Geo * Aeo * m5Ceo * m5Ceo * C * G * C * T * G * G * G * A * G * C * Geo * m5Ceo * Teo * Geo * m5Ceo	GGACCCGCTGGGAGCGCTGC	XXXXXXXXXXXXXXXXXXX
WV-5992	Geo * Geo * Geo * Aeo * Aeo * G * G * C * C * G * G * A * G * G * G * Teo * Geo * Geo * Geo * m5Ceo	GGGAAGGCCGGAGGGTGGGC	XXXXXXXXXXXXXXXXXXX
WV-5993	Geo * Geo * Teo * m5Ceo * m5Ceo * C * T * G * C * C * G * G * C * G * A * Geo * Geo * Aeo * Geo * Aeo	GGTCCCTGCCGGCGAGGAGA	XXXXXXXXXXXXXXXXXXX
WV-5994	Geo * Teo * m5Ceo * Geo * Geo * T * G * T * G * C * T * C * C * C * C * Aeo * Teo * Teo * m5Ceo * Teo	GTCGGTGTGCTCCCCATTCT	XXXXXXXXXXXXXXXXXXX
WV-5995	Geo * Teo * Geo * m5Ceo * Teo * C * C * C * C * A * T * T * C * T * G * Teo * Geo * Geo * Geo * Aeo	GTGCTCCCCATTCTGTGGGA	XXXXXXXXXXXXXXXXXXX
WV-5996	m5Ceo * m5Ceo * Teo * Geo * Geo * T * T * G * C * T * T * C * A * C * A * Geo * m5Ceo * Teo * m5Ceo * m5Ceo	CCTGGTTGCTTCACAGCTCC	XXXXXXXXXXXXXXXXXXX
WV-5997	Geo * Teo * m5Ceo * m5Ceo * Geo * T * G * T * G * C * T * C * A * T * T * Geo * Geo * Geo * Teo * m5Ceo	GTCCGTGTGCTCATTGGGTC	XXXXXXXXXXXXXXXXXXX
WV-5998	Geo * Geo * Geo * Aeo * Geo * G * T * C * C * T * G * C * A * C * T * Teo * Teo * m5Ceo * m5Ceo * m5Ceo	GGGAGGTCCTGCACTTTCCC	XXXXXXXXXXXXXXXXXXX
WV-5999	m5Ceo * m5Ceo * Teo * m5Ceo * Teo * G * C * C * A * A * G * G * C * C * T * Geo * m5Ceo * m5Ceo * Aeo * m5Ceo	CCTCTGCCAAGGCCTGCCAC	XXXXXXXXXXXXXXXXXXX
WV-6000	Aeo * Geo * Teo * Geo * Geo * T * C * C * T * G * G * C * C * A * G * m5Ceo * Teo * m5Ceo	AGTGGTCCTGGGCAGCTCCT	XXXXXXXXXXXXXXXXXXX

	* m5Ceo * Teo		
WV-6408	m5Ceo * m5CeoTeom5CeoAeo * C * T * C * A * C * C * C * A * C * T * m5CeoGeom5Ceom5Ceo * Aeo	CCTCACTCACCCACTCGCCA	X0O0XXXXXXXXXXX0O0X
WV-6471	mG * mAmUmGmC * C * G * C * C * T * C * C * T * C * A * mCmUmCmA * mC	GAUGCCGCCTCCTCACUCAC	X0O0XXXXXXXXXXX0O0X
WV-6472	mA * mUmGmCmC * G * C * C * T * C * C * C * T * C * A * C * mUmCmAmC * mC	AUGCCGCCTCCTCACUCACC	X0O0XXXXXXXXXXX0O0X
WV-6473	mU * mGmCmCmG * C * C * T * C * C * C * T * C * A * C * T * mCmAmCmC * mC	UGCCGCCTCCTCACTCACCC	X0O0XXXXXXXXXXX0O0X
WV-6474	mG * mCmCmGmC * C * T * C * C * C * T * C * A * C * T * C * mAmCmCmC * mA	GCCGCCTCCTCACTCACCCA	X0O0XXXXXXXXXXX0O0X
WV-6475	mC * mCmGmCmC * T * C * C * C * T * C * A * C * T * C * A * mCmCmCmA * mC	CCGCCTCCTCACTCACCCAC	X0O0XXXXXXXXXXX0O0X
WV-6476	mC * mGmCmCmU * C * C * T * C * C * A * C * T * C * A * C * mCmCmAmC * mU	CGCCUCCTCACTCACCCACU	X0O0XXXXXXXXXXX0O0X
WV-6477	mG * mCmCmUmC * C * T * C * A * C * C * T * C * A * C * C * mCmAmCmU * mC	GCCUCCTCACTCACCCACUC	X0O0XXXXXXXXXXX0O0X
WV-6478	mC * mCmUmCmC * T * C * A * C * C * T * C * A * C * C * C * mAmCmUmC * mG	CCUCCTCACTCACCCACUCG	X0O0XXXXXXXXXXX0O0X
WV-6479	mC * mUmCmCmU * C * A * C * T * C * A * C * C * C * A * mCmUmCmG * mC	CUCCUCACTCACCCACUCGC	X0O0XXXXXXXXXXX0O0X
WV-6480	mU * mCmCmUmC * A * C * T * C * A * C * C * A * C * mUmCmGmC * mC	UCCUCACTCACCCACUCGCC	X0O0XXXXXXXXXXX0O0X
WV-6481	mC * mUmCmAmC * T * C * A * C * C * C * A * C * T * C * mGmCmCmA * mC	CUCACTCACCCACTCGCCAC	X0O0XXXXXXXXXXX0O0X
WV-6482	mC * mAmCmUmC * A * C * C * C * A * C * T * C * G * C * mCmAmCmC * mG	CACUCACCCACTCGCCACCG	X0O0XXXXXXXXXXX0O0X
WV-6483	mA * mCmUmCmA * C * C * C * A * C * T * C * G * C * C * mAmCmCmG * mC	ACUCACCCACTCGCCACCGC	X0O0XXXXXXXXXXX0O0X
WV-6484	mC * mUmCmAmC * C * C * A * C * T * C * G * C * C * A * mCmCmGmC * mC	CUCACCCACTCGCCACCGCC	X0O0XXXXXXXXXXX0O0X
WV-6485	mU * mCmAmCmC * C * A * C * T * C * G * C * C * C * A * C * mCmGmCmC * mU	UCACCCACTCGCCACCGCCU	X0O0XXXXXXXXXXX0O0X
WV-6486	mC * mAmCmCmC * A * C * T * C * G * C * C * A * C * C * C * mGmCmCmU * mG	CACCCACTCGCCACCGCCUG	X0O0XXXXXXXXXXX0O0X

WV-6487	mA * mCmCmCmA * C * T * C * G * C * C * A * C * C * G * mCmCmUmG * mC	ACCCACTCGCCACCGCCUGC	X000XXXXXXXXXXX000X
WV-6488	mC * mCmCmAmC * T * C * G * C * C * A * C * C * G * C * mCmUmGmC * mG	CCCACTCGCCACCGCCUGCG	X000XXXXXXXXXXX000X
WV-6489	mC * mCmAmCmU * C * G * C * C * A * C * C * G * C * C * mUmGmCmG * mC	CCACUCGCCACCGCCUGCGC	X000XXXXXXXXXXX000X
WV-6490	R GR CR GR CR AR GR GR CR GR GR UR GR GR CR GR AR GR UR GR GR UR GR AR GR UR GR AR GR GR AR GR GR CR GR GR CR AR UR C	GCGCAGGCGGUGGCGAGUG GGUGAGUGAGGAGGCGGCAUC	000000000000000000000 000000000000 000000000
WV-6491	R GR CR GR CR AR GR GR CR GR GR UR GR GR CR GR AR GR UR GR GR UR GR AR GR UR GR AR GR G	GCGCAGGCGGUGGCGAGUGGG UGAGUGAGG	000000000000000000000 000000000
WV-6492	R UR GR GR CR GR AR GR UR GR GR GR UR GR AR GR UR GR AR GR GR AR GR GR CR GR GR CR AR UR C	UGGCGAGUGGGUGAGUGAGGA GGCGGCAUC	000000000000000000000 000000000
WV-6831	mC * mC * mU * mA * mG * C * G * G * G * A * C * A * C * C * G * mU * mA * mG * mG * mU	CCUAGCGGGACACCGUAGGU	XXXXXXXXXXXXXXXXXXXXX
WV-6832	mC * mU * mU * mU * mC * C * T * A * G * C * G * G * G * A * C * mA * mC * mC * mG * mU	CUUUCCTAGCGGGACACCGU	XXXXXXXXXXXXXXXXXXXX
WV-6833	mC * mU * mC * mU * mU * T * C * C * T * A * G * C * G * G * G * mA * mC * mA * mC * mC	CUCUUTCCTAGCGGGACACC	XXXXXXXXXXXXXXXXXXX
WV-6834	mC * mC * mU * mC * mU * C * T * T * T * C * C * T * A * G * C * mG * mG * mG * mA * mC	CCUCUCTTTCCTAGCGGGAC	XXXXXXXXXXXXXXXXXXX
WV-6835	mA * mC * mC * mU * mC * T * C * T * T * T * C * C * T * A * G * mC * mG * mG * mG * mA	ACCUCTCTTTCCTAGCGGGA	XXXXXXXXXXXXXXXXXXX
WV-6836	mC * mA * mC * mC * mU * C * T * C * T * T * T * C * C * T * A * mG * mC * mG * mG * mG	CACCUCTCTTTCCTAGCGGG	XXXXXXXXXXXXXXXXXXX
WV-6837	mC * mG * mC * mA * mC * C * T * C * T * C * T * T * T * C * C * mU * mA * mG * mC *	CGCACCTCTCTTTCCUAGCG	XXXXXXXXXXXXXXXXXXX

	mG		
WV-6838	mA * mC * mG * mC * mA * C * C * T * C * T * C * T * T * C * mC * mU * mA * mG * mC	ACGCACCTCTCTTTCCUAGC	XXXXXXXXXXXXXXXXXXX
WV-6839	mG * mC * mU * mG * mU * T * T * G * A * C * G * C * A * C * C * mU * mC * mU * mC * mU	GCUGUTTGACGCACCUCUCU	XXXXXXXXXXXXXXXXXXX
WV-6840	mG * mU * mC * mG * mC * T * G * T * T * T * T * G * A * C * G * C * mA * mC * mC * mU * mC	GUCGCTGTTTGACGCACCUC	XXXXXXXXXXXXXXXXXXX
WV-6841	mG * mC * mA * mG * mG * G * A * C * G * G * C * T * G * A * C * mA * mC * mA * mC * mC	GCAGGGACGGCTGACACACC	XXXXXXXXXXXXXXXXXXX
WV-6842	mG * mG * mC * mA * mG * C * A * G * G * G * A * C * G * G * C * mU * mG * mA * mC * mA	GGCAGCAGGGACGGCUGACA	XXXXXXXXXXXXXXXXXXX
WV-6843	mC * mG * mG * mG * mC * A * G * C * C * A * G * G * G * A * C * G * mG * mC * mU * mG * mA	CGGGCAGCAGGGACGGCUGA	XXXXXXXXXXXXXXXXXXX
WV-6844	mC * mC * mG * mG * mG * C * A * G * G * C * A * G * G * G * A * C * C * mG * mG * mC * mU * mG	CCGGGCAGCAGGGACGGCUG	XXXXXXXXXXXXXXXXXXX
WV-6845	mA * mC * mC * mG * mG * G * C * A * G * C * A * G * G * G * A * mC * mG * mG * mC * mU	ACCGGGCAGCAGGGACGGCU	XXXXXXXXXXXXXXXXXXX
WV-6846	mA * mA * mC * mC * mG * G * G * C * C * A * G * C * A * G * G * G * mA * mC * mG * mG * mC	AACCGGGCAGCAGGGACGGC	XXXXXXXXXXXXXXXXXXX
WV-6847	mG * mC * mA * mA * mC * C * G * G * G * C * A * G * C * A * G * mG * mG * mA * mC * mG	GCAACCGGGCAGCAGGGACG	XXXXXXXXXXXXXXXXXXX
WV-6848	mA * mG * mC * mA * mA * C * C * G * G * G * C * A * G * C * A * mG * mG * mG * mA * mC	AGCAACCGGGCAGCAGGGAC	XXXXXXXXXXXXXXXXXXX
WV-6849	mG * mC * mU * mA * mG * A * C * C * C * C * G * C * C * C * C * mC * mA * mA * mA *	GCUAGACCCCGCCCCCAAAA	XXXXXXXXXXXXXXXXXXX

	mA		
WV-6850	mU * mU * mG * mC * mU * A * G * A * C * C * C * C * G * C * C * mC * mC * mA * mA	UUGCUAGACCCCGCCCCCAA	XXXXXXXXXXXXXXXXXXX
WV-6851	mC * mU * mU * mG * mC * T * A * G * A * C * C * C * C * G * C * mC * mC * mC * mA	CUUGCTAGACCCCGCCCCCA	XXXXXXXXXXXXXXXXXXX
WV-6852	mC * mU * mC * mU * mU * G * C * T * A * G * A * C * C * C * C * mG * mC * mC * mC	CUCUUGCTAGACCCCGCCCC	XXXXXXXXXXXXXXXXXXX
WV-6853	mU * mG * mC * mU * mC * T * T * G * C * T * A * G * A * C * C * mC * mC * mG * mC	UGCUCTTGCTAGACCCCGCC	XXXXXXXXXXXXXXXXXXX
WV-6854	mC * mC * mU * mG * mC * T * C * T * T * G * C * T * A * G * A * mC * mC * mC * mG	CCUGCTCTTGCTAGACCCCG	XXXXXXXXXXXXXXXXXXX
WV-6855	mC * mC * mA * mC * mA * C * C * T * G * C * T * C * T * T * G * mC * mU * mA * mG * mA	CCACACCTGCTCTTGCUAGA	XXXXXXXXXXXXXXXXXXX
WV-6856	mC * mC * mC * mA * mC * A * C * C * T * G * C * C * T * C * T * T * mG * mC * mU * mA * mG	CCCACACCTGCTCTTGCUAG	XXXXXXXXXXXXXXXXXXX
WV-6857	mA * mC * mC * mC * mA * C * A * C * C * T * G * C * T * C * T * T * mU * mG * mC * mU * mA	ACCCACACCTGCTCTTGCUA	XXXXXXXXXXXXXXXXXXX
WV-6858	mA * mA * mC * mC * mC * A * C * A * C * C * T * G * C * T * C * T * C * mU * mU * mG * mC * mU	AACCCACACCTGCTCTUUGCU	XXXXXXXXXXXXXXXXXXX
WV-6859	mU * mC * mA * mC * mC * C * T * C * A * G * C * G * A * G * T * mA * mC * mU * mG * mU	UCACCCTCAGCGAGTACUGU	XXXXXXXXXXXXXXXXXXX
WV-6860	mG * mU * mU * mC * mA * C * C * C * T * C * A * G * C * G * A * mG * mU * mA * mC * mU	GUUCACCCTCAGCGAGUACU	XXXXXXXXXXXXXXXXXXX
WV-6861	mC * mU * mU * mG * mU * T * C * A * C * C * C * T * C * A * G * mC * mG * mA * mG *	CUUGUTCACCCTCAGCGAGU	XXXXXXXXXXXXXXXXXXX

	mU		
WV-6862	mG * mU * mC * mU * mU * T * T * C * T * T * G * T * T * C * A * mC * mC * mC * mU * mC	GUCUUTTCTTGTTCACCCUC	XXXXXXXXXXXXXXXXXXX
WV-6863	mG * mG * mU * mC * mU * T * T * T * C * T * G * T * T * T * C * mA * mC * mC * mC * mU	GGUCUTTTCTTGTTCACCCU	XXXXXXXXXXXXXXXXXXX
WV-6864	mC * mC * mU * mC * mC * T * T * G * T * T * T * T * C * T * T * mC * mU * mG * mG * mU	CCUCCTTGTTTTCTTCUGGU	XXXXXXXXXXXXXXXXXXX
WV-6865	mC * mC * mC * mU * mC * C * T * T * G * T * T * T * T * C * T * mU * mC * mU * mG * mG	CCCUCCTTGTTTTCTUCUGG	XXXXXXXXXXXXXXXXXXX
WV-6866	mG * mU * mU * mG * mU * T * T * C * C * C * T * C * C * T * T * mG * mU * mU * mU * mU	GUUGUTTCCCTCCTTGUUUU	XXXXXXXXXXXXXXXXXXX
WV-6867	mG * mG * mU * mU * mG * T * T * T * T * C * C * C * T * C * C * T * mU * mG * mU * mU * mU	GGUUGTTTCCCTCCTTGUUU	XXXXXXXXXXXXXXXXXXX
WV-6868	mC * mG * mG * mU * mU * G * T * T * T * T * C * C * C * T * C * C * C * mU * mU * mG * mU * mU	CGGUUGTTTCCCTCCUUGUU	XXXXXXXXXXXXXXXXXXX
WV-6869	mU * mG * mC * mG * mG * T * T * G * T * T * T * C * C * C * T * mC * mC * mU * mU * mG	UGCGGTTGTTTCCCTCCUUG	XXXXXXXXXXXXXXXXXXX
WV-6870	mC * mU * mG * mC * mG * G * T * T * G * T * T * T * C * C * C * mU * mC * mC * mU * mU	CUGCGGTTGTTTCCCUCCUU	XXXXXXXXXXXXXXXXXXX
WV-6871	mA * mG * mG * mC * mU * G * C * G * G * T * T * G * T * T * T * mC * mC * mC * mU * mC	AGGCUGCGGTTGTTTCCCUC	XXXXXXXXXXXXXXXXXXX
WV-6872	mA * mC * mA * mG * mG * C * T * G * C * G * G * T * T * G * T * mU * mU * mC * mC * mC	ACAGGCTGCGGTTGTUUCCC	XXXXXXXXXXXXXXXXXXX
WV-6873	mG * mC * mU * mA * mC * A * G * G * C * T * G * C * G * G * T * mU * mG * mU * mU *	GCUACAGGCTGCGGTUGUUU	XXXXXXXXXXXXXXXXXXX

	mU		
WV-6874	mU * mG * mC * mU * mA * C * A * G * G * C * T * G * C * G * mU * mU * mG * mU * mU	UGCUACAGGCTGCGGUUGUU	XXXXXXXXXXXXXXXXXXXX
WV-6875	mU * mU * mG * mC * mU * A * C * A * G * G * C * T * G * C * G * mG * mU * mU * mG * mU	UUGCUACAGGCTGCGGUUGU	XXXXXXXXXXXXXXXXXXXX
WV-6876	mG * mC * mU * mU * mG * C * T * A * C * A * G * G * C * T * G * mC * mG * mG * mU * mU	GCUUGCTACAGGCTGCGGUU	XXXXXXXXXXXXXXXXXXXX
WV-6877	mA * mG * mC * mU * mU * G * C * T * A * C * A * G * G * C * T * mG * mC * mG * mG * mU	AGCUUGCTACAGGCTGCGGU	XXXXXXXXXXXXXXXXXXXX
WV-6878	mG * mA * mG * mC * mU * T * G * C * T * A * C * A * G * G * C * mU * mG * mC * mG * mG	GAGCUTGCTACAGGCUGCGG	XXXXXXXXXXXXXXXXXXXX
WV-6879	mC * mA * mG * mA * mG * C * T * T * G * C * T * A * C * A * G * mG * mC * mU * mG * mC	CAGAGCTTGCTACAGGCUGC	XXXXXXXXXXXXXXXXXXXX
WV-6880	mU * mC * mC * mA * mG * A * G * C * T * T * G * C * T * A * C * mA * mG * mG * mC * mU	UCCAGAGCTTGCTACAGGCU	XXXXXXXXXXXXXXXXXXXX
WV-6881	mU * mU * mC * mC * mA * G * A * G * C * T * T * G * C * T * A * mC * mA * mG * mG * mC	UUCCAGAGCTTGCTACAGGC	XXXXXXXXXXXXXXXXXXXX
WV-6882	mC * mC * mU * mG * mA * G * T * T * C * C * A * G * A * G * C * mU * mU * mG * mC * mU	CCUGAGTTCCAGAGCUUGCU	XXXXXXXXXXXXXXXXXXXX
WV-6883	mU * mC * mC * mU * mG * A * G * T * T * C * C * A * G * A * G * mC * mU * mU * mG * mC	UCCUGAGTTCCAGAGCUUGC	XXXXXXXXXXXXXXXXXXXX
WV-6884	mA * mC * mU * mC * mC * T * G * A * G * T * T * C * C * A * G * mA * mG * mC * mU * mU	ACUCCTGAGTTCCAGAGCUU	XXXXXXXXXXXXXXXXXXXX
WV-6885	mG * mC * mG * mC * mG * A * C * T * C * C * T * G * A * G * T * mU * mC * mC * mA *	GCGCGACTCCTGAGTUCCAG	XXXXXXXXXXXXXXXXXXXX

	mG		
WV-6886	mC * mG * mC * mG * mC * G * A * C * T * C * C * T * G * A * G * mU * mU * mC * mC * mA	CGCGCGACTCCTGAGUUCCA	XXXXXXXXXXXXXXXXXXXX
WV-6887	mG * mC * mG * mC * mG * C * G * A * C * T * C * C * T * G * A * mG * mU * mU * mC * mC	GCGCGCGACTCCTGAGUUCC	XXXXXXXXXXXXXXXXXXX
WV-6888	mA * mG * mC * mG * mC * G * C * G * A * C * T * C * C * T * G * mA * mG * mU * mU * mC	AGCGCGCGACTCCTGAGUUC	XXXXXXXXXXXXXXXXXXX
WV-6889	mA * mG * mG * mA * mU * G * C * C * G * C * C * T * C * C * T * mC * mA * mC * mU * mC	AGGAUGCCGCCTCCTCACUC	XXXXXXXXXXXXXXXXXXX
WV-6890	mC * mA * mG * mG * mA * T * G * C * C * G * C * C * T * C * C * mU * mC * mA * mC * mU	CAGGATGCCGCCTCCUCACU	XXXXXXXXXXXXXXXXXXX
WV-6891	mC * mC * mA * mG * mG * A * T * G * C * C * G * C * C * T * C * mC * mU * mC * mA * mC	CCAGGATGCCGCCTCCUCAC	XXXXXXXXXXXXXXXXXXX
WV-6892	mC * mG * mC * mC * mA * G * G * A * T * G * C * C * C * G * C * C * mU * mC * mC * mU * mC	CGCCAGGATGCCGCCUCCUC	XXXXXXXXXXXXXXXXXXX
WV-6893	mC * mC * mG * mC * mC * A * G * G * A * T * G * C * C * C * G * C * mC * mU * mC * mC * mU	CCGCCAGGATGCCGCCUCCU	XXXXXXXXXXXXXXXXXXX
WV-6894	mC * mC * mC * mG * mC * C * A * G * G * A * T * G * C * C * C * G * mC * mC * mU * mC * mC	CCCGCCAGGATGCCGCCUCC	XXXXXXXXXXXXXXXXXXX
WV-6895	mA * mC * mC * mC * mG * C * C * C * A * G * G * A * T * G * C * C * C * mG * mC * mC * mU * mC	ACCCGCCAGGATGCCGCCUC	XXXXXXXXXXXXXXXXXXX
WV-6896	mC * mA * mC * mC * mC * G * C * C * C * A * G * G * A * T * G * C * C * mC * mG * mC * mC * mU	CACCCGCCAGGATGCCGCCU	XXXXXXXXXXXXXXXXXXX
WV-6897	mC * mC * mA * mC * mC * C * G * C * C * C * A * G * G * A * T * G * mC * mC * mG * mC * mC *	CCACCCGCCAGGATGCCGCC	XXXXXXXXXXXXXXXXXXX

	mC		
WV-6898	mG * mC * mC * mA * mC * C * C * G * C * C * A * G * G * A * T * mG * mC * mC * mG * mC	GCCACCCGCCAGGATGCCGC	XXXXXXXXXXXXXXXXXXX
WV-6899	mA * mA * mC * mA * mG * C * C * A * C * C * A * C * C * G * C * C * A * mG * mG * mA * mU * mG	AACAGCCACCCGCCAGGAUG	XXXXXXXXXXXXXXXXXXX
WV-6900	mC * mC * mA * mA * mA * C * A * G * C * C * A * C * C * C * C * G * mC * mC * mA * mG * mG	CCAAACAGCCACCCGCCAGG	XXXXXXXXXXXXXXXXXXX
WV-6901	mC * mC * mC * mA * mA * A * C * A * G * C * C * A * C * C * C * C * mG * mC * mC * mA * mG	CCCAAACAGCCACCCGCCAG	XXXXXXXXXXXXXXXXXXX
WV-6902	mA * mC * mC * mC * mC * A * A * A * C * A * G * C * C * A * C * C * mC * mC * mG * mC * mC	ACCCCAAACAGCCACCCGCC	XXXXXXXXXXXXXXXXXXX
WV-6903	mC * mC * mC * mG * mG * C * A * G * C * C * G * A * A * C * C * mC * mC * mA * mA * mA	CCCGGCAGCCGAACCCCAAA	XXXXXXXXXXXXXXXXXXX
WV-6904	mU * mC * mC * mC * mG * G * C * A * G * C * C * G * A * A * C * mC * mC * mC * mA * mA	UCCCGGCAGCCGAACCCCAA	XXXXXXXXXXXXXXXXXXX
WV-6905	mU * mU * mC * mC * mC * G * G * C * A * G * C * C * G * A * A * mC * mC * mC * mC * mA	UUCCCGGCAGCCGAACCCCA	XXXXXXXXXXXXXXXXXXX
WV-6906	mC * mU * mU * mC * mC * C * G * G * C * A * G * C * C * C * G * A * mA * mC * mC * mC * mC	CUUCCCGGCAGCCGAACCCC	XXXXXXXXXXXXXXXXXXX
WV-6907	mU * mC * mU * mU * mC * C * C * G * G * C * A * G * C * C * C * G * mA * mA * mC * mC * mC	UCUUCCCGGCAGCCGAACCC	XXXXXXXXXXXXXXXXXXX
WV-6908	mC * mU * mC * mU * mU * C * C * C * G * G * C * A * G * C * C * C * mG * mA * mA * mC * mC	CUCUUCCCGGCAGCCGAACC	XXXXXXXXXXXXXXXXXXX
WV-6909	mC * mC * mU * mC * mU * T * C * C * C * G * G * C * A * G * C * C * mC * mG * mA * mA *	CCUCUTCCCGGCAGCCGAAC	XXXXXXXXXXXXXXXXXXX

	mC		
WV-6910	mG * mC * mC * mU * mC * T * T * C * C * C * G * G * C * A * G * mC * mC * mG * mA * mA	GCCUCTTCCCGGCAGCCGAA	XXXXXXXXXXXXXXXXXXX
WV-6911	mC * mG * mC * mC * mU * C * T * T * C * C * C * G * G * C * A * mG * mC * mC * mG * mA	CGCCUCTTCCCGGCAGCCGA	XXXXXXXXXXXXXXXXXXX
WV-6912	mC * mC * mG * mC * mG * C * C * T * C * T * T * C * C * C * G * mG * mC * mA * mG * mC	CCGCGCCTCTTCCCGGCAGC	XXXXXXXXXXXXXXXXXXX
WV-6913	mC * mC * mC * mG * mC * G * C * C * C * T * C * T * T * C * C * C * mG * mG * mC * mA * mG	CCCGCGCCTCTTCCCGGCAG	XXXXXXXXXXXXXXXXXXX
WV-6914	mA * mC * mC * mC * mG * C * G * C * C * T * C * T * T * C * C * C * mC * mG * mG * mC * mA	ACCCGCGCCTCTTCCCGGCA	XXXXXXXXXXXXXXXXXXX
WV-6915	mU * mA * mC * mC * mC * G * C * G * C * C * T * C * T * T * C * C * mC * mC * mG * mG * mC	UACCCGCGCCTCTTCCCGGC	XXXXXXXXXXXXXXXXXXX
WV-6916	mC * mU * mA * mC * mC * C * G * C * C * G * C * C * T * C * T * T * mC * mC * mC * mG * mG	CUACCCGCGCCTCTTCCCGG	XXXXXXXXXXXXXXXXXXX
WV-6917	mU * mU * mC * mC * mU * mA * C * C * C * C * G * C * G * C * C * C * T * C * mU * mU * mC * mC * mC	UUCUACCCGCGCCTCUUCCC	XXXXXXXXXXXXXXXXXXX
WV-6918	mC * mU * mU * mC * mC * mU * A * C * C * C * C * G * C * G * C * C * C * T * mC * mU * mU * mC * mC	CUUCUACCCGCGCCTCUUCC	XXXXXXXXXXXXXXXXXXX
WV-6919	mG * mC * mC * mU * mU * mC * T * A * C * C * C * C * G * C * C * G * C * C * mU * mC * mU * mU * mC	GCUUCTACCCGCGCCUCUUC	XXXXXXXXXXXXXXXXXXX
WV-6920	mC * mG * mC * mC * mU * mU * C * C * T * A * C * C * C * G * C * C * G * C * C * mC * mU * mC * mU * mU	CGCUUCTACCCGCGCCUCUU	XXXXXXXXXXXXXXXXXXX
WV-6921	mC * mC * mC * mG * mC * mU * T * C * C * T * A * C * C * C * C * G * C * C * G * C * mC * mC * mU * mC * mC	CCGCUTCTACCCGCGCCUCU	XXXXXXXXXXXXXXXXXXX

	mU		
WV-6922	mC * mCmUmAmG * C * G * G * G * A * C * A * C * C * G * mUmAmGmG * mU	CCUAGCGGGACACCGUAGGU	X000XXXXXXXXXX000X
WV-6923	mC * mUmUmUmC * C * T * A * G * C * G * G * G * A * C * mAmCmCmG * mU	CUUUCCTAGCGGGACACCGU	X000XXXXXXXXXX000X
WV-6924	mC * mUmCmCmU * T * C * C * T * A * G * C * G * G * G * mAmCmAmC * mC	CUCUUTCCTAGCGGGACACC	X000XXXXXXXXXX000X
WV-6925	mC * mCmUmCmU * C * T * T * T * C * C * T * A * G * C * mGmGmGmA * mC	CCUCUCTTTCCTAGCGGGAC	X000XXXXXXXXXX000X
WV-6926	mA * mCmCmUmC * T * C * T * T * T * C * C * T * A * G * mCmGmGmG * mA	ACCUCTCTTTCCTAGCGGGA	X000XXXXXXXXXX000X
WV-6927	mC * mAmCmCmU * C * T * C * T * T * T * C * C * T * A * mGmCmGmG * mG	CACCUCTCTTTCCTAGCGGG	X000XXXXXXXXXX000X
WV-6928	mC * mGmCmAmC * C * T * C * T * C * T * T * T * C * C * mUmAmGmC * mG	CGCACCTCTCTTTCCUAGCG	X000XXXXXXXXXX000X
WV-6929	mA * mCmGmCmA * C * C * T * C * T * C * T * T * T * C * mCmUmAmG * mC	ACGCACCTCTCTTTCCUAGC	X000XXXXXXXXXX000X
WV-6930	mG * mCmUmGmU * T * T * G * A * C * G * C * A * C * C * mUmCmUmC * mU	GCUGUTTGACGCACCUCUCU	X000XXXXXXXXXX000X
WV-6931	mG * mUmCmGmC * T * G * T * T * T * G * A * C * G * C * mAmCmCmU * mC	GUCGCTGTTTGACGCACCUC	X000XXXXXXXXXX000X
WV-6932	mG * mCmAmGmG * G * A * C * G * G * C * T * G * A * C * mAmCmAmC * mC	GCAGGGACGGCTGACACACC	X000XXXXXXXXXX000X
WV-6933	mG * mGmCmAmG * C * A * G * G * G * A * C * G * G * C * mUmGmAmC * mA	GGCAGCAGGGACGGCUGACA	X000XXXXXXXXXX000X
WV-6934	mC * mGmGmGmC * A * G * C * A * G * G * G * A * C * G * mGmCmUmG * mA	CGGGCAGCAGGGACGGCUGA	X000XXXXXXXXXX000X
WV-6935	mC * mCmGmGmG * C * A * G * C * A * G * G * G * A * C * mGmGmCmU * mG	CCGGGCAGCAGGGACGGCUG	X000XXXXXXXXXX000X
WV-6936	mA * mCmCmGmG * G * C * A * G * C * A * G * G * G * A * mCmGmGmC * mU	ACCGGGCAGCAGGGACGGCU	X000XXXXXXXXXX000X
WV-6937	mA * mAmCmCmG * G * G * C * A * G * C * A * G * G * G * mAmCmGmG * mC	AACCGGGCAGCAGGGACGGC	X000XXXXXXXXXX000X
WV-6938	mG * mCmAmAmC * C * G * G * G * C * A * G * C * A * G * mGmGmAmC * mG	GCAACCGGGCAGCAGGGACG	X000XXXXXXXXXX000X
WV-	mA * mGmCmAmA * C * C * G * G * G * C *	AGCAACCGGGCAGCAGGGAC	X000XXXXXXXXXX000X

6939	A * G * C * A * mGmGmGmA * mC		
WV-6940	mG * mCmUmAmG * A * C * C * C * G * C * C * C * mCmAmAmA * mA	GCUAGACCCCGCCCCCAAAA	X0O0XXXXXXXXXX0O0X
WV-6941	mU * mUmGmCmU * A * G * A * C * C * C * C * G * C * C * mCmCmCmA * mA	UUGCUAGACCCCGCCCCCAA	X0O0XXXXXXXXXXX0O0X
WV-6942	mC * mUmUmGmC * T * A * G * A * C * C * C * C * C * G * C * mCmCmCmC * mA	CUUGCTAGACCCCGCCCCCA	X0O0XXXXXXXXXXX0O0X
WV-6943	mC * mUmCmUmU * G * C * T * A * G * A * C * C * C * C * C * mGmCmCmC * mC	CUCUUGCTAGACCCCGCCCC	X0O0XXXXXXXXXXX0O0X
WV-6944	mU * mGmCmUmC * T * T * G * C * T * A * G * A * C * C * C * mCmCmGmC * mC	UGCUCTTGCTAGACCCCGCC	X0O0XXXXXXXXXXX0O0X
WV-6945	mC * mCmUmGmC * T * C * T * T * G * C * T * * A * G * A * mCmCmCmC * mG	CCUGCTCTTGCTAGACCCCG	X0O0XXXXXXXXXXX0O0X
WV-6946	mC * mCmAmCmA * C * C * T * G * C * T * C * T * T * G * mCmUmAmG * mA	CCACACCTGCTCTTGCUAGA	X0O0XXXXXXXXXXX0O0X
WV-6947	mC * mCmCmAmC * A * C * C * T * G * C * T * C * T * T * mGmCmUmA * mG	CCCACACCTGCTCTTGCUAG	X0O0XXXXXXXXXXX0O0X
WV-6948	mA * mCmCmCmA * C * A * C * C * T * G * C * T * C * T * mUmGmCmU * mA	ACCCACACCTGCTCTUGCUA	X0O0XXXXXXXXXXX0O0X
WV-6949	mA * mAmCmCmC * A * C * A * C * C * T * G * C * T * C * mUmUmGmC * mU	AACCCACACCTGCTCUUGCU	X0O0XXXXXXXXXXX0O0X
WV-6950	mU * mCmAmCmC * C * T * C * A * G * C * G * A * G * T * mAmCmUmG * mU	UCACCCTCAGCGAGTACUGU	X0O0XXXXXXXXXXX0O0X
WV-6951	mG * mUmUmCmA * C * C * C * T * C * A * G * C * G * A * mGmUmAmC * mU	GUUCACCCTCAGCGAGUACU	X0O0XXXXXXXXXXX0O0X
WV-6952	mC * mUmUmGmU * T * C * A * C * C * C * T * C * A * G * mCmGmAmG * mU	CUUGUTCACCCTCAGCGAGU	X0O0XXXXXXXXXXX0O0X
WV-6953	mG * mUmCmUmU * T * T * C * T * T * G * T * T * C * A * mCmCmCmU * mC	GUCUUTTCTTGTTCACCCUC	X0O0XXXXXXXXXXX0O0X
WV-6954	mG * mGmUmCmU * T * T * T * C * T * T * G * T * T * C * mAmCmCmC * mU	GGUCUTTTCTTGTTCACCCU	X0O0XXXXXXXXXXX0O0X
WV-6955	mC * mCmUmCmC * T * T * G * T * T * T * T * T * C * T * T * mCmUmGmG * mU	CCUCCTTGTTTTCTTCUGGU	X0O0XXXXXXXXXXX0O0X
WV-6956	mC * mCmCmUmC * C * T * T * G * T * T * T * T * T * C * T * mUmCmUmG * mG	CCCUCCTTGTTTTCTUCUGG	X0O0XXXXXXXXXXX0O0X
WV-	mG * mUmUmGmU * T * T * C * C * C * T *	GUUGUTTCCCTCCTTGUUUU	X0O0XXXXXXXXXXX0O0X

6957	C * C * T * T * mGmUmUmU * mU		
WV-6958	mG * mGmUmUmG * T * T * T * C * C * C * T * C * C * T * mUmGmUmU * mU	GGUUGTTTCCCTCCTCTGUUU	X0O0XXXXXXXXXXX0O0X
WV-6959	mC * mGmGmUmU * G * T * T * T * C * C * C * T * C * C * C * mUmUmGmU * mU	CGGUUGTTTCCCTCCTCUUGUU	X0O0XXXXXXXXXXXX0O0X
WV-6960	mU * mGmCmGmG * T * T * G * T * T * T * T * C * C * C * T * mCmCmUmU * mG	UGCGGTTGTTTCCCTCCTCUUG	X0O0XXXXXXXXXXXX0O0X
WV-6961	mC * mUmGmCmG * G * T * T * G * T * T * T * T * C * C * C * C * mUmCmCmU * mU	CUGCGGTTGTTTCCCTCCTCCUU	X0O0XXXXXXXXXXXX0O0X
WV-6962	mA * mGmGmCmU * G * C * G * G * T * T * G * T * T * T * mCmCmCmU * mC	AGGCUGCGGTTGTTTCCCTCC	X0O0XXXXXXXXXXXX0O0X
WV-6963	mA * mCmAmGmG * C * T * G * C * G * G * T * T * G * T * mUmUmCmC * mC	ACAGGCTGCGGTTGTTUCCC	X0O0XXXXXXXXXXXX0O0X
WV-6964	mG * mCmUmAmC * A * G * G * C * T * G * C * G * G * T * mUmGmUmU * mU	GCUACAGGCTGCGGTTGTUUU	X0O0XXXXXXXXXXXX0O0X
WV-6965	mU * mGmCmUmA * C * A * G * G * C * T * G * C * G * G * mUmUmGmU * mU	UGCUACAGGCTGCGGTTGTUU	X0O0XXXXXXXXXXXX0O0X
WV-6966	mU * mUmGmCmU * A * C * A * G * G * C * T * G * C * G * mGmUmUmG * mU	UUGCUACAGGCTGCGGTTGTU	X0O0XXXXXXXXXXXX0O0X
WV-6967	mG * mCmUmUmG * C * T * A * C * A * G * G * C * T * G * mCmGmGmU * mU	GCUUGCTACAGGCTGCGGTTU	X0O0XXXXXXXXXXXX0O0X
WV-6968	mA * mGmCmUmU * G * C * T * A * C * A * G * G * C * T * mGmCmGmG * mU	AGCUUGCTACAGGCTGCGGTU	X0O0XXXXXXXXXXXX0O0X
WV-6969	mG * mAmGmCmU * T * G * C * T * A * C * A * G * G * C * mUmGmCmG * mG	GAGCUTGCTACAGGCTGCGGG	X0O0XXXXXXXXXXXX0O0X
WV-6970	mC * mAmGmAmG * C * T * T * G * C * T * A * C * A * G * mGmCmUmG * mC	CAGAGCTTGCTACAGGCTGC	X0O0XXXXXXXXXXXX0O0X
WV-6971	mU * mCmCmAmG * A * G * C * T * T * G * C * T * A * C * mAmGmGmC * mU	UCCAGAGCTTGCTACAGGCU	X0O0XXXXXXXXXXXX0O0X
WV-6972	mU * mUmCmCmA * G * A * G * C * T * T * G * C * T * A * mCmAmGmG * mC	UUCCAGAGCTTGCTACAGGC	X0O0XXXXXXXXXXXX0O0X
WV-6973	mC * mCmUmGmA * G * T * T * C * C * A * G * A * G * C * mUmUmGmC * mU	CCUGAGTTCCAGAGCUUGCU	X0O0XXXXXXXXXXXX0O0X
WV-6974	mU * mCmCmUmG * A * G * T * T * C * C * A * G * A * G * mCmUmUmG * mC	UCCUGAGTTCCAGAGCUUGC	X0O0XXXXXXXXXXXX0O0X
WV-	mA * mCmUmCmC * T * G * A * G * T * T *	ACUCCTGAGTTCCAGAGCUU	X0O0XXXXXXXXXXXX0O0X

6975	C * C * A * G * mAmGmCmU * mU		
WV-6976	mG * mCmGmCmG * A * C * T * C * C * T * G * A * G * mUmCmCmA * mG	GCGCGACTCCTGAGTUCCAG	X0O0XXXXXXXXXX0O0X
WV-6977	mC * mGmCmGmC * G * A * C * T * C * C * T * G * A * G * mUmUmCmC * mA	CGCGCGACTCCTGAGUUCCA	X0O0XXXXXXXXXXX0O0X
WV-6978	mG * mCmGmCmG * C * G * A * C * T * C * C * T * G * A * mGmUmUmC * mC	GCGCGCGACTCCTGAGUUCC	X0O0XXXXXXXXXXX0O0X
WV-6979	mA * mGmCmGmC * G * C * G * A * C * T * C * C * T * G * mAmGmUmU * mC	AGCGCGCGACTCCTGAGUUC	X0O0XXXXXXXXXXX0O0X
WV-6980	mA * mGmGmAmU * G * C * C * G * C * C * T * C * C * T * mCmAmCmU * mC	AGGAUGCCGCCTCCTCACUC	X0O0XXXXXXXXXXX0O0X
WV-6981	mC * mAmGmGmA * T * G * C * C * G * C * C * T * C * C * mUmCmAmC * mU	CAGGATGCCGCCTCCUCACU	X0O0XXXXXXXXXXX0O0X
WV-6982	mC * mCmAmGmG * A * T * G * C * C * G * C * C * T * C * mCmUmCmA * mC	CCAGGATGCCGCCTCCUCAC	X0O0XXXXXXXXXXX0O0X
WV-6983	mC * mGmCmCmA * G * G * A * T * G * C * C * G * C * C * mUmCmCmU * mC	CGCCAGGATGCCGCCUCCUC	X0O0XXXXXXXXXXX0O0X
WV-6984	mC * mCmGmCmC * A * G * G * A * T * G * C * C * G * C * mCmUmCmC * mU	CCGCCAGGATGCCGCCUCCU	X0O0XXXXXXXXXXX0O0X
WV-6985	mC * mCmCmGmC * C * A * G * G * A * T * G * C * C * G * mCmCmUmC * mC	CCCGCCAGGATGCCGCCUCC	X0O0XXXXXXXXXXX0O0X
WV-6986	mA * mCmCmCmG * C * C * A * G * G * A * T * G * C * C * mGmCmCmU * mC	ACCCGCCAGGATGCCGCCUC	X0O0XXXXXXXXXXX0O0X
WV-6987	mC * mAmCmCmC * G * C * C * A * G * G * A * T * G * C * mCmGmCmC * mU	CACCCGCCAGGATGCCGCCU	X0O0XXXXXXXXXXX0O0X
WV-6988	mC * mCmAmCmC * C * G * C * C * A * G * G * A * T * G * mCmCmGmC * mC	CCACCCGCCAGGATGCCGCC	X0O0XXXXXXXXXXX0O0X
WV-6989	mG * mCmCmAmC * C * C * G * C * C * A * G * G * A * T * mGmCmCmG * mC	GCCACCCGCCAGGATGCCGC	X0O0XXXXXXXXXXX0O0X
WV-6990	mA * mAmCmAmG * C * C * A * C * C * C * G * C * C * A * mGmGmAmU * mG	AACAGCCACCCGCCAGGAUG	X0O0XXXXXXXXXXX0O0X
WV-6991	mC * mCmAmAmA * C * A * G * C * C * C * A * C * C * C * G * mCmCmAmG * mG	CCAAACAGCCACCCGCCAGG	X0O0XXXXXXXXXXX0O0X
WV-6992	mC * mCmCmAmA * A * C * A * G * C * C * C * A * C * C * C * mGmCmCmA * mG	CCCAAACAGCCACCCGCCAG	X0O0XXXXXXXXXXX0O0X
WV-	mA * mCmCmCmC * A * A * C * A * G *	ACCCCAAACAGCCACCCGCC	X0O0XXXXXXXXXXX0O0X

6993	C * C * A * C * mCmCmGmC * mC		
WV-6994	mC * mCmCmGmG * C * A * G * C * C * G * A * A * C * C * mCmCmAmA * mA	CCCGGCAGCCGAACCCCAAA	X0O0XXXXXXXXXX0O0X
WV-6995	mU * mCmCmCmG * G * C * A * G * C * C * G * A * A * C * mCmCmCmA * mA	UCCCGGCAGCCGAACCCCAA	X0O0XXXXXXXXXXX0O0X
WV-6996	mU * mUmCmCmC * G * G * C * A * G * C * C * G * A * A * mCmCmCmC * mA	UUCCCGGCAGCCGAACCCCA	X0O0XXXXXXXXXXXX0O0X
WV-6997	mC * mUmUmCmC * C * G * G * C * A * G * C * C * C * G * A * mAmCmCmC * mC	CUUCCCGGCAGCCGAACCCC	X0O0XXXXXXXXXXXXX0O0X
WV-6998	mU * mCmUmUmC * C * C * G * G * C * A * G * C * C * C * G * mAmAmCmC * mC	UCUUCCCGGCAGCCGAACCC	X0O0XXXXXXXXXXXXXX0O0X
WV-6999	mC * mUmCmUmU * C * C * C * G * G * C * A * G * C * C * C * mGmAmAmC * mC	CUCUUCCCGGCAGCCGAACC	X0O0XXXXXXXXXXXXXX0O0X
WV-7000	mC * mCmUmCmU * T * C * C * C * G * G * C * A * G * G * C * mCmGmAmA * mC	CCUCUTCCCGGCAGCCGAAC	X0O0XXXXXXXXXXXXXX0O0X
WV-7001	mG * mCmCmUmC * T * T * C * C * C * G * G * C * A * G * mCmCmGmA * mA	GCCUCTTCCCGGCAGCCGAA	X0O0XXXXXXXXXXXXXX0O0X
WV-7002	mC * mGmCmCmU * C * T * T * C * C * C * G * G * C * A * mGmCmCmG * mA	CGCCUCTTCCCGGCAGCCGA	X0O0XXXXXXXXXXXXXX0O0X
WV-7003	mC * mCmGmCmG * C * C * C * T * C * T * T * C * C * C * G * mGmCmAmG * mC	CCGCGCCTCTTCCCGGCAGC	X0O0XXXXXXXXXXXXXX0O0X
WV-7004	mC * mCmCmGmC * G * C * C * C * T * C * T * T * C * C * C * mGmGmCmA * mG	CCCGCGCCTCTTCCCGGCAG	X0O0XXXXXXXXXXXXXX0O0X
WV-7005	mA * mCmCmCmG * C * G * C * C * C * T * C * T * T * C * C * mCmGmGmC * mA	ACCCGCGCCTCTTCCCGGCA	X0O0XXXXXXXXXXXXXX0O0X
WV-7006	mU * mAmCmCmC * G * C * G * C * C * C * T * C * T * T * C * mCmCmGmG * mC	UACCCGCGCCTCTTCCCGGC	X0O0XXXXXXXXXXXXXX0O0X
WV-7007	mC * mUmAmCmC * C * G * C * G * C * C * C * T * C * T * T * mCmCmCmG * mG	CUACCCGCGCCTCTTCCCGG	X0O0XXXXXXXXXXXXXX0O0X
WV-7008	mU * mUmCmUmA * C * C * C * C * G * C * G * C * C * C * T * C * mUmUmCmC * mC	UUCUACCCGCGCCTCUUCCC	X0O0XXXXXXXXXXXXXX0O0X
WV-7009	mC * mUmUmCmU * A * C * C * C * C * G * C * G * C * C * C * T * mCmUmUmC * mC	CUUCUACCCGCGCCTCUUCC	X0O0XXXXXXXXXXXXXX0O0X
WV-7010	mG * mCmUmUmC * T * A * C * C * C * C * G * C * G * C * C * mUmCmUmU * mC	GCUUCTACCCGCGCCUCUUC	X0O0XXXXXXXXXXXXXX0O0X
WV-	mC * mGmCmUmU * C * T * A * C * C * C *	CGCUUCTACCCGCGCCUCUU	X0O0XXXXXXXXXXXXXX0O0X

7011	G * C * G * C * mCmUmCmU * mU		
WV-7012	mC * mCmGmCmU * T * C * T * A * C * C * C * G * C * G * mCmCmUmC * mU	CCGCUTCTACCCGCGCCUCU	X000XXXXXXXXXX000X
WV-7013	m5Ceo * m5CeoTeoAeoGeo * m5C * G * G * G * A * m5C * A * m5C * m5C * G * TeoAeoGeoGeo * Teo	CCTAGCGGGACACCGTAGGT	X000XXXXXXXXXX000X
WV-7014	m5Ceo * TeoTeoTeom5Ceo * m5C * T * A * G * m5C * G * G * G * A * m5C * Aeom5Ceom5CeoGeo * Teo	CTTTCCTAGCGGGACACCGT	X000XXXXXXXXXX000X
WV-7015	m5Ceo * Teom5CeoTeoTeo * T * m5C * m5C * T * A * G * m5C * G * G * G * Aeom5CeoAeom5Ceo * m5Ceo	CTCTTTCCTAGCGGGACACC	X000XXXXXXXXXX000X
WV-7016	m5Ceo * m5CeoTeom5CeoTeo * m5C * T * T * T * m5C * m5C * T * A * G * m5C * GeoGeoGeoAeo * m5Ceo	CCTCTCTTTCCTAGCGGGAC	X000XXXXXXXXXX000X
WV-7017	Aeo * m5Ceom5CeoTeom5Ceo * T * m5C * T * T * T * m5C * m5C * T * A * G * m5CeoGeoGeoGeo * Aeo	ACCTCTCTTTCCTAGCGGGA	X000XXXXXXXXXX000X
WV-7018	m5Ceo * Aeom5Ceom5CeoTeo * m5C * T * m5C * T * T * T * m5C * m5C * T * A * Geom5CeoGeoGeo * Geo	CACCTCTCTTTCCTAGCGGG	X000XXXXXXXXXX000X
WV-7019	m5Ceo * Geom5CeoAeom5Ceo * m5C * T * m5C * T * m5C * T * T * T * m5C * m5C * TeoAeoGeom5Ceo * Geo	CGCACCTCTCTTTCCTAGCG	X000XXXXXXXXXX000X
WV-7020	Aeo * m5CeoGeom5CeoAeo * m5C * m5C * T * m5C * T * m5C * T * T * T * T * m5C * m5CeoTeoAeoGeo * m5Ceo	ACGCACCTCTCTTTCCTAGC	X000XXXXXXXXXX000X
WV-7021	Geo * m5CeoTeoGeoTeo * T * T * G * A * m5C * G * m5C * A * m5C * m5C * Teom5CeoTeom5Ceo * Teo	GCTGTTTGACGCACCTCTCT	X000XXXXXXXXXX000X
WV-7022	Geo * Teom5CeoGeom5Ceo * T * G * T * T * T * G * A * m5C * G * m5C * Aeom5Ceom5CeoTeo * m5Ceo	GTCGCTGTTTGACGCACCTC	X000XXXXXXXXXX000X
WV-7023	Geo * m5CeoAeoGeoGeo * G * A * m5C * G * G * m5C * T * G * A * m5C * Aeom5CeoAeom5Ceo * m5Ceo	GCAGGGACGGCTGACACACC	X000XXXXXXXXXX000X

WV-7024	Geo * Geom5CeoAeoGeo * m5C * A * G * G * G * A * m5C * G * G * m5C * TeoGeoAeom5Ceo * Aeo	GGCAGCAGGGACGGCTGACA	X000XXXXXXXXXXXX000X
WV-7025	m5Ceo * GeoGeoGeom5Ceo * A * G * m5C * A * G * G * G * A * m5C * G * Geom5CeoTeoGeo * Aeo	CGGGCAGCAGGGACGGCTGA	X000XXXXXXXXXXXX000X
WV-7026	m5Ceo * m5CeoGeoGeoGeo * m5C * A * G * m5C * A * G * G * G * A * m5C * GeoGeom5CeoTeo * Geo	CCGGGCAGCAGGGACGGCTG	X000XXXXXXXXXXXX000X
WV-7027	Aeo * m5Ceom5CeoGeoGeo * G * m5C * A * G * m5C * A * G * G * G * A * m5CeoGeoGeom5Ceo * Teo	ACCGGGCAGCAGGGACGGCT	X000XXXXXXXXXXXX000X
WV-7028	Aeo * Aeom5Ceom5CeoGeo * G * G * m5C * A * G * m5C * A * G * G * G * Aeom5CeoGeoGeo * m5Ceo	AACCGGGCAGCAGGGACGGC	X000XXXXXXXXXXXX000X
WV-7029	Geo * m5CeoAeoAeom5Ceo * m5C * G * G * G * m5C * A * G * m5C * A * G * GeoGeoAeom5Ceo * Geo	GCAACCGGGCAGCAGGGACG	X000XXXXXXXXXXXX000X
WV-7030	Aeo * Geom5CeoAeoAeo * m5C * m5C * G * G * G * m5C * A * G * m5C * A * GeoGeoGeoAeo * m5Ceo	AGCAACCGGGCAGCAGGGAC	X000XXXXXXXXXXXX000X
WV-7031	Geo * m5CeoTeoAeoGeo * A * m5C * m5C * m5C * m5C * m5C * G * m5C * m5C * m5C * m5C * m5CeoAeoAeoAeo * Aeo	GCTAGACCCCGCCCCCAAAA	X000XXXXXXXXXXXX000X
WV-7032	Teo * TeoGeom5CeoTeo * A * G * A * m5C * m5C * m5C * m5C * G * m5C * m5C * m5Ceom5Ceom5CeoAeo * Aeo	TTGCTAGACCCCGCCCCCAA	X000XXXXXXXXXXXX000X
WV-7033	m5Ceo * TeoTeoGeom5Ceo * T * A * G * A * m5C * m5C * m5C * m5C * G * m5C * m5Ceom5Ceom5Ceom5Ceo * Aeo	CTTGCTAGACCCCGCCCCCA	X000XXXXXXXXXXXX000X
WV-7034	m5Ceo * Teom5CeoTeoTeo * G * m5C * T * A * G * A * m5C * m5C * m5C * m5C * Geom5Ceom5Ceom5Ceo * m5Ceo	CTCTTGCTAGACCCCGCCCC	X000XXXXXXXXXXXX000X
WV-7035	Teo * Geom5CeoTeom5Ceo * T * T * G * m5C * T * A * G * A * m5C * m5C * m5Ceom5CeoGeom5Ceo * m5Ceo	TGCTCTTGCTAGACCCCGCC	X000XXXXXXXXXXXX000X

WV-7036	m5Ceo * m5CeoTeoGeom5Ceo * T * m5C * T * T * G * m5C * T * A * G * A * m5Ceom5Ceom5Ceom5Ceo * Geo	CCTGCTCTTGCTAGACCCCG	X00OXXXXXXXXXXXX000X
WV-7037	m5Ceo * m5CeoAeom5CeoAeo * m5C * m5C * T * G * m5C * T * m5C * T * T * G * m5CeoTeoAeoGeo * Aeo	CCACACCTGCTCTTGCTAGA	X00OXXXXXXXXXXXX000X
WV-7038	m5Ceo * m5Ceom5CeoAeom5Ceo * A * m5C * m5C * T * G * m5C * T * m5C * T * T * Geom5CeoTeoAeo * Geo	CCCACACCTGCTCTTGCTAG	X00OXXXXXXXXXXXX000X
WV-7039	Aeo * m5Ceom5Ceom5CeoAeo * m5C * A * m5C * m5C * T * G * m5C * T * m5C * T * TeoGeom5CeoTeo * Aeo	ACCCACACCTGCTCTTGCTA	X00OXXXXXXXXXXXX000X
WV-7040	Aeo * Aeom5Ceom5Ceom5Ceo * A * m5C * A * m5C * m5C * T * G * m5C * T * m5C * TeoTeoGeom5Ceo * Teo	AACCCACACCTGCTCTTGCT	X00OXXXXXXXXXXXX000X
WV-7041	Teo * m5CeoAeom5Ceom5Ceo * m5C * T * m5C * A * G * m5C * G * A * G * T * Aeom5CeoTeoGeo * Teo	TCACCCTCAGCGAGTACTGT	X00OXXXXXXXXXXXX000X
WV-7042	Geo * TeoTeom5CeoAeo * m5C * m5C * m5C * T * m5C * A * G * m5C * G * A * GeoTeoAeom5Ceo * Teo	GTTCACCCTCAGCGAGTACT	X00OXXXXXXXXXXXX000X
WV-7043	m5Ceo * TeoTeoGeoTeo * T * m5C * A * m5C * m5C * m5C * T * m5C * A * G * m5CeoGeoAeoGeo * Teo	CTTGTTCACCCTCAGCGAGT	X00OXXXXXXXXXXXX000X
WV-7044	Geo * Teom5CeoTeoTeo * T * T * m5C * T * T * G * T * T * m5C * A * m5Ceom5Ceom5CeoTeo * m5Ceo	GTCTTTTCTTGTTCACCCTC	X00OXXXXXXXXXXXX000X
WV-7045	Geo * GeoTeom5CeoTeo * T * T * T * m5C * T * T * G * T * T * m5C * Aeom5Ceom5Ceom5Ceo * Teo	GGTCTTTTCTTGTTCACCCT	X00OXXXXXXXXXXXX000X
WV-7046	m5Ceo * m5CeoTeom5Ceom5Ceo * T * T * G * T * T * T * T * m5C * T * T * m5CeoTeoGeoGeo * Teo	CCTCCTTGTTTTCTTCTGGT	X00OXXXXXXXXXXXX000X
WV-7047	m5Ceo * m5Ceom5CeoTeom5Ceo * m5C * T * T * G * T * T * T * T * m5C * T * Teom5CeoTeoGeo * Geo	CCCTCCTTGTTTTCTTCTGG	X00OXXXXXXXXXXXX000X

WV-7048	Geo * TeoTeoGeoTeo * T * T * m5C * m5C * m5C * T * m5C * m5C * T * T * GeoTeoTeoTeo * Teo	GTTGTTTCCCTCCTTGTTTT	X000XXXXXXXXXXX000X
WV-7049	Geo * GeoTeoTeoGeo * T * T * T * m5C * m5C * m5C * T * m5C * m5C * T * TeoGeoTeoTeo * Teo	GGTTGTTTCCCTCCTTGTTT	X000XXXXXXXXXXXX000X
WV-7050	m5Ceo * GeoGeoTeoTeo * G * T * T * T * m5C * m5C * m5C * T * m5C * m5C * m5C * TeoTeoGeoTeo * Teo	CGGTTGTTTCCCTCCTTGTT	X000XXXXXXXXXXX000X
WV-7051	Teo * Geom5CeoGeoGeo * T * T * G * T * T * T * m5C * m5C * m5C * T * T * m5Ceom5CeoTeoTeo * Geo	TGCGGTTGTTTCCCTCCTTG	X000XXXXXXXXXXXX000X
WV-7052	m5Ceo * TeoGeom5CeoGeo * G * T * T * T * G * T * T * T * m5C * m5C * m5C * Teom5Ceom5CeoTeo * Teo	CTGCGGTTGTTTCCCTCCTT	X000XXXXXXXXXXXX000X
WV-7053	Aeo * GeoGeom5CeoTeo * G * m5C * G * G * T * T * G * T * T * T * m5Ceom5Ceom5CeoTeo * m5Ceo	AGGCTGCGGTTGTTTCCCTC	X000XXXXXXXXXXX000X
WV-7054	Aeo * m5CeoAeoGeoGeo * m5C * T * G * m5C * G * G * T * T * G * T * TeoTeom5Ceom5Ceo * m5Ceo	ACAGGCTGCGGTTGTTTCCC	X000XXXXXXXXXXX000X
WV-7055	Geo * m5CeoTeoAeom5Ceo * A * G * G * m5C * T * G * m5C * G * G * T * TeoGeoTeoTeo * Teo	GCTACAGGCTGCGGTTGTTT	X000XXXXXXXXXXX000X
WV-7056	Teo * Geom5CeoTeoAeo * m5C * A * G * G * m5C * T * G * m5C * G * G * TeoTeoGeoTeo * Teo	TGCTACAGGCTGCGGTTGTT	X000XXXXXXXXXXX000X
WV-7057	Teo * TeoGeom5CeoTeo * A * m5C * A * G * G * m5C * T * G * m5C * G * GeoTeoTeoGeo * Teo	TTGCTACAGGCTGCGGTTGT	X000XXXXXXXXXXX000X
WV-7058	Geo * m5CeoTeoTeoGeo * m5C * T * A * m5C * A * G * G * m5C * T * G * m5CeoGeoGeoTeo * Teo	GCTTGCTACAGGCTGCGGTT	X000XXXXXXXXXXX000X
WV-7059	Aeo * Geom5CeoTeoTeo * G * m5C * T * A * m5C * A * G * G * m5C * T * Geom5CeoGeoGeo * Teo	AGCTTGCTACAGGCTGCGGT	X000XXXXXXXXXXX000X

WV-7060	Geo * AeoGeom5CeoTeo * T * G * m5C * T * A * m5C * A * G * G * m5C * TeoGeom5CeoGeo * Geo	GAGCTTGCTACAGGCTGCGG	X000XXXXXXXXXXX000X
WV-7061	m5Ceo * AeoGeoAeoGeo * m5C * T * T * G * m5C * T * A * m5C * A * G * Geom5CeoTeoGeo * m5Ceo	CAGAGCTTGCTACAGGCTGC	X000XXXXXXXXXXXX000X
WV-7062	Teo * m5Ceom5CeoAeoGeo * A * G * m5C * T * T * G * m5C * T * A * m5C * AeoGeoGeom5Ceo * Teo	TCCAGAGCTTGCTACAGGCT	X000XXXXXXXXXXX000X
WV-7063	Teo * Teom5Ceom5CeoAeo * G * A * G * m5C * T * T * G * m5C * T * A * m5CeoAeoGeoGeo * m5Ceo	TTCCAGAGCTTGCTACAGGC	X000XXXXXXXXXXX000X
WV-7064	m5Ceo * m5CeoTeoGeoAeo * G * T * T * m5C * m5C * A * G * A * G * m5C * TeoTeoGeom5Ceo * Teo	CCTGAGTTCCAGAGCTTGCT	X000XXXXXXXXXXX000X
WV-7065	Teo * m5Ceom5CeoTeoGeo * A * G * T * T * m5C * m5C * A * G * A * G * m5CeoTeoTeoGeo * m5Ceo	TCCTGAGTTCCAGAGCTTGC	X000XXXXXXXXXXX000X
WV-7066	Aeo * m5CeoTeom5Ceom5Ceo * T * G * A * G * T * T * m5C * m5C * A * G * AeoGeom5CeoTeo * Teo	ACTCCTGAGTTCCAGAGCTT	X000XXXXXXXXXXX000X
WV-7067	Geo * m5CeoGeom5CeoGeo * A * m5C * T * m5C * m5C * T * G * A * G * T * Teom5Ceom5CeoAeo * Geo	GCGCGACTCCTGAGTTCCAG	X000XXXXXXXXXXX000X
WV-7068	m5Ceo * Geom5CeoGeom5Ceo * G * A * m5C * T * m5C * m5C * T * G * A * G * TeoTeom5Ceom5Ceo * Aeo	CGCGCGACTCCTGAGTTCCA	X000XXXXXXXXXXX000X
WV-7069	Geo * m5CeoGeom5CeoGeo * m5C * G * A * m5C * T * m5C * m5C * T * G * A * GeoTeoTeom5Ceo * m5Ceo	GCGCGCGACTCCTGAGTTCC	X000XXXXXXXXXXX000X
WV-7070	Aeo * Geom5CeoGeom5Ceo * G * m5C * G * A * m5C * T * m5C * m5C * T * G * AeoGeoTeoTeo * m5Ceo	AGCGCGCGACTCCTGAGTTC	X000XXXXXXXXXXX000X
WV-7071	Aeo * GeoGeoAeoTeo * G * m5C * m5C * G * m5C * m5C * T * m5C * m5C * T * m5CeoAeom5CeoTeo * m5Ceo	AGGATGCCGCCTCCTCACTC	X000XXXXXXXXXXX000X

WV-7072	m5Ceo * AeoGeoGeoAeo * T * G * m5C * m5C * G * m5C * m5C * T * m5C * m5C * Teom5CeoAeom5Ceo * Teo	CAGGATGCCGCCTCCTCACT	X000XXXXXXXXXXXX000X
WV-7073	m5Ceo * m5CeoAeoGeoGeo * A * T * G * m5C * m5C * G * m5C * m5C * T * m5C * m5CeoTeom5CeoAeo * m5Ceo	CCAGGATGCCGCCTCCTCAC	X000XXXXXXXXXXXX000X
WV-7074	m5Ceo * Geom5Ceom5CeoAeo * G * G * A * T * G * m5C * m5C * G * m5C * m5C * Teom5Ceom5CeoTeo * m5Ceo	CGCCAGGATGCCGCCTCCTC	X000XXXXXXXXXXXX000X
WV-7075	m5Ceo * m5CeoGeom5Ceom5Ceo * A * G * G * A * T * G * m5C * m5C * G * m5C * m5CeoTeom5Ceom5Ceo * Teo	CCGCCAGGATGCCGCCTCCT	X000XXXXXXXXXXXX000X
WV-7076	m5Ceo * m5Ceom5CeoGeom5Ceo * m5C * A * G * G * A * T * G * m5C * m5C * G * m5Ceom5CeoTeom5Ceo * m5Ceo	CCCGCCAGGATGCCGCCTCC	X000XXXXXXXXXXXX000X
WV-7077	Aeo * m5Ceom5Ceom5CeoGeo * m5C * m5C * A * G * G * A * T * G * m5C * m5C * Geom5Ceom5CeoTeo * m5Ceo	ACCCGCCAGGATGCCGCCTC	X000XXXXXXXXXXXX000X
WV-7078	m5Ceo * Aeom5Ceom5Ceom5Ceo * G * m5C * m5C * A * G * G * A * T * G * m5C * m5CeoGeom5Ceom5Ceo * Teo	CACCCGCCAGGATGCCGCCT	X000XXXXXXXXXXXX000X
WV-7079	m5Ceo * m5CeoAeom5Ceom5Ceo * m5C * G * m5C * m5C * A * G * G * A * T * G * m5Ceom5CeoGeom5Ceo * m5Ceo	CCACCCGCCAGGATGCCGCC	X000XXXXXXXXXXXX000X
WV-7080	Geo * m5Ceom5CeoAeom5Ceo * m5C * m5C * G * m5C * m5C * A * G * G * A * T * Geom5Ceom5CeoGeo * m5Ceo	GCCACCCGCCAGGATGCCGC	X000XXXXXXXXXXXX000X
WV-7081	Aeo * Aeom5CeoAeoGeo * m5C * m5C * A * m5C * m5C * G * m5C * m5C * A * GeoGeoAeoTeo * Geo	AACAGCCACCCGCCAGGATG	X000XXXXXXXXXXXX000X
WV-7082	m5Ceo * m5CeoAeoAeoAeo * m5C * A * G * m5C * m5C * A * m5C * m5C * m5C * G * m5Ceom5CeoAeoGeo * Geo	CCAAACAGCCACCCGCCAGG	X000XXXXXXXXXXXX000X
WV-7083	m5Ceo * m5Ceom5CeoAeoAeo * A * m5C * A * G * m5C * m5C * A * m5C * m5C * m5C * Geom5Ceom5CeoAeo * Geo	CCCAAACAGCCACCCGCCAG	X000XXXXXXXXXXXX000X

WV-7084	Aeo * m5Ceom5Ceom5Ceom5Ceo * A * A * A * m5C * A * G * m5C * m5C * A * m5C * m5Ceom5CeoGeom5Ceo * m5Ceo	ACCCCAAACAGCCACCCGCC	X000XXXXXXXXXXX000X
WV-7085	m5Ceo * m5Ceom5CeoGeoGeo * m5C * A * G * m5C * m5C * G * A * A * m5C * m5C * m5Ceom5CeoAeoAeo * Aeo	CCCGGCAGCCGAACCCCAAA	X000XXXXXXXXXXXX000X
WV-7086	Teo * m5Ceom5Ceom5CeoGeo * G * m5C * A * G * m5C * m5C * G * A * A * m5C * m5Ceom5Ceom5CeoAeo * Aeo	TCCCGGCAGCCGAACCCCAA	X000XXXXXXXXXXX000X
WV-7087	Teo * Teom5Ceom5Ceom5Ceo * G * G * m5C * A * G * m5C * m5C * G * A * A * m5Ceom5Ceom5Ceom5Ceo * Aeo	TTCCCGGCAGCCGAACCCCA	X000XXXXXXXXXXX000X
WV-7088	m5Ceo * TeoTeom5Ceom5Ceo * m5C * G * G * m5C * A * G * m5C * m5C * G * A * Aeom5Ceom5Ceom5Ceo * m5Ceo	CTTCCCGGCAGCCGAACCCC	X000XXXXXXXXXXX000X
WV-7089	Teo * m5CeoTeoTeom5Ceo * m5C * m5C * G * G * m5C * A * G * m5C * m5C * G * AeoAeom5Ceom5Ceo * m5Ceo	TCTTCCCGGCAGCCGAACCC	X000XXXXXXXXXXX000X
WV-7090	m5Ceo * Teom5CeoTeoTeo * m5C * m5C * m5C * G * G * m5C * A * G * m5C * m5C * GeoAeoAeom5Ceo * m5Ceo	CTCTTCCCGGCAGCCGAACC	X000XXXXXXXXXXX000X
WV-7091	m5Ceo * m5CeoTeom5CeoTeo * T * m5C * m5C * m5C * G * G * m5C * A * G * m5C * m5CeoGeoAeoAeo * m5Ceo	CCTCTTCCCGGCAGCCGAAC	X000XXXXXXXXXXX000X
WV-7092	Geo * m5Ceom5CeoTeom5Ceo * T * T * m5C * m5C * m5C * G * G * m5C * A * G * m5Ceom5CeoGeoAeo * Aeo	GCCTCTTCCCGGCAGCCGAA	X000XXXXXXXXXXX000X
WV-7093	m5Ceo * Geom5Ceom5CeoTeo * m5C * T * T * m5C * m5C * m5C * G * G * m5C * A * Geom5Ceom5CeoGeo * Aeo	CGCCTCTTCCCGGCAGCCGA	X000XXXXXXXXXXX000X
WV-7094	m5Ceo * m5CeoGeom5CeoGeo * m5C * m5C * T * m5C * T * T * m5C * m5C * m5C * G * Geom5CeoAeoGeo * m5Ceo	CCGCGCCTCTTCCCGGCAGC	X000XXXXXXXXXXX000X
WV-7095	m5Ceo * m5Ceom5CeoGeom5Ceo * G * m5C * m5C * T * m5C * T * T * m5C * m5C * m5C * GeoGeom5CeoAeo * Geo	CCCGCGCCTCTTCCCGGCAG	X000XXXXXXXXXXX000X

WV-7096	Aeo * m5Ceom5Ceom5CeoGeo * m5C * G * m5C * m5C * T * m5C * T * T * m5C * m5C * m5CeoGeoGeom5Ceo * Aeo	ACCCGCGCCTCTTCCCGGCA	X0O0XXXXXXXXXXX0O0X
WV-7097	Teo * Aeom5Ceom5Ceom5Ceo * G * m5C * G * m5C * m5C * T * m5C * T * T * m5C * m5Ceom5CeoGeoGeo * m5Ceo	TACCCGCGCCTCTTCCCGGC	X0O0XXXXXXXXXXX0O0X
WV-7098	m5Ceo * TeoAeom5Ceom5Ceo * m5C * G * m5C * G * m5C * m5C * T * m5C * T * T * m5Ceom5Ceom5CeoGeo * Geo	CTACCCGCGCCTCTTCCCGG	X0O0XXXXXXXXXX0O0X
WV-7099	Teo * Teom5CeoTeoAeo * m5C * m5C * m5C * G * m5C * G * m5C * m5C * T * m5C * TeoTeom5Ceom5Ceo * m5Ceo	TTCTACCCGCGCCTCTTCCC	X0O0XXXXXXXXXX0O0X
WV-7100	m5Ceo * TeoTeom5CeoTeo * A * m5C * m5C * m5C * G * m5C * G * m5C * m5C * T * m5CeoTeoTeom5Ceo * m5Ceo	CTTCTACCCGCGCCTCTTCC	X0O0XXXXXXXXXX0O0X
WV-7101	Geo * m5CeoTeoTeom5Ceo * T * A * m5C * m5C * m5C * G * m5C * G * m5C * m5C * Teom5CeoTeoTeo * m5Ceo	GCTTCTACCCGCGCCTCTTC	X0O0XXXXXXXXXX0O0X
WV-7102	m5Ceo * Geom5CeoTeoTeo * m5C * T * A * m5C * m5C * m5C * G * m5C * G * m5C * m5CeoTeom5CeoTeo * Teo	CGCTTCTACCCGCGCCTCTT	X0O0XXXXXXXXXX0O0X
WV-7103	m5Ceo * m5CeoGeom5CeoTeo * T * m5C * T * A * m5C * m5C * m5C * G * m5C * G * m5Ceom5CeoTeom5Ceo * Teo	CCGCTTCTACCCGCGCCTCT	X0O0XXXXXXXXXX0O0X
WV-7117	Geo * Teo * Geo * m5Ceo * Teo * G * m5C * G * A * T * m5C * m5C * m5C * m5C * A * Teo * Teo * m5Ceo * m5Ceo * Aeo	GTGCTGCGATCCCCATTCCA	XXXXXXXXXXXXXXXXXX
WV-7118	Geo * TeoGeom5CeoTeo * G * m5C * G * A * T * m5C * m5C * m5C * A * TeoTeom5Ceom5Ceo * Aeo	GTGCTGCGATCCCCATTCCA	X0O0XXXXXXXXXX0O0X
WV-7119	Teo * Geo * Teo * Geo * m5Ceo * T * G * m5C * G * A * T * m5C * m5C * m5C * m5C * Aeo * Teo * Teo * m5Ceo * m5Ceo	TGTGCTGCGATCCCCATTCC	XXXXXXXXXXXXXXXXXX
WV-7120	Teo * GeoTeoGeom5Ceo * T * G * m5C * G * A * T * m5C * m5C * m5C * m5C * AeoTeoTeom5Ceo * m5Ceo	TGTGCTGCGATCCCCATTCC	X0O0XXXXXXXXXX0O0X

WV-7121	mC *S mCmUmCmA *S C *S T *S C *S A *S C *S C *S C *R A *S C *S T *S mCmGmCmC *S mA	CCUCACTCACCCACTCGCCA	SOOOSSSSSSSRSSSOOOS
WV-7122	mC *S mCmUmCmA *S C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S mCmGmCmC *S mA	CCUCACTCACCCACTCGCCA	SOOOSSSRSSSSSSSOOOS
WV-7123	mC *S mCmUmCmA *S C *S T *S C *R A *S C *S C *S C *R A *S C *S T *S mCmGmCmC *S mA	CCUCACTCACCCACTCGCCA	SOOOSSSRSSSRSSSOOOS
WV-7124	mC *S mCmUmCmA *S C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mCmGmCmC *S mA	CCUCACTCACCCACTCGCCA	SOOOSSSRSSRSSSSOOOS
WV-7125	mC *S mC *S mU *S mC *S mA *S C *S T *S C *R A *S C *S C *S C *R A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCUCACTCACCCACTCGCCA	SSSSSSSRSSSRSSSSSSS
WV-7126	mC *S mC *S mU *S mC *S mA *S C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCUCACTCACCCACTCGCCA	SSSSSSSRSSRSSSSSSSS
WV-7127	m5Ceo *S m5CeoTeom5CeoAeo *S C *S T *S C *S A *S C *S C *S C *R A *S C *S T *S m5CeoGeom5Ceom5Ceo *S Aeo	CCTCACTCACCCACTCGCCA	SOOOSSSSSSSRSSSOOOS
WV-7128	m5Ceo *S m5CeoTeom5CeoAeo *S C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S m5CeoGeom5Ceom5Ceo *S Aeo	CCTCACTCACCCACTCGCCA	SOOOSSSRSSSSSSSOOOS
WV-7129	m5Ceo *S m5CeoTeom5CeoAeo *S C *S T *S C *R A *S C *S C *S C *R A *S C *S T *S m5CeoGeom5Ceom5Ceo *S Aeo	CCTCACTCACCCACTCGCCA	SOOOSSSRSSSRSSSOOOS
WV-7130	m5Ceo *S m5CeoTeom5CeoAeo *S C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S m5CeoGeom5Ceom5Ceo *S Aeo	CCTCACTCACCCACTCGCCA	SOOOSSSRSSRSSSSOOOS
WV-7131	m5Ceo *S m5Ceo *S Teo *S m5Ceo *S Aeo *S C *S T *S C *R A *S C *S C *S C *R A *S C *S T *S m5Ceo *S Geo *S m5Ceo *S m5Ceo *S Aeo	CCTCACTCACCCACTCGCCA	SSSSSSSRSSSRSSSSSSS
WV-7132	m5Ceo *S m5Ceo *S Teo *S m5Ceo *S Aeo *S C *S T *S C *R A *S C *S C *R C *S A *S C	CCTCACTCACCCACTCGCCA	SSSSSSSRSSRSSSSSSSS

	*S T *S m5Ceo *S Geo *S m5Ceo *S m5Ceo *S Aeo		
WV-7405	R UR GR GR AR AR UR GR GR GR GR AR UR CR GR CR AR GR CR AR C	UGGAAUGGGGAUCGCAGCAC	OOOOOOOOOOOOO OOOOOO
WV-7434	R GR CR CR GR GR GR AR AR GR AR GR GR CR GR CR GR GR GR UR AR G	GCCGGGAAGAGGGCGCGGGUAG	OOOOOOOOOOOOO OOOOOOO
WV-7435	R AR GR CR CR GR UR CR CR UR GR CR UR GR CR CR CR GR GR U	AGCCGUCCCUGCUGCCCGGU	OOOOOOOOOOOOO OOOOOO
WV-7601	m5Ceo *R m5Ceo *R Teo *R m5Ceo *R Aeo *R C *S T *S C *R A *S C *S C *R C *S A *S C *S T *R m5Ceo *R Geo *R m5Ceo *R m5Ceo *R Aeo	CCTCACTCACCCACTCGCCA	RRRRRSSRSSRSSSRRRRR
WV-7602	m5Ceo *S m5CeoTeom5CeoAeo *R C *S T *S C *R A *S C *S C *R C *S A *S C *S T *R m5CeoGeom5Ceom5Ceo *S Aeo	CCTCACTCACCCACTCGCCA	SOOORSSRSSRSSSROOOS
WV-7603	mC *S mCmUmCmA *S C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S mCmGmC *S mC *S mA	CCUCACTCACCCACTCGCCA	SOOOSSSRSSSSSSOOSS
WV-7604	mC *S mCmUmCmA *S C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mCmGmC *S mC *S mA	CCUCACTCACCCACTCGCCA	SOOOSSSRSSRSSSOOSS
WV-7605	mC *S mCmUmCmA *S C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCUCACTCACCCACTCGCCA	SOOOSSSRSSSSSSSSSSS
WV-7606	mC *S mCmUmCmA *S C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCUCACTCACCCACTCGCCA	SOOOSSSRSSRSSSSSSSS
WV-7657	m5Ceo *R m5Ceo *R Teo *R m5Ceo *R Aeo *R C *S T *S C *S A *S C *S C *R C *S A *S C *S T *R m5Ceo *R Geo *R m5Ceo *R m5Ceo *R Aeo	CCTCACTCACCCACTCGCCA	RRRRRSSSSSRSSSRRRRR
WV-7658	m5Ceo *R m5CeoTeom5CeoAeo *R C *S T *S C *R A *S C *S C *R C *S A *S C *S T *R m5CeoGeom5Ceom5Ceo *R Aeo	CCTCACTCACCCACTCGCCA	ROOORSSRSSRSSSROOOR
WV-7659	m5Ceo *R m5CeoTeom5CeoAeo *R C *S T *S C *R A *S C *S C *S C *S A *S C *S T *R	CCTCACTCACCCACTCGCCA	ROOORSSRSSSSSSROOOR

	m5CeoGeom5Ceom5Ceo *R Aeo		
WV-7773	R UR GR GR AR AR UR GR GR GR GR AR UR CR GR CR AR GR CR AR CR A	UGGAAUGGGGAUCGCAGCACA	OOOOOOOOOOOOO OOOOOOO
WV-7774	mC *S mC *S mU *S mC *S mA *S C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S mCmGmCmC *S mA	CCUCACTCACCCACTCGCCA	SSSSSSSRSSSSSSSOOOS
WV-7775	mC *S mC *S mU *S mC *S mA *S C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mCmGmCmC *S mA	CCUCACTCACCCACTCGCCA	SSSSSSSRSSRSSSSOOOS
WV-7866	Aeo * m5Ceo * m5Ceo * Geo * Geo * G * m5C * A * G * m5C * A * G * G * G * A * m5Ceo * Geo * Geo * m5Ceo * Teo	ACCGGGCAGCAGGGACGGCT	XXXXXXXXXXXXXXXXXXXX
WV-8005	m5Ceo *R m5CeoTeom5CeoAeo *R C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S mCmGmC *S mC *S mA	CCTCACTCACCCACTCGCCA	ROOORSSRSSSSSSSOOSS
WV-8006	m5Ceo *R m5CeoTeom5CeoAeo *R C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mCmGmC *S mC *S mA	CCTCACTCACCCACTCGCCA	ROOORSSRSSRSSSSOOSS
WV-8007	m5Ceo *R m5CeoTeom5CeoAeo *R C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	ROOORSSRSSSSSSSSSS
WV-8008	m5Ceo *R m5CeoTeom5CeoAeo *R C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	ROOORSSRSSRSSSSSSSS
WV-8009	mC *S m5CeoTeom5CeomA *S C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S mCmGmC *S mC *S mA	CCTCACTCACCCACTCGCCA	SOOOSSSRSSSSSSSOOSS
WV-8010	mC *S m5CeoTeom5CeomA *S C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mCmGmC *S mC *S mA	CCTCACTCACCCACTCGCCA	SOOOSSSRSSRSSSSOOSS
WV-8011	mC *S m5CeoTeom5CeomA *S C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	SOOOSSSRSSSSSSSSSSS
WV-8012	mC *S m5CeoTeom5CeomA *S C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	SOOOSSSRSSRSSSSSSSS

WV-8114	mA *S mC *S mC *S mGmG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mC *S mGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SSSOSSSSSRSSRSSSOOS
WV-8115	mA *S m5CeomC *S mGmG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mC *S mGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SOSOSSSSSRSSRSSSOOS
WV-8116	mA *S mC *S m5CeomGmG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mC *S mGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SSOOSSSSSRSSRSSSOOS
WV-8117	mA *S mC *S mC *S mGmG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S m5CeomGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SSSOSSSSSRSSRSSOOOS
WV-8118	mA *S m5Ceom5CeomGmG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mC *S mGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SOOOSSSSSRSSRSSSOOS
WV-8119	mA *S m5CeomC *S mGmG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S m5CeomGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SOSOSSSSSRSSRSSOOOS
WV-8120	mA *S mC *S m5CeomGmG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S m5CeomGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SSOOSSSSSRSSRSSOOOS
WV-8121	mA *S m5Ceo *S m5CeomGmG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S m5CeomGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SSOOSSSSSRSSRSSOOOS
WV-8122	mA *S mC *S mC *S mGmG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mC *S mGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SSSOSSSSRSSRSSSSOOS
WV-8123	mA *S m5CeomC *S mGmG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mC *S mGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SOSOSSSSRSSRSSSSOOS
WV-8124	mA *S mC *S m5CeomGmG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mC *S mGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SSOOSSSSRSSRSSSSOOS
WV-8125	mA *S mC *S mC *S mGmG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S m5CeomGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SSSOSSSSRSSRSSSOOOS

WV-8126	mA *S m5Ceom5CeomGmG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mC *S mGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SOOOSSSSRSSRSSSSOOS
WV-8127	mA *S m5CeomC *S mGmG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S m5CeomGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SOSOSSSSRSSRSSSSOOOS
WV-8128	mA *S mC *S m5CeomGmG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S m5CeomGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SSOOSSSSRSSRSSSSOOOS
WV-8129	mA *S m5Ceo *S m5CeomGmG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S m5CeomGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SSOOSSSSRSSRSSSSOOOS
WV-8311	mA *S mC *S mC *S mG *S mG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mC *S mG *S mG *S mC *S mU	ACCGGGCAGCAGGGACGGCU	SSSSSSSSSRSSRSSSSSS
WV-8312	Aeo *R m5Ceom5CeoGeoGeo *R G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S m5CeoGeoGeom5Ceo *R Teo	ACCGGGCAGCAGGGACGGCT	ROOORSSSSRSSRSSOOR
WV-8313	Aeo *R m5Ceo *R m5Ceo *R Geo *R Geo *R G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S m5Ceo *R Geo *R Geo *R m5Ceo *R Teo	ACCGGGCAGCAGGGACGGCT	RRRRRSSSSRSSRSSRRRR
WV-8314	mA *S mC *S mC *S mGmG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S m5CeoGeoGeom5Ceo *R Teo	ACCGGGCAGCAGGGACGGCT	SSSOSSSSSRSSRSSSOOR
WV-8315	mA *S mC *S mC *S mG *S mG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mC *S mG *S mG *S mC *S mU	ACCGGGCAGCAGGGACGGCU	SSSSSSSSRSSRSSSSSSS
WV-8316	Aeo *R m5Ceom5CeoGeoGeo *R G *S C *S A *S G *R C *S A *S G *R G *S G *S A *R m5CeoGeoGeom5Ceo *R Teo	ACCGGGCAGCAGGGACGGCT	ROOORSSSRSSRSROOOR
WV-8317	Aeo *R m5Ceo *R m5Ceo *R Geo *R Geo *R G *S C *S A *S G *R C *S A *S G *R G *S G *S A *R m5Ceo *R Geo *R Geo *R m5Ceo *R Teo	ACCGGGCAGCAGGGACGGCT	RRRRRSSSRSSRSSRRRRR
WV-8318	mA *S mC *S mC *S mG *S mG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *R m5CeoGeoGeom5Ceo *R Teo	ACCGGGCAGCAGGGACGGCT	SSSSSSSSRSSRSSROOOR

WV-8319	m5Ceo *R m5CeoTeo *R m5CeoAeo *R C *S T *S C *R A *S C *S C *R C *S A *S C *S T *R m5CeoGeo *R m5Ceom5Ceo *R Aeo	CCTCACTCACCCACTCGCCA	RORORSSRSSRSSSRORORR
WV-8320	m5Ceo *R m5CeoTeo *R m5CeoAeo *R C *S T *S C *S A *S C *S C *R C *S A *S C *S T *R m5CeoGeo *R m5Ceom5Ceo *R Aeo	CCTCACTCACCCACTCGCCA	RORORSSSSSRSSSRORORR
WV-8321	m5Ceo *R m5Ceo *R Teom5CeoAeo *R C *S T *S C *R A *S C *S C *R C *S A *S C *S T *R m5CeoGeom5Ceo *R m5Ceo *R Aeo	CCTCACTCACCCACTCGCCA	RROORSSRSSRSSSROORR
WV-8322	m5Ceo *R m5Ceo *R Teo *R m5CeoAeo *R C *S T *S C *S A *S C *S C *R C *S A *S C *S T *R m5CeoGeom5Ceo *R m5Ceo *R Aeo	CCTCACTCACCCACTCGCCA	RRRORSSSSSRSSSROORR
WV-8329	m5Ceo *R m5Ceo *R Teom5CeoAeo *R C *S T *S C *S A *S C *S C *R C *S A *S C *S T *R m5CeoGeom5Ceo *R m5Ceo *R Aeo	CCTCACTCACCCACTCGCCA	RROORSSSSSRSSSROORR
WV-8444	L001mA * mCmCmGmG * G * C * A * G * C * A * G * G * G * A * mCmGmGmC * mU	ACCGGGCAGCAGGGACGGCU	OXOOOXXXXXXXXXXXOOOX
WV-8445	Mod024L001mA * mCmCmGmG * G * C * A * G * C * A * G * G * G * A * mCmGmGmC * mU	ACCGGGCAGCAGGGACGGCU	OXOOOXXXXXXXXXXXOOOX
WV-8446	Mod059L001mA * mCmCmGmG * G * C * A * G * C * A * G * G * G * A * mCmGmGmC * mU	ACCGGGCAGCAGGGACGGCU	OXOOOXXXXXXXXXXXOOOX
WV-8447	Mod007L001mA * mCmCmGmG * G * C * A * G * C * A * G * G * G * A * mCmGmGmC * mU	ACCGGGCAGCAGGGACGGCU	OXOOOXXXXXXXXXXXOOOX
WV-8452	mC *S m5CeoTeom5CeomA *S C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S m5CeomGm5CeomC *S mA	CCTCACTCACCCACTCGCCA	SOOOSSSRSSSSSSSOOOS
WV-8453	mC *S m5CeoTeom5CeomA *S C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S m5CeomGm5CeomC *S mA	CCTCACTCACCCACTCGCCA	SOOOSSSRSSRSSSSOOOS
WV-8454	mC *S m5CeoTeom5CeomA *S C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S mC *S mGmC *S mC *S mA	CCTCACTCACCCACTCGCCA	SOOOSSSRSSSSSSSOSS
WV-	mC *S m5CeoTeom5CeomA *S C *S T *S C *R	CCTCACTCACCCACTCGCCA	SOOOSSSRSSRSSSSSOSS

8455	A *S C *S C *R C *S A *S C *S T *S mC *S mGmC *S mC *S mA		
WV-8456	m5Ceo *R m5CeoTeom5CeoAeo *R C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S m5CeomGm5CeomC *S mA	CCTCACTCACCCACTCGCCA	ROOORSSRSSSSSSOOOS
WV-8457	m5Ceo *R m5CeoTeom5CeoAeo *R C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S m5CeomGm5CeomC *S mA	CCTCACTCACCCACTCGCCA	ROOORSSRSSRSSSSOOOS
WV-8458	m5Ceo *R m5CeoTeom5CeoAeo *R C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S mC *S mGmC *S mC *S mA	CCTCACTCACCCACTCGCCA	ROOORSSRSSSSSSSSOSS
WV-8459	m5Ceo *R m5CeoTeom5CeoAeo *R C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mC *S mGmC *S mC *S mA	CCTCACTCACCCACTCGCCA	ROOORSSRSSRSSSSSOSS
WV-8460	m5Ceo *R m5Ceo *R Teo *R m5Ceo *R Aeo *R C *S T *S C *R A *S C *S C *S C *S A *S C *S T *R m5Ceo *R Geo *R m5Ceo *R m5Ceo *R Aeo	CCTCACTCACCCACTCGCCA	RRRRRSSRSSSSSSRRRRR
WV-8461	m5Ceo *R m5Ceo *R Teom5CeoAeo *R C *S T *S C *R A *S C *S C *S C *S A *S C *S T *R m5CeoGeom5Ceo *R m5Ceo *R Aeo	CCTCACTCACCCACTCGCCA	RROORSSRSSSSSSROORR
WV-8462	mA *S mCmCmGmG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mCmGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SOOOSSSSSRSSRSSOOOS
WV-8463	mA *S mCmCmGmG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mCmGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SOOOSSSSSRSSRSSOOOS
WV-8464	mA *S mCmCmGmG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mC *S mG *S mG *S mC *S mU	ACCGGGCAGCAGGGACGGCU	SOOOSSSSSRSSRSSSSSS
WV-8465	mA *S mCmCmGmG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mC *S mG *S mG *S mC *S mU	ACCGGGCAGCAGGGACGGCU	SOOOSSSSSRSSRSSSSSS
WV-8466	Aeo *R m5Ceom5CeoGeoGeo *R G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mCmGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	ROOORSSSSRSSRSSOOOS

WV-8467	Aeo *R m5Ceom5CeoGeoGeo *R G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mCmGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	ROOORSSSRSSRSSSOOOS
WV-8468	Aeo *R m5Ceom5CeoGeoGeo *R G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mC *S mGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	ROOORSSSSRSSRSSSOOS
WV-8469	Aeo *R m5Ceom5CeoGeoGeo *R G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mC *S mGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	ROOORSSSRSSRSSSSOOS
WV-8470	Aeo *R m5Ceom5CeoGeoGeo *R G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mC *S mG *S mG *S mC *S mU	ACCGGGCAGCAGGGACGGCU	ROOORSSSSRSSRSSSSSS
WV-8471	Aeo *R m5Ceom5CeoGeoGeo *R G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mC *S mG *S mG *S mC *S mU	ACCGGGCAGCAGGGACGGCU	ROOORSSSRSSRSSSSSSS
WV-8472	mA *S m5Ceom5CeomG *S mG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mCmGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SOOSSSSSSRSSRSSOOOS
WV-8473	mA *S m5Ceom5CeomG *S mG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mCmGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SOOSSSSSRSSRSSSOOOS
WV-8474	mA *S m5Ceom5CeomG *S mG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mC *S mGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SOOSSSSSSRSSRSSSOOS
WV-8475	mA *S m5Ceom5CeomG *S mG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mC *S mGmGmC *S mU	ACCGGGCAGCAGGGACGGCU	SOOSSSSSRSSRSSSSOOS
WV-8476	mA *S m5Ceom5CeomG *S mG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mC *S mG *S mG *S mC *S mU	ACCGGGCAGCAGGGACGGCU	SOOSSSSSSRSSRSSSSSS
WV-8477	mA *S m5Ceom5CeomG *S mG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mC *S mG *S mG *S mC *S mU	ACCGGGCAGCAGGGACGGCU	SOOSSSSSRSSRSSSSSSS
WV-8547	m5Ceo * m5CeoTeom5CeoAeo * C * T * C * A * C * C * C * A * C * T * mCmGmC * mC * mA	CCTCACTCACCCACTCGCCA	XOOOXXXXXXXXXXOOXX

WV-8548	m5Ceo * m5CeoTeom5CeoAeo * C * T * C * A * C * C * C * A * C * T * mC * mG * mC * mC * mA	CCTCACTCACCCACTCGCCA	XOOOXXXXXXXXXXXXXXX
WV-8549	mC * m5CeoTeom5CeomA * C * T * C * A * C * C * C * A * C * T * mCmGmC * mC * mA	CCTCACTCACCCACTCGCCA	XOOOXXXXXXXXXXXXXOOXX
WV-8550	mC * m5CeoTeom5CeomA * C * T * C * A * C * C * C * A * C * T * mC * mG * mC * mC * mA	CCTCACTCACCCACTCGCCA	XOOOXXXXXXXXXXXXXXXX
WV-8551	mC * m5CeoTeom5CeomA * C * T * C * A * C * C * C * A * C * T * mC * mGmC * mC * mA	CCTCACTCACCCACTCGCCA	XOOOXXXXXXXXXXXXOXX
WV-8568	mA *S m5Ceom5CeoGeomG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mC *S mG *S mG *S mC *S mU	ACCGGGCAGCAGGGACGGCU	SOOOSSSSSRSSRSSSSSS
WV-8569	mA *S m5Ceom5CeoGeomG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mC *S mG *S mG *S mC *S mU	ACCGGGCAGCAGGGACGGCU	SOOOSSSSRSSRSSSSSSS
WV-8594	Aeo * m5Ceom5CeoGeoGeo * G * C * A * G * C * A * G * G * G * A * mC * mG * mG * mC * mU	ACCGGGCAGCAGGGACGGCU	XOOOXXXXXXXXXXXXXXX
WV-8595	mA * m5Ceom5CeoGeomG * G * C * A * G * C * A * G * G * G * A * mC * mG * mG * mC * mU	ACCGGGCAGCAGGGACGGCU	XOOOXXXXXXXXXXXXXXX
WV-8691	mA *S m5Ceom5CeoGeomG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mC *S mGmG *S mC *S mU	ACCGGGCAGCAGGGACGGCU	SOOOSSSSSRSSRSSSOSS
WV-8692	mA *S m5Ceom5CeoGeomG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S mC *S mGmG *S mC *S mU	ACCGGGCAGCAGGGACGGCU	SOOOSSSSRSSRSSSSOSS
WV-8693	mA * m5Ceom5CeoGeomG * G * C * A * G * C * A * G * G * G * A * mC * mGmG * mC * mU	ACCGGGCAGCAGGGACGGCU	XOOOXXXXXXXXXXXXOXX
WV-8694	mA *S m5Ceom5CeoGeomG *S G *S C *S A *S G *S C *R A *S G *S G *R G *S A *S mCmGmG *S mC *S mU	ACCGGGCAGCAGGGACGGCU	SOOOSSSSSRSSRSSSOOSS
WV-8695	mA *S m5Ceom5CeoGeomG *S G *S C *S A *S G *R C *S A *S G *R G *S G *S A *S	ACCGGGCAGCAGGGACGGCU	SOOOSSSSRSSRSSSOOSS

	mCmGmG *S mC *S mU		
WV-8696	mA * m5Ceom5CeoGeomG * G * C * A * G * C * A * G * G * G * A * mCmGmG * mC * mU	ACCGGGCAGCAGGGACGGCU	XOOOXXXXXXXXXXOOXX
WV-9062	L001mC *S m5CeoTeom5CeomA *S C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	OSOOOSSSRSSSSSSSSSS
WV-9063	Mod007L001mC *S m5CeoTeom5CeomA *S C *S T *S C *R A *S C *S C *S C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	OSOOOSSSRSSSSSSSSSS
WV-9228	R GR GR UR GR GR CR GR AR GR UR GR GR GR UR GR AR GR UR GR AR GR GR AR G	GGUGGGCGAGUGGGGUGAGUG AGGAG	OOOOOOOOOOOOOOOOO OOOOOO
WV-9285	L001mC *S m5CeoTeom5CeomA *S C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mC *S mGmC *S mC *S mA	CCTCACTCACCCACTCGCCA	OSOOOSSSRSSRSSSSSOSS
WV-9286	Mod007L001mC *S m5CeoTeom5CeomA *S C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mC *S mGmC *S mC *S mA	CCTCACTCACCCACTCGCCA	OSOOOSSSRSSRSSSSSOSS
WV-9380	L001mC *S m5CeoTeom5CeomA *S C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	OSOOOSSSRSSRSSSSSSS
WV-9381	Mod007L001mC *S m5CeoTeom5CeomA *S C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	OSOOOSSSRSSRSSSSSSS
WV-9394	mC *S m5CeoTeom5CeomA *S C *S T *S CA *S C *S C *S C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	SOOOSSSOSSSSSSSSSSS
WV-9395	mC *S m5CeoTeom5CeomA *S C *S T *S CA *S C *S CC *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	SOOOSSSOSSOSSSSSSS
WV-9396	mC *S m5CeoTeom5CeomA *S C *S T *S C5MSdA *S C *S C *S C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	SOOOSSSOSSSSSSSSSSS
WV-9397	mC *S m5CeoTeom5CeomA *S C *S T *S C5MSdA *S C *S C5MSdC *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	SOOOSSSOSSOSSSSSSSS

WV-9398	mC *S m5CeoTeom5CeomA *S C *S T *S C5MRdA *S C *S C *S C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	SOOOSSSOSSSSSSSSSS
WV-9399	mC *S m5CeoTeom5CeomA *S C *S T *S C5MRdA *S C *S C5MRdC *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	SOOOSSSOSSOSSSSSSSS
WV-9421	Mod059L00 lmC *S m5CeoTeom5CeomA *S C *S T *S C *R A *S C *S C *R C *S A *S C *S T *S mC *S mG *S mC *S mC *S mA	CCTCACTCACCCACTCGCCA	OSOOOSSSRSSRSSSSSSS

WV-9486	mU * Aeom5Ceom5CeomC * G * C * G * C * C * T * C * T * T * C * mC * mC * mG * mG * mC	UACCCGCGCCTCTTCCCGGC	XOOOXXXXXX XXXXXXX
WV-9487	mC * TeoAeom5CeomC * C * G * C * G * C * C * T * C * T * T * mC * mC * mC * mG * mG	CTACCCGCGCCTCTTCCCGG	XOOOXXXXXX XXXXXXX
WV-9488	mG * GeoGeom5CeomU * C * T * C * C * T * C * C * A * G * A * G * mC * mU * mC * mG * mA	GGGCUCTCCTCAGAGCUCGA	XOOOXXXXXX XXXXXXX
WV-9489	mG * GeoGeoTeomG * T * C * G * G * G * C * T * T * T * T * C * mG * mC * mC * mU * mC	GGGTGTCGGGCTTTCGCCUC	XOOOXXXXXX XXXXXXX
WV-9490	mG * m5CeoAeoTeomC * C * G * G * G * C * C * C * C * C * G * G * mC * mC * mU * mU * mC	GCATCCGGGCCCCGGGCUUC	XOOOXXXXXX XXXXXXX
WV-9491	mC * m5CeoTeoTeomC * C * C * T * G * A * A * G * G * T * T * mC * mC * mU * mC * mC	CCTTCCCTGAAGGTTCCUCC	XOOOXXXXXX XXXXXXX
WV-9492	mC * m5Ceom5CeoGeomG * C * C * C * C * T * A * G * C * G * C * mG * mC * mG * mA * mC	CCCGGCCCCCTAGCGCGCGAC	XOOOXXXXXX XXXXXXX
WV-9493	m5Ceo * m5Ceom5CeoGeoGeo * C * C * C * C * T * A * G * C * G * C * Geom5CeoGeoAeo * m5Ceo	CCCGGCCCCCTAGCGCGCGAC	XOOOXXXXXX XXXOOOX
WV-9494	mG * TeoGeom5CeomU * G * C * G * A * T * C * C * C * C * A * mU * mU * mC * mC * mA	GTGCUGCGATCCCCAUUCCA	XOOOXXXXXX XXXXXXX
WV-9505	mC * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * SC * RA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	SOOOSSS RSSSRSSSSSSS
WV-9506	mC * Sm5CeoTeom5CeomA * SC * ST * SC * SA * SC * SC * SC * RA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	SOOOSSS SSSSRSSSSSSS
WV-	mC * Sm5CeoTeom5CeomA * SC * ST * SC * SA * SC *	CCTCACTCACCCACTCGCCA	SOOOSSS SSSRSSSSSSS

9507	SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	SOOOSSS RSSRSSSSSSSS
WV-9508	mC * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SfC * SfG * SfC * SfC * SfA	CCTCACTCACCCACTCGCCA	SOOOSSS RSSSRSSSSSSS
WV-9509	mC * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * SC * RA * SC * ST * SfC * SfG * SfC * SfC * SfA	CCTCACTCACCCACTCGCCA	SOOOSSS RSSSRSSSSSSS
WV-9510	mC * m5CeoTeom5CeomA * C * T * C * A * C * C * C * A * C * T * fC * fG * fC * fC * fA	CCTCACTCACCCACTCGCCA	XOOOXXXXXXX XXXXXXX
WV-9694	mC * mCmCmGmG * C * C * C * C * T * A * G * C * G * C * mGmCmGmA * mC	CCCGGCCCCTAGCGCGCGAC	XOOOXXXXXXX XXXXOOOX
WV-9695	mU * mAmCmAmG * G * C * T * G * C * G * G * T * T * G * mUmUmUmC * mC	UACAGGCTGCGGTTGUUUCC	XOOOXXXXXXX XXXXOOOX

WV-10406	mG * AeoTeoGeomC * C * G * C * C * T * C * C * T * C * A * mC * mU * mC * mA * mC	GATGCCGCCTCCTCACUCAC	XOOOXXXXXXX XXXXXXX
WV-10407	mA * TeoGeom5CeomC * G * C * C * T * C * C * T * C * A * C * mU * mC * mA * mC * mC	ATGCCGCCTCCTCACUCACC	XOOOXXXXXXX XXXXXXX
WV-10408	mU * Geom5Ceom5CeomG * C * C * T * C * C * T * C * A * C * T * mC * mA * mC * mC * mC	UGCCGCCTCCTCACTCACCC	XOOOXXXXXXX XXXXXXX
WV-10409	mG * m5Ceom5CeoGeomC * C * T * C * C * T * C * A * C * T * C * mA * mC * mC * mC * mA	GCCGCCTCCTCACTCACCCA	XOOOXXXXXXX XXXXXXX
WV-10410	mC * m5CeoGeom5CeomC * T * C * C * T * C * A * C * T * C * A * mC * mC * mC * mA * mC	CCGCCTCCTCACTCACCCAC	XOOOXXXXXXX XXXXXXX
WV-10411	mC * Geom5Ceom5CeomU * C * C * T * C * A * C * T * C * A * C * mC * mA * mC * mU	CGCCUCCTCACTCACCCACU	XOOOXXXXXXX XXXXXXX
WV-10412	mG * m5Ceom5CeoTeomC * C * T * C * A * C * T * C * A * C * C * mC * mA * mC * mU * mC	GCCTCCTCACTCACCCACUC	XOOOXXXXXXX XXXXXXX
WV-10413	mC * m5CeoTeom5CeomC * T * C * A * C * C * T * C * A * C * C * C * mA * mC * mU * mC * mG	CCTCCTCACTCACCCACUCG	XOOOXXXXXXX XXXXXXX
WV-10414	mC * Teom5Ceom5CeomU * C * A * C * T * C * A * C * C * C * A * mC * mU * mC * mG * mC	CTCCUCACTCACCCACUCGC	XOOOXXXXXXX XXXXXXX
WV-10415	mU * m5Ceom5CeoTeomC * A * C * T * C * A * C * C * C * A * C * mU * mC * mG * mC * mC	UCCTCACTCACCCACUCGCC	XOOOXXXXXXX XXXXXXX
WV-10416	mC * Teom5CeoAeomC * T * C * A * C * C * C * A * C * T * C * mG * mC * mC * mA * mC	CTCACTCACCCACTCGCCAC	XOOOXXXXXXX XXXXXXX

WV-10417	mC * Aeom5CeoTeomC * A * C * C * C * A * C * T * C * G * C * mC * mA * mC * mC * mG	CACTCACCCACTCGCCACCG	X000XXXXXX XXXXXXXX
WV-10418	mA * m5CeoTeom5CeomA * C * C * C * A * C * T * C * G * C * C * mA * mC * mC * mG * mC	ACTCACCCACTCGCCACCGC	X000XXXXXX XXXXXXXX
WV-10419	mC * Teom5CeoAeomC * C * C * A * C * T * C * G * C * C * A * mC * mC * mG * mC * mC	CTCACCCACTCGCCACCGCC	X000XXXXXX XXXXXXXX
WV-10420	mU * m5CeoAeom5CeomC * C * A * C * T * C * G * C * C * A * C * mC * mG * mC * mC * mU	UCACCCACTCGCCACCGCCU	X000XXXXXX XXXXXXXX
WV-10421	mC * Aeom5Ceom5CeomC * A * C * T * C * G * C * C * A * C * C * mG * mC * mC * mU * mG	CACCCACTCGCCACCGCCUG	X000XXXXXX XXXXXXXX
WV-10422	mA * m5Ceom5Ceom5CeomA * C * T * C * G * C * C * A * C * C * G * mC * mC * mU * mG * mC	ACCCACTCGCCACCGCCUGC	X000XXXXXX XXXXXXXX
WV-10423	mC * m5Ceom5CeoAeomC * T * C * G * C * C * A * C * C * G * C * mC * mU * mG * mC * mG	CCCACTCGCCACCGCCUGCG	X000XXXXXX XXXXXXXX
WV-10424	mC * m5CeoAeom5CeomU * C * G * C * C * A * C * C * C * G * C * C * mU * mG * mC * mG * mC	CCACUCGCCACCGCCUGCGC	X000XXXXXX XXXXXXXX
WV-10425	mU * m5CeoAeom5CeomU * C * A * C * C * C * A * C * C * T * C * G * mC * mC * mA * mC * mC	UCACUCACCCACTCGCCACC	X000XXXXXX XXXXXXXX
WV-10426	fC * fC * fU * fC * fA * fC * mU * mC * mA * mC * mC * mC * mA * mC * fU * fC * fG * fC * fC * fA	CCUCACUCACCCACUCGCCA	XXXXXXXXXX XXXXXXXX
WV-10427	m5Ceo * m5Ceo * m5Ceo * Geo * Geo * C * C * C * C * T * A * G * C * C * G * C * Geo * m5Ceo * Geo * Aeo * m5Ceo	CCCGGCCCCTAGCGCGCGAC	XXXXXXXXXX XXXXXXXX
WV-10428	Geo * m5Ceo * m5Ceo * m5Ceo * C * T * A * G * C * G * C * G * G * C * G * C * C * G * Aeo * m5Ceo * Teo * m5Ceo	GCCCCTAGCGCGCGACTC	XXXXXXXXXX XXXXXX
WV-10429	Geo * m5Ceo * m5Ceo * C * C * T * A * G * C * G * C * G * C * G * C * C * G * A * m5Ceo * Teo * m5Ceo	GCCCCTAGCGCGCGACTC	XXXXXXXXXX XXXXXX
WV-10430	Geo * m5Ceo * m5Ceo * m5Ceo * m5Ceo * m5Ceo * T * A * G * C * G * C * C * G * C * Geo * Aeo * m5Ceo * Teo * m5Ceo	GCCCCTAGCGCGCGACTC	XXXXXXXXXX XXXXXX
WV-10431	Geo * m5Ceom5Ceom5Ceom5Ceo * T * A * G * C * G * C * G * C * C * GeoAeom5Ceo * Teo * m5Ceo	GCCCCTAGCGCGCGACTC	X000XXXXXX XX00XX
WV-10844	mG * m5CeoTeoTeomG * G * T * G * T * G * T * C * A * G * C * mC * mG * mU * mC * mC	GCTTGGTGTGTCAGCCGUCC	X000XXXXXX XXXXXXXX
WV-10845	mC * TeoTeoGeomG * T * G * T * G * T * C * A * G * C * C * mG * mU * mC * mC * mC	CTTGGTGTGTCAGCCGUCCC	X000XXXXXX XXXXXXXX
WV-10846	mG * Teom5CeoAeomG * C * C * G * T * C * C * C * T * G * C * mU * mG * mC * mC * mC	GTCAGCCGTCCCTGCUGCCC	X000XXXXXX XXXXXXXX

WV-10847	mG * m5Ceom5CeoGeomU * C * C * C * T * G * C * T * G * C * C * mC * mG * mU * mU	GCCGUCCCTGCTGCCCGGUU	X000XXXXXX XXXXXXXX
WV-10848	mG * Teom5Ceom5CeomC * T * G * C * T * G * C * C * C * C * G * G * mU * mU * mG * mC * mU	GTCCCTGCTGCCCGGUUGCU	X000XXXXXX XXXXXXXX
WV-10849	mC * m5CeoTeoGeomC * T * G * C * C * C * G * G * T * T * G * mC * mU * mU * mC * mU	CCTGCTGCCCGGTTGCUUCU	X000XXXXXX XXXXXXXX
WV-10850	mC * m5CeoGeom5CeomA * G * C * C * C * T * G * T * T * A * G * C * A * mA * mG * mC * mU * mC	CCGCAGCCTGTAGCAAGCUC	X000XXXXXX XXXXXXXX
WV-10851	mG * m5CeoGeoGeomU * T * G * C * G * G * T * T * G * C * C * T * mG * mC * mG * mC * mC	GCGGUTGCGGTGCCTGCGCC	X000XXXXXX XXXXXXXX
WV-10852	mG * TeoTeoGeomC * G * G * T * G * C * C * T * T * G * C * C * G * mC * mC * mC * mG * mC	GTTGCGGTGCCTGCGCCCGC	X000XXXXXX XXXXXXXX
WV-10853	mG * Geom5CeoGeomG * A * G * G * C * G * C * C * A * G * G * C * mG * mG * mU * mU * mG * mG	GGCGGAGGCGCAGGCGGUGG	X000XXXXXX XXXXXXXX
WV-10854	mG * m5CeoAeoGeomG * C * G * G * T * T * G * G * C * C * G * A * G * mU * mG * mG * mG * mU	GCAGGCGGTGGCGAGUGGGU	X000XXXXXX XXXXXXXX
WV-10855	mG * m5CeoGeoGeomC * A * T * C * C * C * T * G * G * G * C * G * G * mG * mU * mG * mG * mC	GCGGCATCCTGGCGGGUGGC	X000XXXXXX XXXXXXXX
WV-10856	mG * m5CeoAeoTeomC * C * T * G * G * C * G * G * G * G * T * G * mG * mC * mU * mG * mU	GCATCCTGGCGGGTGGCUGU	X000XXXXXX XXXXXXXX
WV-10857	mG * m5CeoTeoGeomG * G * T * G * T * C * G * G * G * G * C * T * mU * mU * mC * mG * mC	GCTGGGTGTCGGGCTUUCGC	X000XXXXXX XXXXXXXX
WV-10858	mA * TeoTeoGeomC * C * T * G * C * A * T * C * C * G * G * mG * mC * mC * mC * mC	ATTGCCTGCATCCGGGCCCC	X000XXXXXX XXXXXXXX
WV-10859	mU * Geom5Ceom5CeomU * G * C * A * T * C * C * G * G * G * C * mC * mC * mC * mG * mG	UGCCUGCATCCGGGCCCCGG	X000XXXXXX XXXXXXXX
WV-10860	mC * TeoTeom5CeomC * T * T * G * C * T * T * T * T * C * C * C * mG * mC * mC * mC * mU	CTTCCTTGCTTTCCCGCCCU	X000XXXXXX XXXXXXXX
WV-10861	mU * m5Ceom5CeoTeomU * G * C * T * T * T * C * C * C * C * G * C * mC * mC * mU * mC * mA	UCCTUGCTTTCCCGCCCUCA	X000XXXXXX XXXXXXXX
WV-11039	m5Ceo * m5Ceo * m5Ceo * Geo * Geo * m5C * m5C * m5C * m5C * T * A * G * m5C * G * m5C * Geo * m5Ceo * Geo * Aeo * m5Ceo	CCCGGCCCCTAGCGCGCGAC	XXXXXXXXXX XXXXXXXX
WV-11040	Geo * m5Ceo * m5Ceo * m5Ceo * m5Ceo * T * A * G * m5C * G * m5C * G * m5C * Geo * Aeo * m5Ceo * Teo * m5Ceo	GCCCCTAGCGCGCGACTC	XXXXXXXXXX XXXXXX

WV-11041	Geo * m5Ceom5Ceom5Ceom5Ceo * T * A * G * m5C * G * m5C * G * m5C * GeoAeom5Ceo * Teo * m5Ceo	GCCCCTAGCGCGCGACTC	XOOOXXXXXXX XXOOXX
WV-11042	m5Ceo * Rm5Ceo * Rm5Ceo * RGeo * RGeo * Rm5C * Sm5C * Sm5C * Sm5C * ST * RA * SG * Sm5C * SG * Sm5C * SGeo * Rm5Ceo * RGeo * RAeo * Rm5Ceo	CCCGGCCCCCTAGCGCGCGAC	RRRRRSSSSRS SSSSRRRR
WV-11043	m5Ceo * Rm5Ceo * Rm5Ceo * SGeo * RGeo * Rm5C * Sm5C * Sm5C * Sm5C * ST * RA * SG * Sm5C * SG * Sm5C * SGeo * Rm5Ceo * RGeo * RAeo * Rm5Ceo	CCCGGCCCCCTAGCGCGCGAC	RRSRRSSSSRS SSSSRRRR
WV-11044	m5Ceo * Rm5Ceo * Rm5Ceo * RGeo * RGeo * Rm5C * Sm5C * Sm5C * Sm5C * ST * RA * SG * Sm5C * SG * Sm5C * SGeo * Rm5Ceo * RGeo * RAeo * Rm5Ceo	CCCGGCCCCCTAGCGCGCGAC	RRRRRSSSSR SSSSSRSRR
WV-11045	m5Ceo * Sm5Ceo * Sm5Ceo * RGeo * SGeo * Sm5C * Sm5C * Sm5C * Sm5C * ST * RA * SG * Sm5C * SG * Sm5C * SGeo * Sm5Ceo * RGeo * SAeo * Sm5Ceo	CCCGGCCCCCTAGCGCGCGAC	SSRSSSSSSRS SSSSSRSS
WV-11046	m5Ceo * Sm5Ceo * Sm5Ceo * SGeo * SGeo * Sm5C * Sm5C * Sm5C * Sm5C * ST * RA * SG * Sm5C * SG * Sm5C * SGeo * Sm5Ceo * SGeo * SAeo * Sm5Ceo	CCCGGCCCCCTAGCGCGCGAC	SSSSSSSSS RSSSSSSSS
WV-11532	mC * Sm5Ceon001Teon001m5Ceon001mA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	SnXnXnXSSSR SSRSSSSSSS
WV-11963	mC * mCmUmCmA * C * T * C * A * C * C * C * A * C * BrdU * mCmGmCmC * mA	CCUCACTCACCCACTCGCCA	XOOOXXXXXXX XXXXOOOX
WV-11964	m5Ceo * m5CeoTeom5CeoAeo * C * T * C * A * C * C * C * A * C * BrdU * m5CeoGeom5Ceom5Ceo * Aeo	CCTCACTCACCCACTCGCCA	XOOOXXXXXXX XXXXOOOX
WV-11965	m5Ceo * Sm5CeoTeom5CeoAeo * SC * ST * SC * RA * SC * SC * RC * SA * SC * SBrdU * Sm5CeoGeom5Ceom5Ceo * SAeo	CCTCACTCACCCACTCGCCA	SOOOSSS RSSRSSSSOOOS
WV-11966	mC * m5CeoTeom5CeomA * C * T * C * A * C * C * C * A * C * BrdU * mC * mG * mC * mA	CCTCACTCACCCACTCGCCA	XOOOXXXXXXX XXXXXXXX
WV-11967	mC * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * SBrdU * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	SOOOSSS RSSRSSSSSSS
WV-12048	rUrGrGrCrGrArGrUrGrGrGrUrGrArGrGrG	UGGCGAGUGGGGUGAGUGAGG	OOOOOOOOO OOOOOOOOO
WV-12439	m5Ceo * Teom5CeoAeom5Ceo * T * C * A * C * C * C * A * C * T * C * mG * mC * mC * mA * mC	CTCACTCACCCACTCGCCAC	XOOOXXXXXXX XXXXXXX

WV-12440	Teo * m5Ceom5CeoTeom5Ceo * A * C * T * C * A * C * C * C * A * C * mU * mC * mG * mC * mC	TCCTCACTCACCCACUCGCC	X000XXXXXX XXXXXXX
WV-12441	Teo * Geom5Ceom5CeoGeo * C * C * T * C * C * T * C * A * C * T * mC * mA * mC * mC * mC	TGCCGCCTCCTCACTCACCC	X000XXXXXX XXXXXXX
WV-12442	Geo * m5CeoGeom5CeoGeo * A * C * T * C * C * T * G * A * G * T * mU * mC * mC * mA * mG	GCGCGACTCCTGAGTUCCAG	X000XXXXXX XXXXXXX
WV-12443	Geo * AeoGeom5CeoTeo * T * G * C * T * A * C * A * G * G * C * mU * mG * mC * mG * mG	GAGCTTGCTACAGGCUGCGG	X000XXXXXX XXXXXXX
WV-12444	m5Ceo * AeoGeoGeoAeo * T * G * C * C * G * C * C * T * C * C * mU * mC * mA * mC * mU	CAGGATGCCGCCTCCUCACU	X000XXXXXX XXXXXXX
WV-12445	mC * mU * mC * mA * mC * T * C * A * C * C * C * C * A * C * T * C * Geom5Ceom5CeoAeo * m5Ceo	CUCACTCACCCACTCGCCAC	XXXXXXXXXX XXXX000X
WV-12446	mC * mC * mU * mC * mA * C * T * C * A * C * C * C * C * A * C * C * T * m5CeoGeom5Ceom5Ceo * Aeo	CCUCACTCACCCACTCGCCA	XXXXXXXXXX XXXX000X
WV-12447	mU * mC * mC * mU * mC * A * C * T * C * A * C * C * C * C * A * C * Teom5CeoGeom5Ceo * m5Ceo	UCCUCACTCACCCACTCGCC	XXXXXXXXXX XXXX000X
WV-12448	mU * mG * mC * mC * mG * C * C * T * C * C * T * C * C * A * C * T * m5CeoAeom5Ceom5Ceo * m5Ceo	UGCCGCCTCCTCACTCACCC	XXXXXXXXXX XXXX000X
WV-12449	mG * mC * mG * mC * mG * A * C * T * C * C * T * G * A * G * T * Teom5Ceom5CeoAeo * Geo	GCGCGACTCCTGAGTTCCAG	XXXXXXXXXX XXXX000X
WV-12450	mG * mA * mG * mC * mU * T * G * C * T * A * C * C * A * G * G * C * TeoGeom5CeoGeo * Geo	GAGCUTGCTACAGGCTGCGG	XXXXXXXXXX XXXX000X
WV-12451	mC * mA * mG * mG * mA * T * G * C * C * G * C * C * T * C * C * Teom5CeoAeom5Ceo * Teo	CAGGATGCCGCCTCCTCACT	XXXXXXXXXX XXXX000X
WV-12480	m5Ceo * Teom5CeoAeom5Ceo * T * C * A * C * C * C * C * A * C * T * C * Geom5Ceom5CeoAeo * m5Ceo	CTCACTCACCCACTCGCCAC	X000XXXXXX XXXX000X
WV-12481	Teo * m5Ceom5CeoTeom5Ceo * A * C * T * C * A * C * C * C * A * C * C * Teom5CeoGeom5Ceo * m5Ceo	TCCTCACTCACCCACTCGCC	X000XXXXXX XXXX000X
WV-12482	Teo * Geom5Ceom5CeoGeo * C * C * T * C * C * T * C * A * C * C * T * m5CeoAeom5Ceom5Ceo * m5Ceo	TGCCGCCTCCTCACTCACCC	X000XXXXXX XXXX000X
WV-12483	Geo * m5CeoGeom5CeoGeo * A * C * T * C * C * T * G * A * G * T * Teom5Ceom5CeoAeo * Geo	GCGCGACTCCTGAGTTCCAG	X000XXXXXX XXXX000X
WV-12484	Geo * AeoGeom5CeoTeo * T * G * C * T * A * C * A * G * G * C * TeoGeom5CeoGeo * Geo	GAGCTTGCTACAGGCTGCGG	X000XXXXXX XXXX000X
WV-12485	m5Ceo * AeoGeoGeoAeo * mA * T * G * C * C * G * C * C * T * C * C * Teom5CeoAeom5Ceo * Teo	CAGGAATGCCGCCTCCTCACT	X000XXXXXX XXXX000X

WV-12486	m5Ceo * AeoGeoGeoAeo * T * G * C * C * G * C * C * T * C * C * Teom5CeoAeom5Ceo * Teo	CAGGATGCCGCCTCCTCACT	XOOOXXXXXX XXXXOOOX
WV-12487	Teo * m5Ceom5CeoTeoTeo * G * C * T * T * T * C * C * C * G * C * m5Ceom5CeoTeom5Ceo * Aeo	TCCTTGCTTTCCCGCCCTCA	XOOOXXXXXX XXXXOOOX
WV-12488	Geo * m5CeoAeoTeom5Ceo * C * G * G * G * C * C * C * C * G * G * Geom5CeoTeoTeo * m5Ceo	GCATCCGGGCCCCGGGCTTC	XOOOXXXXXX XXXXOOOX
WV-12489	Teo * m5Ceom5CeoTeoTeo * G * C * T * T * T * C * C * C * G * C * mC * mC * mU * mC * mA	TCCTTGCTTTCCCGCCCUCA	XOOOXXXXXX XXXXXXXX
WV-12490	Geo * m5CeoAeoTeom5Ceo * C * G * G * G * C * C * C * C * G * G * mG * mC * mU * mU * mC	GCATCCGGGCCCCGGGCUUC	XOOOXXXXXX XXXXXXXX
WV-12491	mU * mC * mC * mU * mU * G * C * T * T * T * C * C * C * G * C * m5Ceom5CeoTeom5Ceo * Aeo	UCCUUGCTTTCCCGCCCTCA	XXXXXXXXXX XXXXOOOX
WV-12492	mG * mC * mA * mU * mC * C * G * G * G * C * C * C * C * G * G * Geom5CeoTeoTeo * m5Ceo	GCAUCCGGGCCCCGGGCTTC	XXXXXXXXXX XXXXOOOX
WV-12497	m5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CTCACTCACCCACTCGCCA	OOOSSRSSRSS SSSSS
WV-12498	Teom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	TCACTCACCCACTCGCCA	OOSSRSSRSS SSSSS
WV-12545	L001mC * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	OSOOOSSS RSSRSSSSSSS
WV-12546	Mod085L001mC * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	OSOOOSSS RSSRSSSSSSS
WV-12547	Mod086L001mC * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	OSOOOSSS RSSRSSSSSSS
WV-12548	Mod012L001mC * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	OSOOOSSS RSSRSSSSSSS
WV-12549	mC * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmAL004	CCTCACTCACCCACTCGCCA	SOOOSSS RSSRSSSSSSS
WV-12550	mC * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmAL004Mod085	CCTCACTCACCCACTCGCCA	SOOOSSS RSSRSSSSSSS

WV-12551	mC * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmAL004Mod086	CCTCACTCACCCACTCGCCA	SOOOSSS RSSRSSSSSSS
WV-12552	mC * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmAL004Mod012	CCTCACTCACCCACTCGCCA	SOOOSSS RSSRSSSSSSS
WV-12575	m5lC * m5CeoTeom5CeoAeo * C * T * C * A * C * C * C * A * C * T * m5CeoGeom5Ceom5Ceo * lA	CCTCACTCACCCACTCGCCA	XOOOXXXXXX XXXX0OOOX
WV-12576	m5lC * m5CeoTeom5CeoAeo * mC * mU * mC * mA * mC * mC * mC * mA * mC * mU * m5CeoGeom5Ceom5Ceo * lA	CCTCACUCACCCACUCGCCA	XOOOXXXXXX XXXX0OOOX
WV-12577	fC * fCfUfCfA * C * T * C * A * C * C * C * A * C * T * fCfGfCfC * fA	CCUCACTCACCCACTCGCCA	XOOOXXXXXX XXXX0OOOX
WV-12578	fC * fC * fU * fC * fA * C * T * C * A * C * C * C * A * C * T * fC * fG * fC * fC * fA	CCUCACTCACCCACTCGCCA	XXXXXXXXXX XXXXXXX
WV-12579	m5lC * m5CeoTeom5CeomA * C * T * C * A * C * C * C * C * A * C * T * mC * mG * mC * mC * lA	CCTCACTCACCCACTCGCCA	XOOOXXXXXX XXXXXXX
WV-12580	fC * m5CeoTeom5CeofA * C * T * C * A * C * C * C * A * C * T * fC * fG * fC * fC * fA	CCTCACTCACCCACTCGCCA	XOOOXXXXXX XXXXXXX
WV-12581	mC * m5CeoTeom5CeomA * mC * mU * mC * mA * mC * mC * mC * mA * mC * mU * mC * mG * mC * mC * mA	CCTCACUCACCCACUCGCCA	XOOOXXXXXX XXXXXXX
WV-12582	m5lC * m5CeoTeom5CeomA * mC * mU * mC * mA * mC * mC * mC * mA * mC * mU * mC * mG * mC * mC * lA	CCTCACUCACCCACUCGCCA	XOOOXXXXXX XXXXXXX
WV-12583	fC * m5CeoTeom5CeofA * mC * mU * mC * mA * mC * mC * mC * mA * mC * mU * fC * fG * fC * fC * fA	CCTCACUCACCCACUCGCCA	XOOOXXXXXX XXXXXXX
WV-12893	mC * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * SC * SA * SC * SBrdU * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	SOOOSSS RSSSSSSSSS SS
WV-13305	m5Ceo * Rm5Ceon001Teon001m5Ceon001Aeo * RC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	RnXnXnXRSSRS SRSSSSSSS
WV-13306	m5Ceo * Sm5CeoTeom5CeoAeo * RC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	SOORSSRSS RSSSSSSSS
WV-13307	m5Ceo * Sm5Ceon001Teon001m5Ceon001Aeo * RC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmC * SmG *	CCTCACTCACCCACTCGCCA	SnXnXnXRSSR SSRSSSSSSS

	SmC * SmC * SmA		
WV-13308	m5Ceo * Rm5CeoTeom5CeoAeo * RC * ST * SC * RA * SC * SC * SC * RA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	ROOORSSRSSS RSSSSSS
WV-13309	m5Ceo * Rm5Ceon001Teon001m5Ceon001Aeo * RC * ST * SC * RA * SC * SC * SC * RA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	RnXnXnXRSSRSSS RSSSSSSS
WV-13310	m5Ceo * Sm5CeoTeom5CeoAeo * RC * ST * SC * RA * SC * SC * SC * RA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	SOOORSSRSSSRS SSSSSS
WV-13311	m5Ceo * Sm5Ceon001Teon001m5Ceon001Aeo * RC * ST * SC * RA * SC * SC * SC * RA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	SnXnXnXRSSRSS SRSSSSSSS
WV-13312	mC * Sm5Ceon001Teon001m5Ceon001mA * SC * ST * SC * RA * SC * SC * SC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	SnXnXnXSSSRSS SSSSSSS SS
WV-13313	m5Ceo * Rm5Ceon001Teon001m5Ceon001Aeo * RC * ST * SC * RA * SC * SC * SC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	RnXnXnXRSSRS SSSSSSS SS
WV-13803	Teo * Geon001m5Ceon001m5Ceon001Geo * C * C * C * T * C * C * T * C * A * C * T * mC * mA * mC * mC * mC	TGCCGCCTCCTCACTCACCC	XnXnXnXXXXX XXXXX XXXX
WV-13804	Teo * Geom5Ceom5CeoGeo * C * C * T * C * C * T * C * A * C * T * mCn001mAn001mCn001mC * mC	TGCCGCCTCCTCACTCACCC	XOOOXXXXXXX XXXXnXnXnXX
WV-13805	Teo * Geon001m5Ceon001m5Ceon001Geo * C * C * T * C * C * T * C * A * C * T * mCn001mAn001mCn001mC * mC	TGCCGCCTCCTCACTCACCC	XnXnXnXXXXX XXXXX XnXnXnXX
WV-13806	Geo * m5Ceon001Geon001m5Ceon001Geo * A * C * T * C * C * T * G * A * G * T * Teom5Ceom5CeoAeo * Geo	GCGCGACTCCTGAGTTCCAG	XnXnXnXXXXX XXXXX XOOOX
WV-13807	Geo * m5CeoGeom5CeoGeo * A * C * T * C * C * T * G * A * G * T * Teon001m5Ceon001m5Ceon001Aeo * Geo	GCGCGACTCCTGAGTTCCAG	XOOOXXXXXXX XXXXnXnXnXX
WV-13808	Geo * m5Ceon001Geon001m5Ceon001Geo * A * C * T * C * C * T * G * A * G * T * Teon001m5Ceon001m5Ceon001Aeo * Geo	GCGCGACTCCTGAGTTCCAG	XnXnXnXXXX XXXXXXX XnXnXnXX
WV-14552	m5Ceo * Rm5CeoTeom5CeoAeo * RC * ST * SC * RA * SC * SC * RC * SA * SC * ST * Rm5Ceo * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	ROOORSSRSSR SSSRSSSS

WV-14553	m5Ceo * Rm5Ceon001Teon001m5Ceon001Aeo * RC * ST * SC * RA * SC * SC * RC * SA * SC * ST * Rm5Ceo * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	RnXnXnXRSSRSS RSSSRSSSS
WV-14554	m5Ceo * Rm5CeoTeom5CeoAeo * RC * ST * SC * RA * SC * SC * SC * RA * SC * ST * Rm5Ceo * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	ROOORSSRSS SRSSRSSSS
WV-14555	m5Ceo * Rm5Ceon001Teon001m5Ceon001Aeo * RC * ST * SC * RA * SC * SC * SC * RA * SC * ST * Rm5Ceo * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	RnXnXnXRSSRS SSRSSRSSSS
WV-14758	mC * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmCmGmCmCmA	CCTCACTCACCCACTCGCCA	SOOOSSS RSSRSSSSOOOO
WV-14772	mC * Sm5CeoTeom5CeomA * SC * ST * SC * SA * SC * SC * SC * SA * SC * ST * SmC * SmG * SmC * SmC * SmA	CCTCACTCACCCACTCGCCA	SOOOSSS SSSSSSSSS SSS
WV-15049	mU * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmU * SmG * SmU * SmU * SmA	UCTCACTCACCCACTGUUA	SOOOSSS RSSRSSSSSSS
WV-15050	mU * Sm5CeoTeom5CeomA * SC * ST * SC * RA * SC * SC * RC * SA * SC * ST * SmG * SmA * SmC * SmU * SmC	UCTCACTCACCCACTGACUC	SOOOSSS RSSRSSSSSSS
WV-15051	mC * Sm5CeoTeom5CeomA * SG * SG * RC * ST * SG * RG * ST * ST * RA * ST * SmC * SmG * SmC * SmC * SmA	CCTCAGGCTGGTTATCGCCA	SOOOSSRS SRSSRSSSSS

WV-15870	Aeo * m5CeoTeom5CeoAeo * C * C * C * A * C * T * C * G * C * C * mA * mC * mC * mG * mC	ACTCACCCACTCGCCACCGC	XOOOXXXXX XXXXXXXXX
WV-15871	lA * m5CeoTeom5CeolA * C * C * C * A * C * T * C * G * C * C * mA * mC * mC * mG * mC	ACTCACCCACTCGCCACCGC	XOOOXXXXX XXXXXXXXX
WV-15872	Aeo * m5CeoTeom5CeoAeom5Ceo * C * C * A * C * T * C * G * C * C * mA * mC * mC * mG * mC	ACTCACCCACTCGCCACCGC	XOOOOXXXX XXXXXXXX
WV-15873	m5Ceo * Teom5CeoAeom5Ceo * C * C * A * C * T * C * G * C * C * A * mC * mC * mG * mC * mC	CTCACCCACTCGCCACCGCC	XOOOXXXXX XXXXXXXX
WV-15874	m5lC * Teom5CeoAeom5lC * C * C * A * C * T * C * G * C * C * A * mC * mC * mG * mC * mC	CTCACCCACTCGCCACCGCC	XOOOXXXXX XXXXXXXX
WV-15875	Aeo * m5CeoTeom5CeoAeom5Ceo * C * C * A * C * T * C * G * C * C * A * mC * mC * mG * mC	ACTCACCCACTCGCCACCGC	XOOOOXXXX XXXXXXXX

WV-15876	Aeo * m5CeoTeom5CeoAeom5Ceo * C * C * A * C * T * C * G * C * C * A * mC * mC * mG * mC * mC	ACTCACCCACTCGCCACCGCC	XOOOOXXXXX XXXXXXXXXX
WV-15877	mG * AeoTeoGeomC * C * G * C * C * T * C * C * T * C * A * m5Ceo * Teo * m5Ceo * Aeo * m5Ceo	GATGCCGCCTCCTCACTCAC	XOOOXXXXXX XXXXXXXXX
WV-15878	mG * AeoTeoGeomC * C * G * C * C * T * C * C * T * C * A * m5lC * Teo * m5Ceo * Aeo * m5lC	GATGCCGCCTCCTCACTCAC	XOOOXXXXXX XXXXXXXXX
WV-15879	mG * AeoTeoGeomC * C * G * C * C * T * C * C * T * C * Aeo * m5Ceo * Teo * m5Ceo * Aeo * m5Ceo	GATGCCGCCTCCTCACTCAC	XOOOXXXXXX XXXXXXXXX
WV-15880	fA * fC * fU * fC * fA * fC * mC * mC * mA * mC * mU * mC * mG * mC * fC * fA * fC * fC * fG * fC	ACUCACCCACUCGCCACCGC	XXXXXXXXXX XXXXXXXXX
WV-15881	fG * fA * fU * fG * fC * fC * mG * mC * mC * mU * mC * mC * mU * mC * fA * fC * fU * fC * fA * fC	GAUGCCGCCUCCUCACUCAC	XXXXXXXXXX XXXXXXXXX
WV-15906	lA * m5CeoTeom5CeoAeom5lC * C * C * A * C * T * C * G * C * C * A * mC * mC * mG * mC * mC	ACTCACCCACTCGCCACCGCC	XOOOOXXXXX XXXXXXXXXX
WV-15907	mG * AeoTeoGeomC * C * G * C * C * T * C * C * T * C * A * m5CeoTeom5CeoAeo * m5Ceo	GATGCCGCCTCCTCACTCAC	XOOOXXXXXX XXXXXOOOX
WV-15908	mG * AeoTeoGeomC * C * G * C * C * T * C * C * T * C * Aeom5CeoTeom5CeoAeo * m5Ceo	GATGCCGCCTCCTCACTCAC	XOOOXXXXXX XXXXOOOOX
WV-15909	mG * AeoTeoGeomC * C * G * C * C * T * C * C * T * C * A * m5lCTeom5CeoAeo * m5lC	GATGCCGCCTCCTCACTCAC	XOOOXXXXXX XXXXXOOOX
WV-15910	mG * AeoTeoGeomC * C * G * C * C * T * C * C * T * C * lAm5CeoTeom5CeoAeo * m5lC	GATGCCGCCTCCTCACTCAC	XOOOXXXXXX XXXXOOOOX
WV-15911	mG * AeoTeoGeomC * C * G * C * C * T * C * C * T * C * lA * m5Ceo * Teo * m5Ceo * Aeo * m5lC	GATGCCGCCTCCTCACTCAC	XOOOXXXXXX XXXXXXXXX

Key to Table 1A:

The present disclosure notes that some sequences, due to their length, are divided into multiple lines in Table 1A (e.g., WV-9421, WV-9399, WV-9398, WV-9397, WV-9396, etc.); however, these sequences, as are all oligonucleotides in Table 1A, are single-stranded (unless otherwise noted).

Moieties and modifications listed in the Tables (or compounds used to construct oligonucleotides comprising these moieties or modifications:

l: LNA sugar moieties (2'–O–CH_2–4'), e.g., lA [if between 5'-end group(s) and internucleotidic linkage, or between

internucleotidic linkages; if at 5'-end and without 5'-end groups; or if at 3'-end (e.g., in WV-

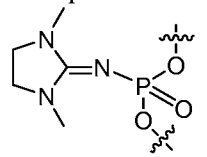
12575)]; and m5lC [if between 5'-end group(s) and internucleotidic linkages, or between internucleotidic linkages;

if at 5'-end and without 5'-end groups (e.g., in WV-12575); or if at 3'-end]

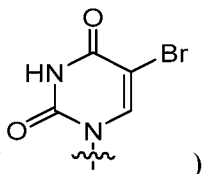
m: 2'-OMe

m5: methyl at 5-position of C (nucleobase is 5-methylcytosine)

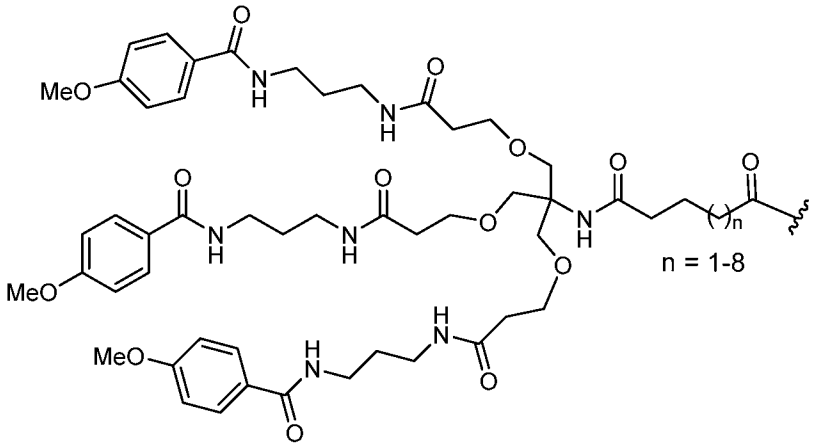
m5Ceo: 5-methyl 2'-O-methoxyethyl C
5MRd: 5'-methyl group wherein the 5'-C is in the Rp configuration, 2'-deoxy
5MSd: 5'-methyl group wherein the 5'-C is in the Sp configuration, 2'-deoxy.
OMe: 2'-OMe
eo: 2'-MOE (2'−$OCH_2CH_2OCH_3$);
F, f: 2'-F;
r: 2'-OH;
O, PO: phoshodiester (phosphate); can be an end group, or a linkage, e.g., a linkage between linker and oligonucleotide chain, an internucleotidic linkage, etc. Phosphodiesters indicated in the Stereochemistry/Internucleotidic Linkages column are not reproduced in the Modified Sequence column; if no internucleotidic linkage is indicated in the Modified Sequence column, it is a phosphodiester.
*, PS: Phosphorothioate; this can be an end group, or a linkage, e.g., a linkage between linker and oligonucleotide chain, an internucleotidic linkage, etc.
R, Rp: Phosphorothioate in Rp conformation; note that *R indicates a single phosphorothioate in the Rp conformation
S, Sp: Phosphorothioate in Sp conformation; note that *S indicates a single phosphorothioate in the Sp conformation

n001: 

nX: stereorandom n001
X: Stereorandom phosphorothioate
L001 : −NH−$(CH_2)_6$− linker (also known as a C6 linker, C6 amine linker or C6 amino linker), connected to Mod, if any, through −NH−, and the 5'-end of the oligonucleotide chain through either a phosphate linkage (O or PO) or phosphorothioate linkage (* if the phosphorothioate not chirally controlled; can also be *Sp* if chirally controlled and has an *Sp* configuration, and *Rp* if chirally controlled and has an *Rp* configuration) as illustrated. If no Mod is present, L001 is connected to −H, e.g., in WV-9380 or WV-9285. For example, in WV-9381, L001 is connected to Mod007 through –NH− (forming an amide group –C(O)−NH−), and is connected to the oligonucleotide chain through a phosphate linkage (indicated by bold underlined in **O**SOOOSSSRSSRSSSSSSSS); in WV-9062, L001 is not connected to any Mod, but to –H, through –NH−, and is connected to the oligonucleotide chain through a phosphate linkage (indicated by bold underlined in **O**SOOOSSSRSSSSSSSSSSS).
Mod007:

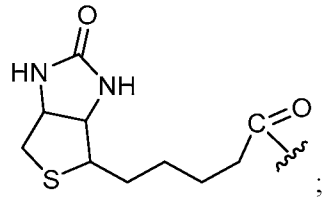
BrdU: a nucleoside unit wherein the nucleobase is BrU () and wherein the sugar is 2-deoxyribose (as widely found in natural DNA; 2'-deoxy (d));
L004: linker having the structure of −$NH(CH_2)_4CH(CH_2OH)CH_2$−, wherein −NH− is connected to Mod (through −C(O)−) or −H, and the −CH_2−

connecting site is connected to a linkage, *e.g.*, phosphodiester (−O−P(O)(OH)−O−. May exist as a salt form. May be illustrated in the Table as O or PO), phosphorothioate (−O−P(O)(SH)−O−. May exist as a salt form. May be illustrated in the Table as * if the phosphorothioate not chirally controlled; *S, S, or *S*p, if chirally controlled and has an *S*p configuration, and *R, R, or *R*p, if chirally controlled and has an *R*p configuration), or phosphorodithioate (−O−P(S)(SH)−O−. May exist as a salt form. May be illustrated in the Table as PS2 or : or D) linkage, at the 3'-end of an oligonucleotide chain. For example, an asterisk immediately preceding a L004 (e.g., *L004) indicates that the linkage is a phosphorothioate linkage, and the absence of an asterisk immediately preceding L004 indicates that the linkage is a phosphodiester linkage. For example, in WV-12549, which terminates in mAL004, the linker L004 is connected (via the $-CH_2-$ site) to the phosphodiester linkage at the 3' position at the 3'-terminal sugar (which is 2'-OMe and connected to the nucleobase A), and the L004 linker is connected via −NH− to −H; similarly, in WV-12552, WV-12550, and WV-12551, the L004 linker is connected (via the $-CH_2-$ site) to the phosphodiester linkage at the 3' position of the 3'-terminal sugar, and the L004 is connected via −NH− to Mod012 (WV-12552), Mod085 (WV-12550) or Mod086 (WV-12551);



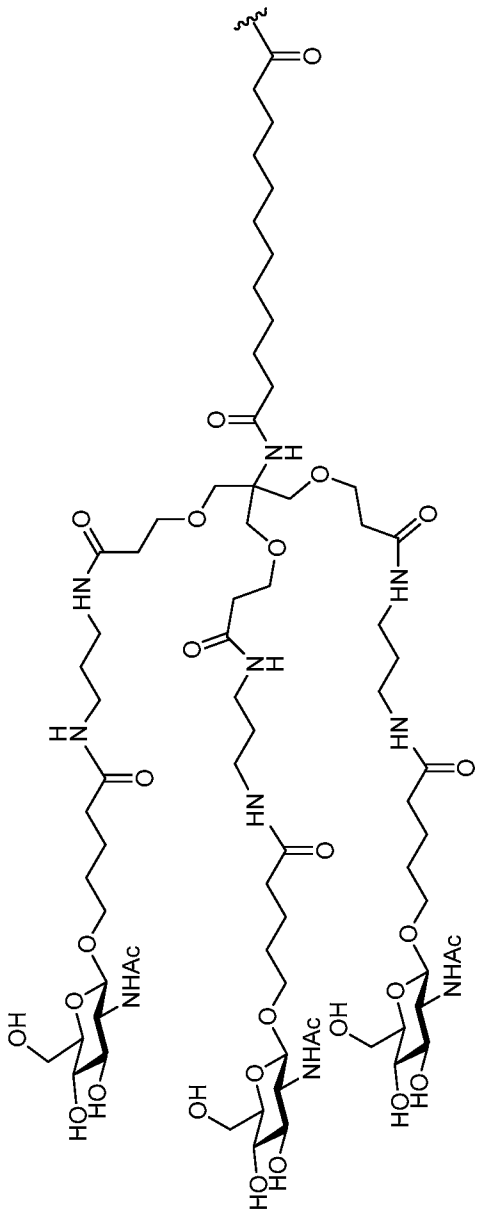
In Mod007, n = 8.

Mod012 (with −C(O)− connecting to −NH− of a linker such as L001):

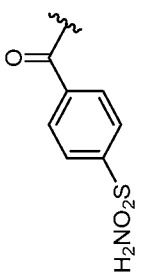


;

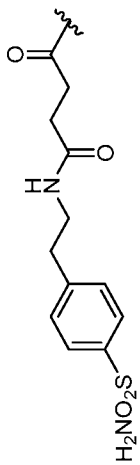
Mod024:



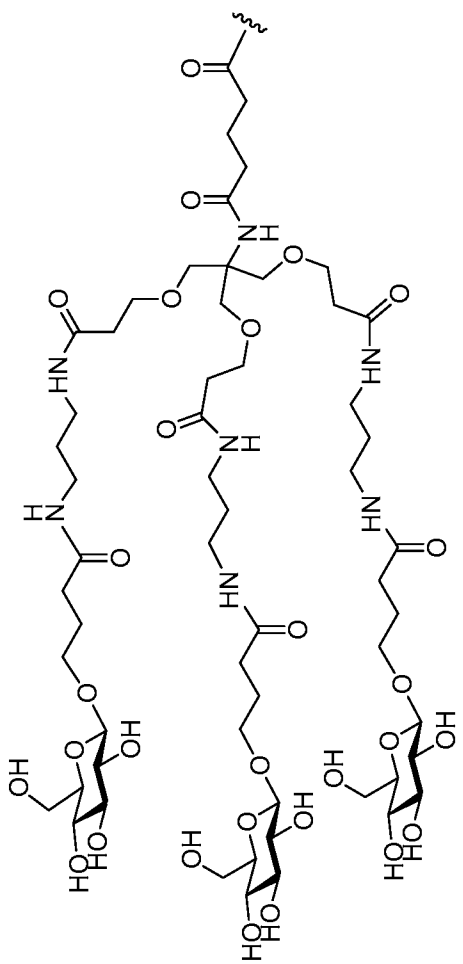
Mod027:



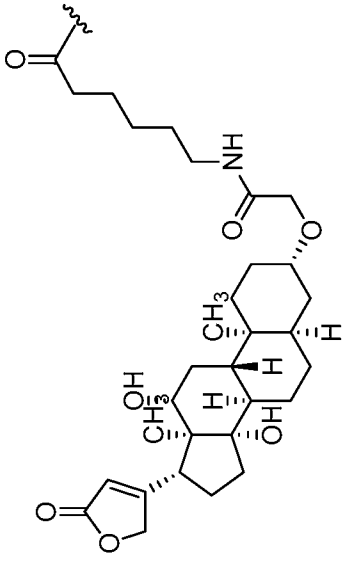
Mod028:



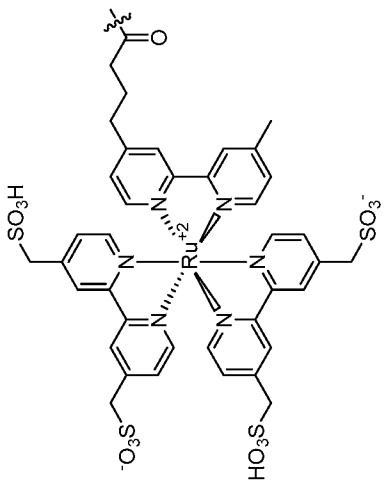
Mod059:



Mod085 (with –C(O)– connecting to –NH– of a linker such as L001 or L004):



Mod086 (with –C(O)– connecting to –NH– of L001 or L004):



[00773] **Oligonucleotides**

[00774] In some embodiments, provided C9orf72 oligonucleotides can direct a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product. In some embodiments, a C9orf72 target gene comprises a hexanucleotide repeat expansion.

[00775] In some embodiments, a provided C9orf72 oligonucleotide has a structural element or format or portion thereof described herein.

[00776] In some embodiments, a provided C9orf72 oligonucleotide capable of directing a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product has a structural element or format or portion thereof described herein.

[00777] In some embodiments, a provided C9orf72 oligonucleotide capable of directing a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product has the format of any oligonucleotide disclosed herein, *e.g.*, in Table 1A or in the Figures, or otherwise disclosed herein, or a structural element or format or portion thereof.

[00778] In some embodiments, a common pattern of backbone chiral centers (*e.g.*, a pattern of backbone chiral centers in a C9orf72 oligonucleotide) 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 in the Sp configuration, and O represents a phosphodiester. wherein R represents a phosphorothioate in the Rp configuration.

[00779] In some embodiments, provided C9orf72 oligonucleotides comprise at least two pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages. In some embodiments, provided C9orf72 oligonucleotides comprise at least 3 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages. In some embodiments, provided C9orf72 oligonucleotides comprise at least 4 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages. In some embodiments, provided C9orf72 oligonucleotides comprise at least 5 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages. In some embodiments, provided C9orf72 oligonucleotides comprise at least 6 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages. In some embodiments, provided C9orf72 oligonucleotides comprise at least 7 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages. In some embodiments, provided C9orf72 oligonucleotides comprise at least 8 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages. In some embodiments, provided C9orf72 oligonucleotides comprise at least 9 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages. In some embodiments, provided C9orf72 oligonucleotides comprise at least 10

pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages. In some embodiments, provided C9orf72 oligonucleotides comprise at least two pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages; and further comprise a block comprising 5 or more consecutive phosphorothioate internucleotidic linkages, wherein at least one phosphorothioate linkage is chirally controlled. In some embodiments, provided C9orf72 oligonucleotides comprise at least 3 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages; and further comprise a block comprising 5 or more consecutive phosphorothioate internucleotidic linkages, wherein at least one phosphorothioate linkage is chirally controlled. In some embodiments, provided C9orf72 oligonucleotides comprise at least 4 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages; and further comprise a block comprising 5 or more consecutive phosphorothioate internucleotidic linkages, wherein at least one phosphorothioate linkage is chirally controlled. In some embodiments, provided C9orf72 oligonucleotides comprise at least 5 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages; and further comprise a block comprising 5 or more consecutive phosphorothioate internucleotidic linkages, wherein at least one phosphorothioate linkage is chirally controlled. In some embodiments, provided C9orf72 oligonucleotides comprise at least 6 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages; and further comprise a block comprising 5 or more consecutive phosphorothioate internucleotidic linkages, wherein at least one phosphorothioate linkage is chirally controlled. In some embodiments, provided C9orf72 oligonucleotides comprise at least 7 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages; and further comprise a block comprising 5 or more consecutive phosphorothioate internucleotidic linkages, wherein at least one phosphorothioate linkage is chirally controlled. In some embodiments, provided C9orf72 oligonucleotides comprise at least 8 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages; and further comprise a block comprising 5 or more consecutive phosphorothioate internucleotidic linkages, wherein at least one phosphorothioate linkage is chirally controlled. In some embodiments, provided C9orf72 oligonucleotides comprise at least 9 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages; and further comprise a block comprising 5 or more consecutive phosphorothioate internucleotidic linkages, wherein at least one phosphorothioate linkage is chirally controlled. In some embodiments, provided C9orf72 oligonucleotides comprise at least 10 pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages; and further comprise a block comprising 5 or more consecutive phosphorothioate internucleotidic linkages, wherein at least one phosphorothioate linkage is chirally controlled. In some embodiments, provided C9orf72 oligonucleotides comprise at least two pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages; and further comprise a block

comprising 3, 4, 5, 6, 7 or more consecutive phosphorothioate internucleotidic linkages, wherein at least one phosphorothioate linkage is chirally controlled. In some embodiments, provided C9orf72 oligonucleotides comprise at least two pairs of alternating phosphodiester and phosphorothioate internucleotidic linkages; and further comprise a block comprising 5 or more consecutive phosphodiester internucleotidic linkages, wherein at least one phosphorothioate linkage is chirally controlled. In some embodiments, provided C9orf72 oligonucleotides comprise one or more natural phosphate linkages and one or more modified internucleotidic linkages. Provided oligonucleotides can comprise various number of natural phosphate linkages. In some embodiments, provided C9orf72 oligonucleotides are capable of directing a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product. In some embodiments, a C9orf72 target gene comprises a repeat expansion. In some embodiments, 5% or more of the internucleotidic linkages of provided C9orf72 oligonucleotides are natural phosphate linkages. In some embodiments, 10% or more of the internucleotidic linkages of provided C9orf72 oligonucleotides are natural phosphate linkages. In some embodiments, 15% or more of the internucleotidic linkages of provided C9orf72 oligonucleotides are natural phosphate linkages. In some embodiments, 20% or more of the internucleotidic linkages of provided C9orf72 oligonucleotides are natural phosphate linkages. In some embodiments, 25% or more of the internucleotidic linkages of provided C9orf72 oligonucleotides are natural phosphate linkages. In some embodiments, 30% or more of the internucleotidic linkages of provided C9orf72 oligonucleotides are natural phosphate linkages. In some embodiments, 35% or more of the internucleotidic linkages of provided C9orf72 oligonucleotides are natural phosphate linkages. In some embodiments, 40% or more of the internucleotidic linkages of provided C9orf72 oligonucleotides are natural phosphate linkages

[00780] In some embodiments, provided C9orf72 oligonucleotides can bind to a transcript, and improve C9orf72 knockdown of the transcript. In some embodiments, provided C9orf72 oligonucleotides improve C9orf72 knockdown, with efficiency greater than a comparable oligonucleotide under one or more suitable conditions.

[00781] In some embodiments, a provided improved C9orf72 knockdown is at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190% more than, or 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or more fold of, that of a comparable oligonucleotide under one or more suitable conditions.

[00782] In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by administration of a C9orf72 oligonucleotide. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by knockdown directed by a C9orf72 oligonucleotide. In some

embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by RNase H-mediated C9orf72 knockdown directed by a C9orf72 oligonucleotide. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by administration of a C9orf72 oligonucleotide in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by knockdown directed by a C9orf72 oligonucleotide in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by RNase H-mediated C9orf72 knockdown directed by a C9orf72 oligonucleotide in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by administration of a C9orf72 oligonucleotide in a cell(s) in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by knockdown directed by a C9orf72 oligonucleotide in a cell(s) in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by RNase H-mediated C9orf72 knockdown directed by a C9orf72 oligonucleotide in a cell(s) in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by administration of a C9orf72 oligonucleotide at a concentration of 1 uM or less in a cell(s) in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by knockdown directed by a C9orf72 oligonucleotide at a concentration of 1 uM or less in a cell(s) in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by RNase H-mediated C9orf72 knockdown directed by a C9orf72 oligonucleotide at a concentration of 1 uM or less in a cell(s) in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by administration of a C9orf72 oligonucleotide at a concentration of 10 uM or less in a cell(s) in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, or 80% by knockdown directed by a C9orf72 oligonucleotide at a concentration of 10 uM or less in a cell(s) in vitro. In some embodiments, expression or level of a C9orf72 target gene or its gene product is decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%,

40%, 45%, 50%, 60%, 70%, or 80% by RNase H-mediated C9orf72 knockdown directed by a C9orf72 oligonucleotide at a concentration of 10 uM or less in a cell(s) in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 10% at a concentration of 1 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 10% at a concentration of 5 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 10% at a concentration of 10 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 20% at a concentration of 1 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 20% at a concentration of 5 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 20% at a concentration of 10 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 30% at a concentration of 1 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 30% at a concentration of 5 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 30% at a concentration of 10 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 40% at a concentration of 1 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a

non-repeat expansion-containing C9orf72 transcript by at least 40% at a concentration of 5 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 40% at a concentration of 10 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 50% at a concentration of 1 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 50% at a concentration of 5 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 50% at a concentration of 10 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 75% at a concentration of 1 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 75% at a concentration of 5 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 75% at a concentration of 10 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 90% at a concentration of 1 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 90% at a concentration of 5 nm or less in a cell in vitro. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, level and/or activity of a repeat expansion-containing C9orf72 transcript relative to that of a non-repeat expansion-containing C9orf72 transcript by at least 90% at a concentration of 10 nm or less in a cell in vitro.

[00783] In some embodiments, IC50 is inhibitory concentration to decrease expression or level or a C9orf72 target gene or its gene product by 50% in a cell(s) in vitro. In some embodiments, a C9orf72

oligonucleotide has an IC50 of no more than about 10 nM in a cell(s) in vitro. In some embodiments, a C9orf72 oligonucleotide has an IC50 of no more than about 5 nM in a cell(s) in vitro. In some embodiments, a C9orf72 oligonucleotide has an IC50 of no more than about 2 nM in a cell(s) in vitro. In some embodiments, a C9orf72 oligonucleotide has an IC50 of no more than about 1 nM in a cell(s) in vitro. In some embodiments, a C9orf72 oligonucleotide has an IC50 of no more than about 0.5 nM in a cell(s) in vitro. In some embodiments, a C9orf72 oligonucleotide has an IC50 of no more than about 0.1 nM in a cell(s) in vitro. In some embodiments, a C9orf72 oligonucleotide has an IC50 of no more than about 0.01 nM in a cell(s) in vitro. In some embodiments, a C9orf72 oligonucleotide has an IC50 of no more than about 0.001 nM in a cell(s) in vitro.

[00784] In some embodiments, a provided C9orf72 oligonucleotide comprises any pattern of stereochemistry described herein. In some embodiments, a provided C9orf72 oligonucleotide comprises any pattern of stereochemistry described herein and is capable of directing RNase H-mediated C9orf72 knockdown. In some embodiments, a provided C9orf72 oligonucleotide comprises any pattern of stereochemistry described herein and is capable of directing RNase H-mediated C9orf72 knockdown.

[00785] In some embodiments, a provided C9orf72 oligonucleotide comprises any modification or pattern of modification described herein. In some embodiments, a provided C9orf72 oligonucleotide comprises any pattern of modification described herein and is capable of directing RNase H-mediated C9orf72 knockdown. In some embodiments, a modification or pattern of modification is a modification or pattern of modifications at the 2' position of a sugar. In some embodiments, a modification or pattern of modification is a modification or pattern of modifications at the 2' position of a sugar, including but not limited to, 2'-deoxy, 2'-F, 2'-OMe, 2'-MOE, and 2'-OR1, wherein R1 is optionally substituted C1-6 alkyl.

[00786] In some embodiments, the present disclosure demonstrates that *S*p internucleotidic linkages, among other things, at the 5'- and 3'-ends can improve oligonucleotide stability. In some embodiments, the present disclosure demonstrates that, among other things, natural phosphate linkages and/or *R*p internucleotidic linkages can improve removal of oligonucleotides from a system. As appreciated by a person having ordinary skill in the art, various assays known in the art can be utilized to assess such properties in accordance with the present disclosure.

[00787] In some embodiments, provided C9orf72 oligonucleotides capable of directing C9orf72 knockdown comprise one or more modified sugar moieties. In some embodiments, a modified sugar moiety comprises a 2'-modification. In some embodiments, a modified sugar moiety comprises a 2'-modification. In some embodiments, a 2'-modification is 2'-OR^1. In some embodiments, a 2'-modification is a 2'-OMe. In some embodiments, a 2'-modification is a 2'-MOE. In some embodiments, a 2'-modification is an LNA sugar modification. In some embodiments, a 2'-modification is 2'-F. In

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

[00788] In some embodiments, provided C9orf72 oligonucleotides capable of directing C9orf72 knockdown comprise one or more 2'-F. In some embodiments, provided C9orf72 oligonucleotides capable of directing C9orf72 knockdown comprise at least one 2'-OMe. In some embodiments, provided C9orf72 oligonucleotides capable of directing C9orf72 knockdown comprise at least two or more consecutive 2'-F. In some embodiments, provided C9orf72 oligonucleotides capable of directing C9orf72 knockdown comprise at least two or more consecutive 2'-OMe.

[00789] In some embodiments, provided C9orf72 oligonucleotides capable of directing C9orf72 knockdown comprise alternating 2'-F modified sugar moieties and 2'-OR^1 modified sugar moieties. In some embodiments, provided C9orf72 oligonucleotides capable of directing C9orf72 knockdown comprise alternating 2'-F modified sugar moieties and 2'-OMe modified sugar moieties, *e.g.*, [(2'-F)(2'-OMe)]x, [(2'-OMe)(2'-F)]x, etc., wherein x is 1-50. In some embodiments, provided C9orf72 oligonucleotides capable of directing C9orf72 knockdown comprise at least two pairs of alternating 2'-F and 2'-OMe modifications. In some embodiments, provided C9orf72 oligonucleotides comprises alternating phosphodiester and phosphorothioate internucleotidic linkages, *e.g.*, [(PO)(PS)]x, [(PS)(PO)]x, etc., wherein x is 1-50.

[00790] In some embodiments, the present disclosure provides a C9orf72 oligonucleotide composition comprising a first plurality of oligonucleotides, wherein:

oligonucleotides of the first plurality have the same base sequence; and

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

[00791] In some embodiments, provided C9orf72 oligonucleotides comprise one or more 2'-F. In some embodiments, in provided C9orf72 oligonucleotides, a nucleoside comprising a 2'-modification is followed by a modified internucleotidic linkage. In some embodiments, in provided C9orf72 oligonucleotides, 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 Sp. In some embodiments, in provided C9orf72 oligonucleotides, a nucleoside comprising a 2'-modification is followed by an Sp chiral internucleotidic linkage. In some embodiments, in provided C9orf72 oligonucleotides, a nucleoside comprising a 2'-F is followed by an Sp chiral internucleotidic linkage. In some embodiments, in provided C9orf72 oligonucleotides, a nucleoside comprising a 2'-modification is preceded by an Sp chiral internucleotidic linkage. In some embodiments, in provided C9orf72 oligonucleotides, a nucleoside comprising a 2'-F is preceded by an Sp chiral internucleotidic linkage. In some embodiments, a chiral internucleotidic linkage is Rp. In some embodiments, in provided C9orf72 oligonucleotides, a nucleoside comprising a 2'-modification is followed by an Rp chiral internucleotidic linkage. In some embodiments, in provided C9orf72 oligonucleotides, a nucleoside comprising a 2'-F is followed by an Rp chiral internucleotidic linkage. In some embodiments, in provided C9orf72 oligonucleotides, a nucleoside comprising a 2'-modification is preceded by an Rp chiral internucleotidic linkage. In some embodiments, in provided C9orf72 oligonucleotides, a nucleoside comprising a 2'-F is preceded by an Rp chiral internucleotidic linkage. In some embodiments, provided C9orf72 oligonucleotides are capable of directing a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product. In some embodiments, a C9orf72 target gene comprises a repeat expansion. In some embodiments, C9orf72 oligonucleotides of the first plurality comprise one or more natural phosphate linkages and one or more modified internucleotidic linkages.

[00792] In some embodiments, provided compositions alter transcript C9orf72 knockdown so that an undesired target and/or biological function are suppressed. In some embodiments, in such cases provided composition can also induce cleavage of the transcript after hybridization.

[00793]

[00794] In some embodiments, compared to a reference condition, provided chirally controlled C9orf72 oligonucleotide compositions are surprisingly effective. In some embodiments, desired biological effects (*e.g.*, as measured by increased levels of desired mRNA, proteins, etc., decreased levels of undesired mRNA, proteins, etc.) can be enhanced by more than 5, 10, 15, 20, 25, 30, 40, 50, or 100 fold. In some embodiments, a change is measured by increase of a desired mRNA level compared to a reference condition.

[00795] In some embodiments, provided C9orf72 oligonucleotides contain increased levels of one or more isotopes. In some embodiments, provided C9orf72 oligonucleotides are labeled, *e.g.*, by one or more isotopes of one or more elements, *e.g.*, hydrogen, carbon, nitrogen, etc. In some embodiments, provided C9orf72 oligonucleotides in provided compositions, *e.g.*, C9orf72 oligonucleotides of a first plurality, comprise base modifications, sugar modifications, and/or internucleotidic linkage modifications,

wherein the oligonucleotides contain an enriched level of deuterium. In some embodiments, provided C9orf72 oligonucleotides are labeled with deuterium (replacing $-^{1}H$ with $-^{2}H$) at one or more positions. In some embodiments, one or more ^{1}H of a C9orf72 oligonucleotide or any moiety conjugated to the oligonucleotide (*e.g.*, a targeting moiety, etc.) is substituted with ^{2}H. Such oligonucleotides can be used in any composition or method described herein.

[00796] In some embodiments, the present disclosure provides a C9orf72 oligonucleotide composition comprising a first plurality of oligonucleotides which:

1) have a common base sequence complementary to a C9orf72 target sequence in a transcript; and

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

[00797] In some embodiments, the present disclosure provides a C9orf72 oligonucleotide composition comprising a first plurality of oligonucleotides capable of directing C9orf72 knockdown, wherein a C9orf72 oligonucleotides type is defined by:

1) base sequence;

2) pattern of backbone linkages;

3) pattern of backbone chiral centers; and

4) pattern of backbone phosphorus modifications,

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

the oligonucleotide composition being characterized in that, when it is contacted with the transcript in a C9orf72 knockdown system, C9orf72 knockdown-mediated C9orf72 knockdown of the transcript is improved relative to that observed under reference conditions selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[00798] In some embodiments, the present disclosure provides a C9orf72 oligonucleotide composition comprising a first plurality of oligonucleotides, wherein: oligonucleotides of the first plurality have the same base sequence; oligonucleotides of the first plurality comprise structural elements (a) 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more nucleoside units comprising 2'−F, 2'-OMe, 2'-deoxy and/or 2'-MOE modified sugar moieties; (b) 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more modified internucleotidic linkages, (c) 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more chirally controlled modified internucleotidic linkages, and (d) 2, 3, 4, 5, 6, 7, 8, 9, 10 or more natural phosphate linkages. In some embodiments, the oligonucleotides of the first plurality comprise structural elements (a), (b) and (c). In some embodiments, the oligonucleotides of the first plurality comprise structural elements (b), (c) and (d). In some embodiments, the oligonucleotides

of the first plurality comprise structural elements (a), (b) and (d). In some embodiments, the oligonucleotides of the first plurality comprise structural elements (a), (c) and (d). In some embodiments, the oligonucleotides of the first plurality comprise structural elements (a) and (b). In some embodiments, the oligonucleotides of the first plurality comprise structural elements (a) and (c). In some embodiments, the oligonucleotides of the first plurality comprise structural elements (a) and (d). In some embodiments, the oligonucleotides of the first plurality comprise structural elements (b) and (c). In some embodiments, the oligonucleotides of the first plurality comprise structural elements (b) and (d). In some embodiments, the oligonucleotides of the first plurality comprise structural elements (c) and (d).

[00799] 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**.

[00800] As demonstrated in the present disclosure, in some embodiments, a provided C9orf72 oligonucleotide composition is characterized in that, when it is contacted with the transcript in a C9orf72 knockdown system, C9orf72 knockdown-mediated C9orf72 knockdown of the transcript is improved relative to that observed under reference conditions selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof. In some embodiments, C9orf72 knockdown is increased 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 fold or more. In some embodiments, as exemplified in the present disclosure, levels of the plurality of oligonucleotides, *e.g.*, a first plurality of oligonucleotides, in provided compositions are pre-determined.

[00801] In some embodiments, a common base sequence and length may be referred to as a common base sequence. In some embodiments, C9orf72 oligonucleotides having a common base sequence may have the same pattern of nucleoside modifications, *e.g.*, sugar modifications, base modifications, etc. In some embodiments, a pattern of nucleoside modifications may be represented by a combination of locations and modifications. In some embodiments, a pattern of backbone linkages comprises locations and types (*e.g.*, phosphate, phosphorothioate, substituted phosphorothioate, etc.) of each internucleotidic linkages. A pattern of backbone chiral centers of a C9orf72 oligonucleotide can be designated by a combination of linkage phosphorus stereochemistry (*R*p/*S*p) from 5' to 3'. As exemplified above, locations of non-chiral linkages may be obtained, for example, from pattern of backbone linkages.

[00802] In some embodiments, the present disclosure provides a C9orf72 oligonucleotide composition comprising a first plurality of oligonucleotides capable of directing C9orf72 knockdown, wherein oligonucleotides are of a particular oligonucleotide type characterized by:

1) a common base sequence and length;

2) a common pattern of backbone linkages; and

3) a common pattern of backbone chiral centers;

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

[00803] As understood by a person having ordinary skill in the art, a stereorandom or racemic preparation of oligonucleotides is prepared by non-stereoselective and/or low-stereoselective coupling of nucleotide monomers, typically without using any chiral auxiliaries, chiral modification reagents, and/or chiral catalysts. In some embodiments, in a substantially racemic (or chirally uncontrolled) preparation of oligonucleotides, all or most coupling steps are not chirally controlled in that the coupling steps are not specifically conducted to provide enhanced stereoselectivity. An example substantially racemic preparation of oligonucleotides is the preparation of phosphorothioate oligonucleotides through sulfurizing phosphite triesters from commonly used phosphoramidite oligonucleotide synthesis with either tetraethylthiuram disulfide or (TETD) or 3H-1, 2-bensodithiol-3-one 1, 1-dioxide (BDTD), a well-known process in the art. In some embodiments, substantially racemic preparation of oligonucleotides provides substantially racemic oligonucleotide compositions (or chirally uncontrolled oligonucleotide compositions). In some embodiments, at least one coupling of a nucleotide monomer has a diastereoselectivity lower than about 60:40, 70:30, 80:20, 85:15, 90:10, 91:9, 92:8, 97:3, 98:2, or 99:1.

[00804] As understood by a person having ordinary skill in the art, in some embodiments, diastereoselectivity of a coupling or a linkage can be assessed through the diastereoselectivity of a dimer formation under the same or comparable conditions, wherein the dimer has the same 5'- and 3'-nucleosides and internucleotidic linkage.

[00805] In some embodiments, C9orf72 oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of base modifications. In some embodiments, C9orf72 oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments, C9orf72 oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have identical structures.

[00806] In some embodiments, C9orf72 oligonucleotides of a C9orf72 oligonucleotide type have a common pattern of backbone phosphorus modifications and a common pattern of sugar modifications. In some embodiments, C9orf72 oligonucleotides of a C9orf72 oligonucleotide type have a common pattern of backbone phosphorus modifications and a common pattern of base modifications. In some

embodiments, C9orf72 oligonucleotides of a C9orf72 oligonucleotide type have a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments, C9orf72 oligonucleotides of a C9orf72 oligonucleotide type are identical.

[00807] In some embodiments, a C9orf72 oligonucleotide is a substantially pure preparation of a C9orf72 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.

[00808] In some embodiments, at least about 20% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 25% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 30% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 35% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 40% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 45% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 50% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 55% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 60% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 65% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 70% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 75% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 80% of the

oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 85% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 90% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 92% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 94% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 95% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, at least about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, greater than about 99% of the oligonucleotides in the composition have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers. In some embodiments, purity of a C9orf72 oligonucleotide of a C9orf72 oligonucleotide can be expressed as the percentage of oligonucleotides in the composition that have a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers.

[00809] In some embodiments, C9orf72 oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications. In some embodiments, C9orf72 oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments, C9orf72 oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of sugar modifications. In some embodiments, C9orf72 oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of base modifications. In some embodiments, C9orf72 oligonucleotides having a common base sequence and length, a common pattern of backbone linkages,

and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments, C9orf72 oligonucleotides having a common base sequence and length, a common pattern of backbone linkages, and a common pattern of backbone chiral centers are identical.

[00810] As noted above and understood in the art, in some embodiments, the base sequence of a C9orf72 oligonucleotide may refer to the identity and/or modification status of nucleoside residues (*e.g.*, of sugar and/or base components, relative to standard naturally occurring nucleotides such as adenine, cytosine, guanosine, thymine, and uracil) in the oligonucleotide and/or to the hybridization character (*i.e.*, the ability to hybridize with particular complementary residues) of such residues.

[00811] In some embodiments, purity of a C9orf72 oligonucleotide can be controlled by stereoselectivity of each coupling step in its preparation process. In some embodiments, a coupling step has a stereoselectivity (*e.g.*, diastereoselectivity) of 60% (60% of the new internucleotidic linkage formed from the coupling step has the intended stereochemistry).

[00812] In some embodiments, provided compositions comprise oligonucleotides containing one or more residues which are modified at the sugar moiety. In some embodiments, provided compositions comprise oligonucleotides containing one or more residues which are modified at the 2' position of the sugar moiety (referred to herein as a "2'-modification"). Examples of such modifications are described above and herein and include, but are not limited to, 2'-OMe, 2'-MOE, 2'-LNA, 2'-F, FRNA, FANA, *S*-cEt, etc. In some embodiments, provided compositions comprise oligonucleotides containing one or more residues which are 2'-modified. For example, in some embodiments, provided C9orf72 oligonucleotides contain one or more residues which are 2'-O-methoxyethyl (2'-MOE)-modified residues. In some embodiments, provided compositions comprise oligonucleotides which do not contain any 2'-modifications. In some embodiments, provided compositions are oligonucleotides which do not contain any 2'-MOE residues. That is, in some embodiments, provided C9orf72 oligonucleotides are not MOE-modified. Additional example sugar modifications are described in the present disclosure.

[00813] In some embodiments, a sugar moiety without a 2'-modification is a sugar moiety found in a natural DNA nucleoside.

[00814] A person of ordinary skill in the art understands that various regions of a C9orf72 target transcript can be targeted by provided compositions and methods. In some embodiments, a base sequence of provided C9orf72 oligonucleotides comprises an intron sequence. In some embodiments, a base sequence of provided C9orf72 oligonucleotides comprises an exon sequence. In some embodiments, a base sequence of provided C9orf72 oligonucleotides comprises an intron and an exon sequence.

[00815] As understood by a person having ordinary skill in the art, provided C9orf72 oligonucleotides and compositions, among other things, can target a great number of nucleic acid

polymers. For instance, in some embodiments, provided C9orf72 oligonucleotides and compositions may target a transcript of a nucleic acid sequence, wherein a common base sequence of oligonucleotides (*e.g.*, a base sequence of a C9orf72 oligonucleotide type) comprises or is a sequence complementary to a sequence of the transcript.

[00816] In some embodiments, as described in this disclosure, provided C9orf72 oligonucleotides and compositions may provide new cleavage patterns, higher cleavage rate, higher cleavage degree, higher cleavage selectivity, etc. In some embodiments, provided compositions can selectively suppress (*e.g.*, cleave) a transcript from a C9orf72 target nucleic acid sequence which has one or more similar sequences exist within a subject or a population, each of the target and its similar sequences contains a specific nucleotidic characteristic sequence element that defines the target sequence relative to the similar sequences.

[00817] In some embodiments, a similar sequence has greater than 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity with a C9orf72 target sequence. In some embodiments, a C9orf72 target sequence is a disease-causing copy of a nucleic acid sequence comprising one or more mutations, and a similar sequence is a copy not causing the disease (wild type). In some embodiments, a C9orf72 target sequence comprises a mutation, wherein a similar sequence is the corresponding wild-type sequence. In some embodiments, a C9orf72 target sequence is a mutant allele, while a similar sequence is a wild-type allele. In some embodiments, a C9orf72 target sequence is in an intron comprising a hexanucleotide repeat expansion. In some embodiments, the region of a C9orf72 target sequence that is complementary to a common base sequence of a provided C9orf72 oligonucleotide composition differs from the corresponding region of a similar sequence at less than 5, less than 4, less than 3, less than 2, or only 1 base pairs.

[00818] In some embodiments, a common base sequence comprises or is a sequence complementary to a characteristic sequence element. In some embodiments, a common base sequence comprises a sequence complementary to a characteristic sequence element. In some embodiments, a common base sequence is a sequence complementary to a characteristic sequence element. In some embodiments, a common base sequence comprises or is a sequence 100% complementary to a characteristic sequence element. In some embodiments, a common base sequence comprises a sequence 100% complementary to a characteristic sequence element. In some embodiments, a common base sequence is a sequence 100% complementary to a characteristic sequence element.

[00819] Among other things, the present disclosure recognizes that a base sequence may have impact on oligonucleotide properties. In some embodiments, a base sequence may have impact on cleavage pattern of a C9orf72 target when oligonucleotides having the base sequence are utilized for suppressing a C9orf72 target, *e.g.*, through a pathway involving RNase H: for example, structurally

similar (all phosphorothioate linkages, all stereorandom) oligonucleotides have different sequences may have different cleavage patterns.

[00820] As a person having ordinary skill in the art understands, provided C9orf72 oligonucleotide compositions and methods have various uses as known by a person having ordinary skill in the art. Methods for assessing provided compositions, and properties and uses thereof, are also widely known and practiced by a person having ordinary skill in the art. Example properties, uses, and/or methods include but are not limited to those described in WO/2014/012081 and WO/2015/107425.

[00821] In some embodiments, a chiral internucleotidic linkage has the structure of Formula **I**. 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**. In some embodiments, each chiral internucleotidic linkage in a single oligonucleotide of a provided composition is a phosphorothioate.

[00822] In some embodiments, C9orf72 oligonucleotides of the present disclosure comprise one or more modified sugar moieties. In some embodiments, C9orf72 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.

[00823] In some embodiments, a sugar modification is a 2'-modification. Commonly used 2'-modifications include but are not limited to 2'−OR^1, wherein R^1 is not hydrogen. In some embodiments, a modification is 2'−OR, wherein R is optionally substituted aliphatic. In some embodiments, a modification is 2'−OMe. In some embodiments, a modification is 2'-*O*-MOE. In some embodiments, the present disclosure demonstrates that inclusion and/or location of particular chirally pure internucleotidic linkages can provide stability improvements comparable to or better than those achieved through use of modified backbone linkages, bases, and/or sugars. In some embodiments, a provided single oligonucleotide of a provided composition has no modifications on the sugars. In some embodiments, a provided single oligonucleotide of a provided composition has no modifications on 2'-positions of the sugars (*i.e.*, the two groups at the 2'-position are either −H/−H or −H/−OH). In some embodiments, a provided single oligonucleotide of a provided composition does not have any 2'-MOE modifications.

[00824] In some embodiments, a 2'-modification is −O−L− or −L− which connects the 2'-carbon of a sugar moiety to another carbon of a sugar moiety. In some embodiments, a 2'-modification is −O−L− or −L− which connects the 2'-carbon of a sugar moiety to the 4'-carbon of a sugar moiety. In some embodiments, a 2'-modification is *S*-cEt. In some embodiments, a modified sugar moiety is an

LNA moiety.

[00825] 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.

[00826] 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.

[00827] In some embodiments, a 2'-modification is −F. In some embodiments, a 2'-modification is FANA. In some embodiments, a 2'-modification is FRNA.

[00828] In some embodiments, a sugar modification is a 5'-modification, *e.g.*, *R*-5'-Me, *S*-5'-Me, etc.

[00829] 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.

[00830] 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.

[00831] In some embodiments, a C9orf72 oligonucleotide is selected from the group consisting of the C9orf72 oligonucleotides disclosed herein, and any C9orf72 oligonucleotide of any format described herein. Those skilled in the art, reading the present specification, will appreciate that the present disclosure specifically does not exclude the possibility that any oligonucleotide described herein which is labeled as a C9orf72 oligonucleotide may also or alternatively operate through another mechanism (e.g., as an antisense oligonucleotide; mediating knock-down via a RNase H mechanism; sterically hindering translation; or any other biochemical mechanism).

[00832] In some embodiments, an antisense oligonucleotide (ASO) is or comprises a C9orf72 oligonucleotide selected from the group consisting of: any C9orf72 oligonucleotide disclosed herein, and any oligonucleotide of any format described herein. Those skilled in the art, reading the present specification, will appreciate that the present disclosure specifically does not exclude the possibility that any oligonucleotide described herein which is labeled as an antisense oligonucleotide (ASO) may also or alternatively operate through another mechanism (e.g., as a C9orf72 knockdown utilizing RISC); the disclosure also notes that various oligonucleotides may operate via different mechanisms (utilizing RNase H, sterically blocking translation or other post-transcriptional processes, changing the conformation of a C9orf72 target nucleic acid, etc.).

Chirally Controlled Oligonucleotides and Chirally Controlled Oligonucleotide Compositions

[00833] In some embodiments, provided C9orf72 oligonucleotides are capable of directing a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product. In some embodiments, a C9orf72 target gene comprises a repeat expansion. In some embodiments, a C9orf72 target gene comprises a hexanucleotide repeat expansion.

[00834] The present disclosure provides chirally controlled C9orf72 oligonucleotides, and chirally controlled C9orf72 oligonucleotide compositions which are of high crude purity and of high diastereomeric purity. In some embodiments, the present disclosure provides chirally controlled C9orf72 oligonucleotides, and chirally controlled C9orf72 oligonucleotide compositions which are of high crude purity. In some embodiments, the present disclosure provides chirally controlled C9orf72 oligonucleotides, and chirally controlled C9orf72 oligonucleotide compositions which are of high

diastereomeric purity.

[00835] In some embodiments, a C9orf72 oligonucleotide is a substantially pure preparation of a C9orf72 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.

[00836] In some embodiments, the present disclosure provides a chirally controlled C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 oligonucleotide comprises at least one phosphate diester internucleotidic linkage. In certain embodiments, the present disclosure provides a chirally controlled C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 oligonucleotide comprises at least one phosphorothioate triester internucleotidic linkage. In certain embodiments, the present disclosure provides a chirally controlled C9orf72 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 C9orf72 oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least one phosphorothioate triester internucleotidic linkage.

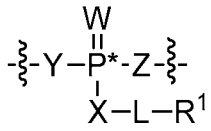
[00837] **Internucleotidic linkages**

[00838] In some embodiments, provided C9orf72 oligonucleotides are capable of directing a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product. In some embodiments, a C9orf72 target gene comprises a repeat expansion. In some embodiments, provided C9orf72 oligonucleotides comprise any internucleotidic linkage described herein or known in the art.

[00839] In some embodiments, a C9orf72 oligonucleotide can comprise any internucleotidic linkage described herein or known in the art.

[00840] 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 a C9orf72 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.

[00841] In certain embodiments, a internucleotidic linkage has the structure of Formula **I**:



(I)

wherein each variable is as defined and described below. In some embodiments, a linkage of Formula **I** is chiral. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide comprising one or more modified internucleotidic linkages of Formula **I**. In some embodiments, the present disclosure provides a chirally controlled C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 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.

[00842] In some embodiments, the present disclosure provides a chirally controlled C9orf72 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 C9orf72 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 C9orf72 oligonucleotide is characterized by a repeating pattern of alternating stereochemisty.

[00843] In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide, 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**, disclosed herein.

[00844] 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 $-\!\!\lesssim$ independently represents a connection to a nucleoside.

[00845] In some embodiments, a chirally controlled C9orf72 oligonucleotide comprises one or

more modified internucleotidic phosphorus linkages. Examples of such modified internucleotidic phosphorus linkages are described further herein.

[00846] In some embodiments, a chirally controlled C9orf72 oligonucleotide comprises different internucleotidic phosphorus linkages. In some embodiments, a chirally controlled C9orf72 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.

[00847] 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.

[00848] In some embodiments, a chirally controlled C9orf72 oligonucleotide is linked to a solid support. In some embodiments, a chirally controlled C9orf72 oligonucleotide is cleaved from a solid support.

[00849] In some embodiments, a chirally controlled C9orf72 oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least two consecutive modified internucleotidic linkages. In some embodiments, a chirally controlled C9orf72 oligonucleotide comprises at least one phosphate diester internucleotidic linkage and at least two consecutive phosphorothioate triester internucleotidic linkages.

[00850] In some embodiments, the present disclosure provides compositions comprising or consisting of a plurality of provided C9orf72 oligonucleotides (*e.g.*, chirally controlled C9orf72 oligonucleotide compositions). In some embodiments, all such provided C9orf72 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.

[00851] In some embodiments, a C9orf72 oligonucleotide can comprise any internucleotidic linkage described herein or known in the art. In some embodiments, a C9orf72 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 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.

[00852] In some embodiments, the present disclosure provides C9orf72 oligonucleotides comprising one or more modified internucleotidic linkages independently having the structure of Formula **I**, disclosed herein.

[00853] 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, a C9orf72 oligonucleotide comprises one or more internucleotidic linkages of Formula **I** wherein each P* is independently *R*p or *S*p. In some embodiments, a C9orf72 oligonucleotide comprises one or more internucleotidic linkages of Formula **I** wherein each P* is *R*p. In some embodiments, a C9orf72 oligonucleotide comprises one or more internucleotidic linkages of Formula **I** wherein each P* is *S*p. In some embodiments, a C9orf72 oligonucleotide comprises at least one internucleotidic linkage of Formula **I** wherein P* is *R*p. In some embodiments, a C9orf72 oligonucleotide comprises at least one internucleotidic linkage of Formula **I** wherein P* is *S*p. In some embodiments, a C9orf72 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.

[00854] 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, a C9orf72 oligonucleotide comprises at least one internucleotidic linkage of Formula **I** wherein W is O. In some embodiments, a C9orf72 oligonucleotide comprises at least one internucleotidic linkage of Formula **I** wherein W is S. In some embodiments, a C9orf72 oligonucleotide comprises at least one internucleotidic linkage of Formula **I** wherein W is Se.

[00855] In some embodiments of Formula **I**, a C9orf72 oligonucleotide comprises at least one internucleotidic linkage of Formula **I** wherein W is O. In some embodiments, a C9orf72 oligonucleotide comprises at least one internucleotidic linkage of Formula **I** wherein W is S.

[00856] 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.

[00857] 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.

[00858] 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.

[00859] In some embodiments, R is optionally substituted phenyl. In some embodiments, R is substituted phenyl. In some embodiments, R is phenyl.

[00860] 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.

[00861] In some embodiments, R is an optionally substituted aryl. In some embodiments, R is an optionally substituted bicyclic aryl ring.

[00862] 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.

[00863] 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.

[00864] 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.

[00865] 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.

[00866] 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.

[00867] 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.

[00868] 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.

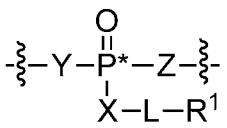
[00869] In some embodiments, R is an optionally substituted heterocyclyl. In some embodiments, R is an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is a 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.

[00870] 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.

[00871] 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.

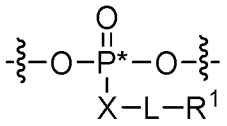
[00872] In some embodiments, a structure of Formula I is a structure of Formula I as described in WO2017/210647.–In some embodiments, the internucleotidic linkage of Formula **I** has the structure of Formula **I-a**:



(I-a)

wherein each variable is independently described in the present disclosure, as in Formula **I**.

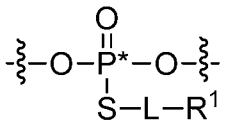
[00873] In some embodiments, the internucleotidic linkage of Formula **I** has the structure of Formula **I-b**:



(I-b)

wherein each variable is independently described in the present disclosure, as in Formula **I**.

[00874] 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;

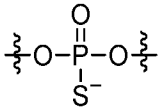
–Cy– is an optionally substituted bivalent ring selected from phenylene, carbocyclylene, arylene, heteroarylene, and heterocyclylene;

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

each independently represents a connection to a nucleoside; and

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

[00875] 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.

[00876] In some embodiments, the present disclosure provides a chirally controlled C9orf72 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**.

[00877] 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.**

[00878] 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.

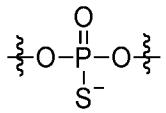
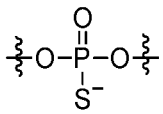
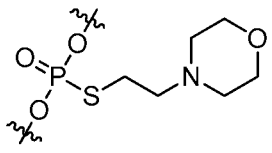
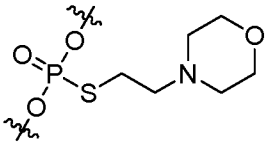
[00879] Non-limiting examples of internucleotidic linkages also include those described in the art, including, but not limited to, those described in any of: Gryaznov, S.; Chen, J.-K. J. Am. Chem. Soc. 1994, 116, 3143, Jones et al. J. Org. Chem. 1993, 58, 2983, Koshkin et al. 1998 Tetrahedron 54: 3607-3630, 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.

[00880] In some embodiments, the present disclosure provides a chirally controlled C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 oligonucleotide comprising at least one phosphate diester internucleotidic linkage and at least five phosphorothioate triester linkages having the structure of Formula **I-c**.

[00881] In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide comprising a sequence found in any oligonucleotide disclosed herein. In some embodiments, the present disclosure provides a chirally controlled C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 oligonucleotide comprising the sequence of any oligonucleotide disclosed herein. In some embodiments, the present disclosure provides a chirally controlled C9orf72 oligonucleotide having the sequence of any oligonucleotide disclosed herein. In some embodiments, the present disclosure provides a chirally controlled C9orf72 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.

[00882] In some embodiments, the present disclosure provides a chirally controlled C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 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 C9orf72 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  .

[00883] 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).

[00884] 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 a C9orf72 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 a C9orf72 oligonucleotide.

[00885] 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.

[00886] 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.

[00887] 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.

[00888] 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

a C9orf72 oligonucleotide or oligonucleotide composition) and also interacts with a C9orf72 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.

[00889] Examples of such targeting agents include, but are not limited to, proteins (*e.g.* Transferrin), C9orf72 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.

[00890] 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.

[00891] In some embodiments, a P-modification moiety is characterized in that it facilitates cell specific delivery.

[00892] 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.

[00893] 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.

Bases (Nucleobases)

[00894] In some embodiments, provided C9orf72 oligonucleotides are capable of directing a

decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product. In some embodiments, a C9orf72 target gene comprises a repeat expansion. In some embodiments, provided C9orf72 oligonucleotides comprise any nucleobase described herein or known in the art.

[00895] In some embodiments, a nucleobase present in a provided C9orf72 oligonucleotide is a natural nucleobase or a modified nucleobase derived from a natural nucleobase. Examples include, but are not limited to, uracil, thymine, adenine, cytosine, and guanine having their respective amino groups protected by acyl protecting groups, 2-fluorouracil, 2-fluorocytosine, 5-bromouracil, 5-iodouracil, 2,6-diaminopurine, azacytosine, pyrimidine analogs such as pseudoisocytosine and pseudouracil and other modified nucleobases such as 8-substituted purines, xanthine, or hypoxanthine (the latter two being the natural degradation products). Example modified nucleobases are disclosed in Chiu and Rana, RNA, 2003, 9, 1034-1048, Limbach et al. Nucleic Acids Research, 1994, 22, 2183-2196 and Revankar and Rao, Comprehensive Natural Products Chemistry, vol. 7, 313. In some embodiments, a modified nucleobase is substituted uracil, thymine, adenine, cytosine, or guanine. In some embodiments, a modified nucleobase is a functional replacement, *e.g.*, in terms of hydrogen bonding and/or base pairing, of uracil, thymine, adenine, cytosine, or guanine. In some embodiments, a nucleobase is optionally substituted uracil, thymine, adenine, cytosine, 5-methylcytosine, or guanine. In some embodiments, a nucleobase is uracil, thymine, adenine, cytosine, 5-methylcytosine, or guanine.

[00896] In some embodiments, a modified base is optionally substituted adenine, cytosine, guanine, thymine, or uracil. In some embodiments, a modified nucleobase is independently adenine, cytosine, guanine, thymine or uracil, modified by one or more modifications by which:

(1) a nucleobase is modified by one or more optionally substituted groups independently selected from acyl, halogen, amino, azide, alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, heteroaryl, carboxyl, hydroxyl, biotin, avidin, streptavidin, substituted silyl, and combinations thereof;

(2) one or more atoms of a nucleobase are independently replaced with a different atom selected from carbon, nitrogen and sulfur;

(3) one or more double bonds in a nucleobase are independently hydrogenated; or

(4) one or more aryl or heteroaryl rings are independently inserted into a nucleobase.

[00897] In some embodiments, a modified nucleobase is a modified nucleobase as shown in the art, e.g., WO2017/210647. Modified nucleobases also include expanded-size nucleobases in which one or more aryl rings, such as phenyl rings, have been added. Nucleic base replacements described in the Glen Research catalog (Glen Research, Sterling, Virginia); Krueger AT et al, Acc. Chem. Res., 2007, 40, 141-150; Kool, ET, Acc. Chem. Res., 2002, 35, 936-943; Benner S.A., et al., Nat. Rev. Genet., 2005, 6, 553-543; Romesberg, F.E., et al., Curr. Opin. Chem. Biol., 2003, 7, 723-733; Hirao, I., Curr. Opin. Chem.

Biol., 2006, 10, 622-627, are contemplated as useful for the synthesis of the nucleic acids described herein. In some embodiments, an expanded-size nucleobase is an expanded-size nucleobase as shown in the art, e.g., WO2017/210647 Herein, modified nucleobases also encompass structures that are not considered nucleobases but are other moieties such as, but not limited to, corrin- or porphyrin-derived rings. Porphyrin-derived base replacements have been described in Morales-Rojas, H and Kool, ET, Org. Lett., 2002, 4, 4377-4380. In some embodiments, a porphyrin-derived ring is a porphyrin-derived ring as shown in the art, e.g., WO2017/219647 In some embodiments, a modified nucleobase is a modified nucleobase as shown in the art, e.g., WO2017/219647 In some embodiments, a modified nucleobase is fluorescent. Examples of such fluorescent modified nucleobases include phenanthrene, pyrene, stillbene, isoxanthine, isozanthopterin, terphenyl, terthiophene, benzoterthiophene, coumarin, lumazine, tethered stillbene, benzo-uracil, and naphtho-uracil, as shown in the art, e.g., WO2017/210647 In some embodiments, a nucleobase or modified nucleobase is selected from: C5-propyne T, C5-propyne C, C5-Thiazole, Phenoxazine, 2-Thio-thymine, 5-Triazolylphenyl-thymine, Diaminopurine, and N2-Aminopropylguanine.

[00898] In some embodiments, a modified nucleobase is selected from: 5-substituted pyrimidines, 6- azapyrimidines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6 and 0-6 substituted purines. In certain embodiments, modified nucleobases are selected from: 2-aminopropyladenine, 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N- methyladenine, 2-propyladenine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (-C≡C-CH_3) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4- thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo, particularly 5-bromo, 5-trifluoromethyl, 5-halouracil, and 5-halocytosine, 7-methylguanine, 7-methyladenine, 2-F-adenine, 2-aminoadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 6-N- benzoyladenine, 2-N-isobutyrylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N- benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size- expanded bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as l,3-diazaphenoxazine-2-one, l,3-diazaphenothiazine-2-one and 9-(2-aminoethoxy)-l,3-diazaphenoxazine-2- one (G-clamp). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example, 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2- pyridone. Further nucleobases include those disclosed in United States Patent No. 3,687,808, those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, Kroschwitz, J.I., Ed., John Wiley & Sons, 1990, 858-859; Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613; Sanghvi, Y.S., Chapter 15, Antisense Research and Applications, Crooke, S.T. and Lebleu, B., Eds., CRC Press, 1993,

273-288; and those disclosed in Chapters 6 and 15, Antisense Drug Technology, Crooke S.T., Ed., CRC Press, 2008, 163-166 and 442-443.

[00899] Example United States patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include without limitation, US2003/0158403, U.S. 3,687,808; 4,845,205; 5,130,302; 5,134,066; 5, 175,273; 5,367,066; 5,432,272; 5,434,257; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594, 121; 5,596,091; 5,614,617; 5,645,985; 5,681,941; 5,750,692; 5,763,588; 5,830,653; and 6,005,096.

[00900] In some embodiments, a modified nucleobase is unsubstituted. In some embodiments, a modified nucleobase is substituted. In some embodiments, a modified nucleobase is substituted such that it contains, *e.g.*, heteroatoms, alkyl groups, or linking moieties connected to fluorescent moieties, biotin or avidin moieties, or other protein or peptides. In some embodiments, a modified nucleobase is a "universal base" that is not a nucleobase in the most classical sense, but that functions similarly to a nucleobase. One representative example of such a universal base is 3-nitropyrrole.

[00901] In some embodiments, other nucleosides can also be used in the process disclosed herein and include nucleosides that incorporate modified nucleobases, or nucleobases covalently bound to modified sugars. Some examples of nucleosides that incorporate modified nucleobases include 4-acetylcytidine; 5-(carboxyhydroxylmethyl)uridine; 2''-*O*-methylcytidine; 5-carboxymethylaminomethyl-2-thiouridine; 5-carboxymethylaminomethyluridine; dihydrouridine; 2''-*O*-methylpseudouridine; beta,D-galactosylqueosine; 2''-*O*-methylguanosine; N^6-isopentenyladenosine; 1-methyladenosine; 1-methylpseudouridine; 1-methylguanosine; l-methylinosine; 2,2-dimethylguanosine; 2-methyladenosine; 2-methylguanosine; N^7-methylguanosine; 3-methyl-cytidine; 5-methylcytidine; 5-hydroxymethylcytidine; 5-formylcytosine; 5-carboxylcytosine; N^6-methyladenosine; 7-methylguanosine; 5-methylaminoethyluridine; 5-methoxyaminomethyl-2-thiouridine; beta,D-mannosylqueosine; 5-methoxycarbonylmethyluridine; 5-methoxyuridine; 2-methylthio-N^6-isopentenyladenosine; *N*-((9-beta,D-ribofuranosyl-2-methylthiopurine-6-yl)carbamoyl)threonine; *N*-((9-beta,D-ribofuranosylpurine-6-yl)-*N*-methylcarbamoyl)threonine; uridine-5-oxyacetic acid methylester; uridine-5-oxyacetic acid (v); pseudouridine; queosine; 2-thiocytidine; 5-methyl-2-thiouridine; 2-thiouridine; 4-thiouridine; 5-methyluridine; 2''-*O*-methyl-5-methyluridine; and 2''-*O*-methyluridine.

[00902] In some embodiments, nucleosides include 6-modified bicyclic nucleosides that have either (*R*) or (*S*)-chirality at the 6-position and include the analogs described in US Patent No. 7,399,845. In other embodiments, nucleosides include 5''-modified bicyclic nucleosides that have either (*R*) or (*S*)-chirality at the 5-position and include the analogs described in US Patent Application Publication No. 20070287831.

[00903] In some embodiments, a nucleobase or modified nucleobase comprises one or more

biomolecule binding moieties such as *e.g.*, antibodies, antibody fragments, biotin, avidin, streptavidin, receptor ligands, or chelating moieties. In other embodiments, a nucleobase or modified nucleobase is 5-bromouracil, 5-iodouracil, or 2,6-diaminopurine. In some embodiments, a nucleobase or modified nucleobase is modified by substitution with a fluorescent or biomolecule binding moiety. In some embodiments, the substituent on a nucleobase or modified nucleobase is a fluorescent moiety. In some embodiments, the substituent on a nucleobase or modified nucleobase is biotin or avidin.

[00904] Representative U.S. patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Pat. No. 3,687,808, as well as U.S. Pat. Nos. 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,457,191; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,681,941; 5,750,692; 6,015,886; 6,147,200; 6,166,197; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, the modified nucleobases, sugars, and internucleotidic linkages of each of which are incorporated by reference.

[00905] In some embodiments, a base is optionally substituted A, T, C, G or U, wherein one or more $-NH_2$ are independently and optionally replaced with $-C(-L-R^1)_3$, one or more $-NH-$ are independently and optionally replaced with $-C(-L-R^1)_2-$, one or more $=N-$ are independently and optionally replaced with $-C(-L-R^1)-$, one or more $=CH-$ are independently and optionally replaced with $=N-$, and one or more $=O$ are independently and optionally replaced with $=S$, $=N(-L-R^1)$, or $=C(-L-R^1)_2$, wherein two or more $-L-R^1$ are optionally taken together with their intervening atoms to form a 3-30 membered bicyclic or polycyclic ring having 0-10 heteroatom ring atoms. In some embodiments, a modified base is optionally substituted A, T, C, G or U, wherein one or more $-NH_2$ are independently and optionally replaced with $-C(-L-R^1)_3$, one or more $-NH-$ are independently and optionally replaced with $-C(-L-R^1)_2-$, one or more $=N-$ are independently and optionally replaced with $-C(-L-R^1)-$, one or more $=CH-$ are independently and optionally replaced with $=N-$, and one or more $=O$ are independently and optionally replaced with $=S$, $=N(-L-R^1)$, or $=C(-L-R^1)_2$, wherein two or more $-L-R^1$ are optionally taken together with their intervening atoms to form a 3-30 membered bicyclic or polycyclic ring having 0-10 heteroatom ring atoms, wherein the modified base is different than the natural A, T, C, G and U. In some embodiments, a base is optionally substituted A, T, C, G or U. In some embodiments, a modified base is substituted A, T, C, G or U, wherein the modified base is different than the natural A, T, C, G and U.

[00906] In some embodiments, a nucleoside is any 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.

[00907] Example nucleobases are also 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.

[00908] In some embodiments, a C9orf72 oligonucleotides comprises a nucleobase, synthetic or modified nucleobase, nucleoside or nucleotide, or modified nucleoside or modified nucleotide described in Feldman et al. 2017 J. Am. Chem. Soc. 139: 11427-11433, Feldman et al. 2017 Proc. Natl. Acad. Sci. USA 114: E6478-E6479, Hwang et al. 2009 Nucl. Acids Res. 37: 4757-4763, Hwang et al. 2008 J. Am. Chem. Soc. 130: 14872-14882, Lavergne et al. 2012 Chem. Eur. J. 18: 1231-1239, Lavergne et al. 2013 J. Am. Chem. Soc. 135: 5408-5419, Ledbetter et al. 2018 J. Am. Chem. Soc. 140: 758-765, Malyshev et al. 2009 J. Am. Chem. Soc. 131: 14620-14621, Seo et al. 2009 ChemBioChem 10: 2394-2400, including, but not limited to: d3FB, d2Py analogs, d2Py, d3MPy, d4MPy, d5MPy, d34DMPy, d35DMPy, d45DMPy, d5FM, d5PrM, d5SICS, dFEMO, dMMO2, dNaM, dNM01, dTPT3, nucleotides with 2'-azido, 2'-chloro, 2'-amino or arabinose sugars, isocarbostiryl-, napthyl- and azaindole-nucleotides, and modifications and derivatives and functionalized versions thereof, including but not limited to those in which the sugar comprises a 2'-modification and/or other modification, and dMMO2 derivatives with meta-chlorine, -bromine, -iodine, -methyl, or -propinyl substituents.

[00909] **Sugars**

[00910] In some embodiments, provided C9orf72 oligonucleotides are capable of directing a decrease in the expression, level and/or activity of a C9orf72 target gene or its gene product. In some embodiments, a C9orf72 target gene comprises a repeat expansion. In some embodiments, provided C9orf72 oligonucleotides comprise any sugar described herein or known in the art.

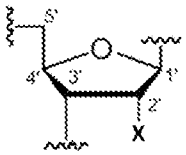
[00911] In some embodiments, provided C9orf72 oligonucleotides capable of directing C9orf72 knockdown comprise one or more modified sugar moieties beside the natural sugar moieties.

[00912] The most common naturally occurring nucleotides are comprised of ribose sugars linked to the nucleobases adenosine (A), cytosine (C), guanine (G), and thymine (T) or uracil (U). Also contemplated are modified nucleotides wherein a phosphate group or linkage phosphorus in the nucleotides can be linked to various positions of a sugar or modified sugar. As non-limiting examples, the phosphate group or linkage phosphorus can be linked to the 2'', 3'', 4'' or 5'' hydroxyl moiety of a sugar or modified sugar. Nucleotides that incorporate modified nucleobases as described herein are also contemplated in this context. In some embodiments, nucleotides or modified nucleotides comprising an unprotected –OH moiety are used in accordance with methods of the present disclosure.

[00913] In some embodiments, a C9orf72 oligonucleotide can comprise any base (nucleobase), modified base or base analog described herein or known in the art. In some embodiments, a C9orf72 oligonucleotide can comprise any base 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; internucleotidic linkage; stereochemistry 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.

[00914] In some embodiments, a C9orf72 oligonucleotide can comprise any sugar.

[00915] In some embodiments, a sugar has a structure of:



X= H, OH, F, OMe or MOE

[00916] Modified sugars can be incorporated into a provided C9orf72 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

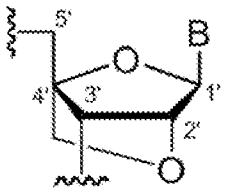
described in the present disclosure; –O–(C_1–C_{10} alkyl), –S–(C_1–C_{10} alkyl), –NH–(C_1–C_{10} alkyl), or –N(C_1–C_{10} alkyl)$_2$; –O–(C_2–C_{10} alkenyl), –S–(C_2–C_{10} alkenyl), –NH–(C_2–C_{10} alkenyl), or –N(C_2–C_{10} alkenyl)$_2$; –O–(C_2–C_{10} alkynyl), –S–(C_2–C_{10} alkynyl), –NH–(C_2–C_{10} 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)$_n$OCH_3, and –O(CH_2)$_n$NH_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.

[00917] In some embodiments, a 2'-modification is 2'-F.

[00918] 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.

[00919] 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:

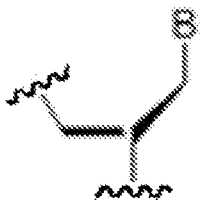


wherein B is a base.

[00920] 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.

[00921] 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).

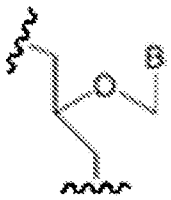
[00922] Non-limiting examples of modified sugars include glycerol, which form glycerol nucleic acid (GNA). One example of a GNA is shown below and is described in Zhang, R *et al.*, *J. Am. Chem. Soc.*, 2008, *130*, 5846-5847; Zhang L, *et al.*, *J. Am. Chem. Soc.*, 2005, *127*, 4174-4175 and Tsai CH *et al.*, *PNAS*, 2007, 14598-14603. In some embodiments, a nucleoside has a structure of:



Wherein B is a base.

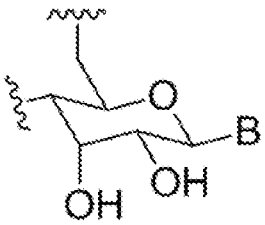
[00923] A flexible nucleic acid (FNA) based on the mixed acetal aminal of formyl glycerol, is

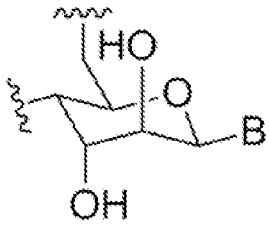
described in Joyce GF *et al.*, *PNAS*, 1987, *84*, 4398-4402 and Heuberger BD and Switzer C, *J. Am. Chem. Soc.*, 2008, *130*, 412-413. In some embodiments, a nucleoside has a structure of:

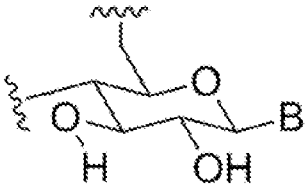


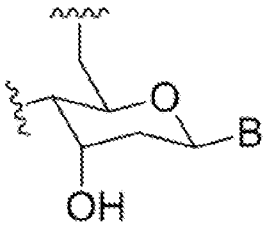
Wherein B is a base.

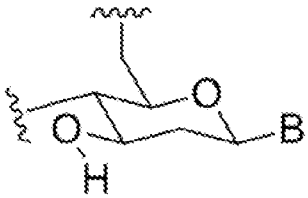
[00924] Additional non-limiting examples of modified sugars and/or modified nucleosides and/or modified nucleotides include hexopyranosyl (6' to 4'), pentopyranosyl (4' to 2'), pentopyranosyl (4' to 3'), 5'-deoxy-5'-C-malonyl, squaryldiamide, and tetrofuranosyl (3' to 2') sugars. In some embodiments, a modified nucleoside comprises a hexopyranosyl (6' to 4') sugar and has the structure of any one in the following formulae:





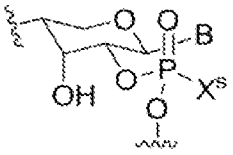


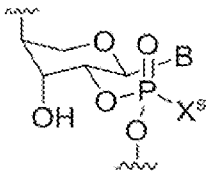


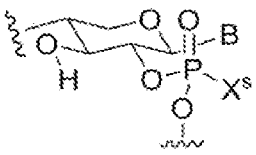


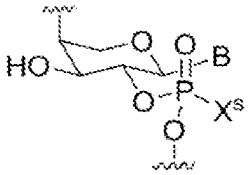
wherein X^s corresponds to the P-modification group "-XLR^1" described herein wherein XLR^1 is equivalent to X-L-R^1 and X, L, and R^1 are as defined in Formula **I**, disclosed herein, and B is a base.

[00925] In some embodiments, a modified nucleotide comprises a pentopyranosyl (4' to 2') sugar and has a structure of any one in the following formulae:







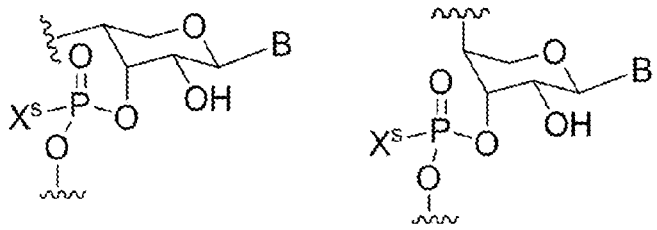


,

wherein X^s corresponds to the P-modification group "-XLR^1" described herein, wherein XLR^1 is

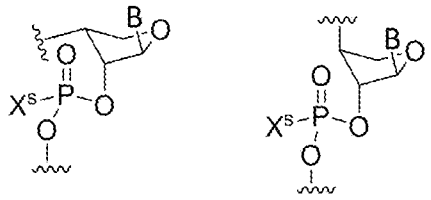
equivalent to X-L-R^1 and X, L, and R^1 are as defined in Formula **I**, disclosed herein, and B is a base.

[00926] In some embodiments, a modified nucleotide comprises a pentopyranosyl (4' to 3') sugar and is of any one in the following formulae:



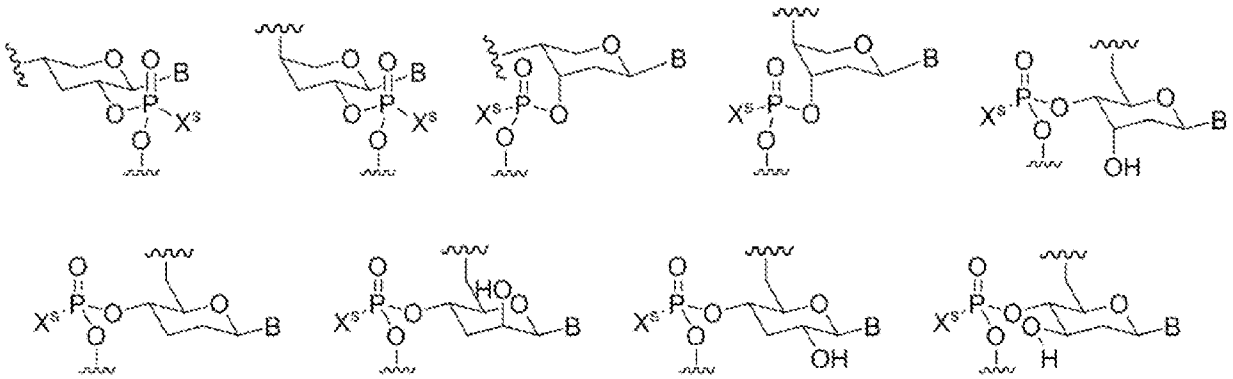
wherein X^s corresponds to the P-modification group "-XLR^1" described herein, wherein XLR^1 is equivalent to X-L-R^1 and X, L, and R^1 are as defined in Formula **I**, disclosed herein, and B is a base.

[00927] 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.

[00928] In some embodiments, a modified nucleotide comprises a modified sugar and is of any one in the following formulae:

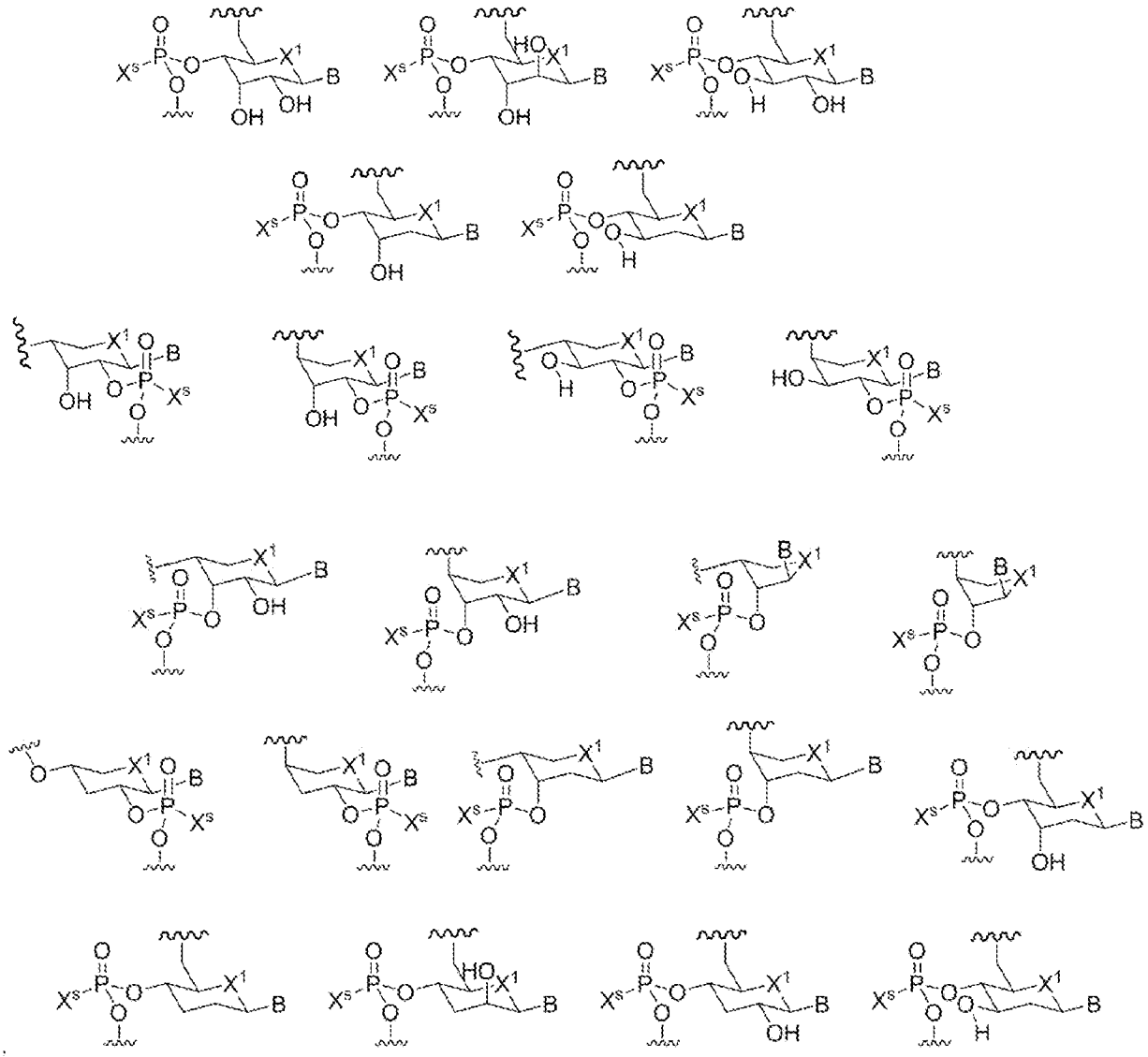


wherein X^s corresponds to the P-modification group "-XLR^1" described herein, wherein XLR^1 is equivalent to X-L-R^1 and X, L, and R^1 are as defined in Formula **I**, disclosed herein, and B is a base.

[00929] 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.

[00930] 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–



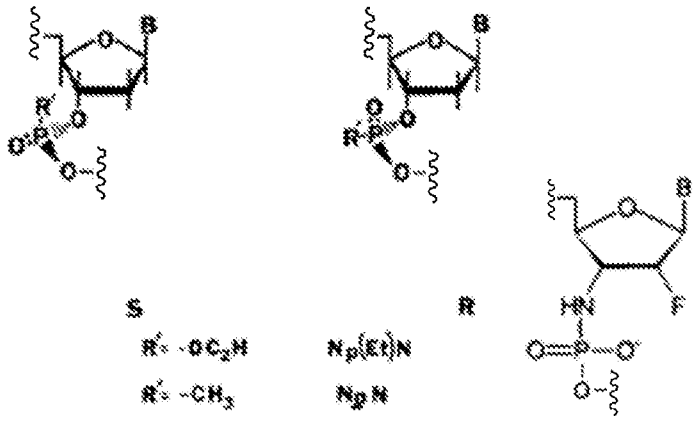
[00931] Modified sugars can be prepared by methods known in the art, including, but not limited to: A. Eschenmoser, Science (1999), 284:2118; M. Bohringer et al, Helv. Chim. Acta (1992), 75:1416-1477; M. Egli et al, J. Am. Chem. Soc. (2006), 128(33):10847-56; A. Eschenmoser in Chemical Synthesis: Gnosis 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.

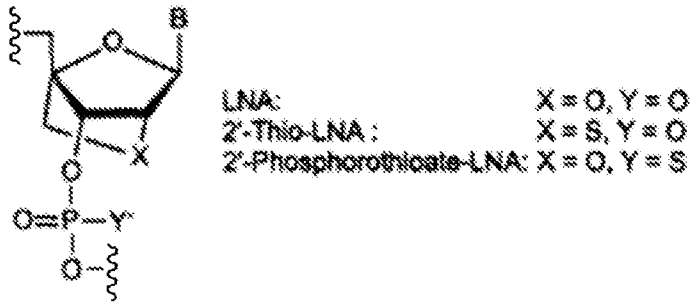
[00932] In some embodiments, a modified sugar moiety is an optionally substituted pentose or hexose moiety. In some embodiments, a modified sugar moiety is an optionally substituted pentose moiety. In some embodiments, a modified sugar moiety is an optionally substituted hexose moiety. In some embodiments, 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.

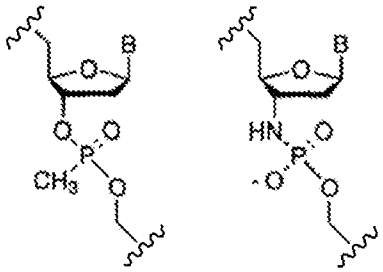
[00933] In some embodiments, an example modified nucleotide is selected from:



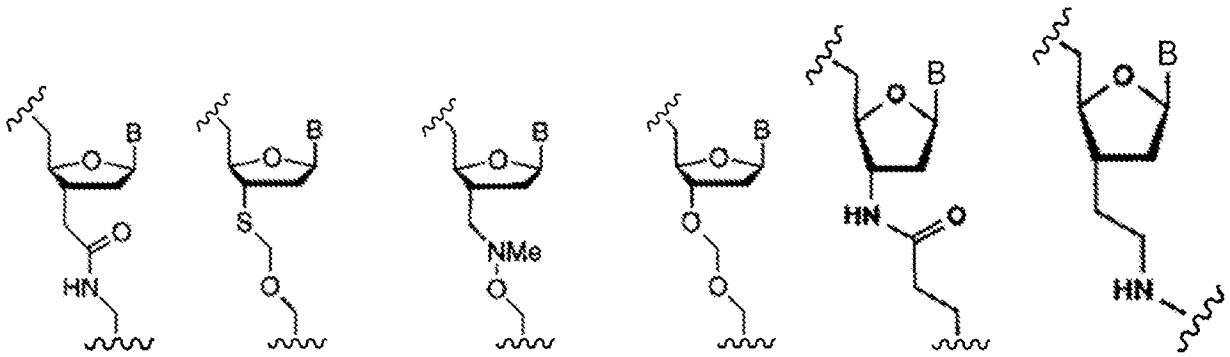
2'-Fluoro N3'-P5'-phosphoramidate

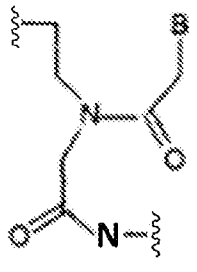


PS-LNA



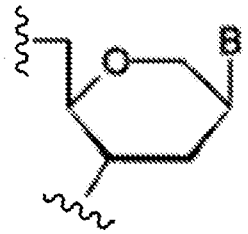
In some embodiments, a nucleotide has a structure selected from any of:



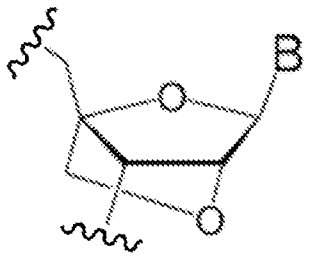


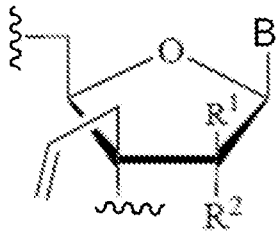
PNA

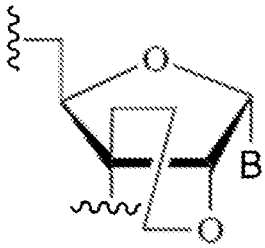
In some embodiments, a modified nucleoside has a structure selected from:



HNA

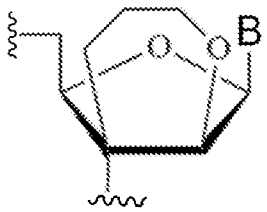


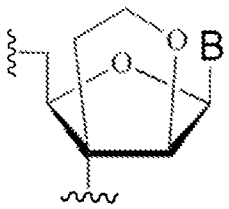




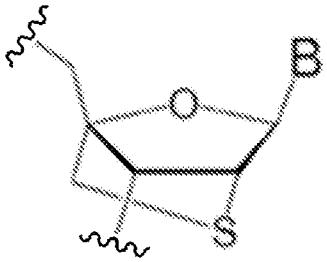
beta-D-oxy-LNA

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

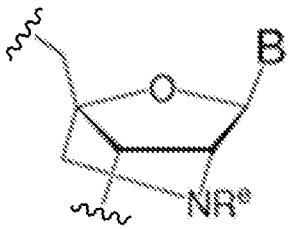




2'-O,3'-C-linked bicyclic

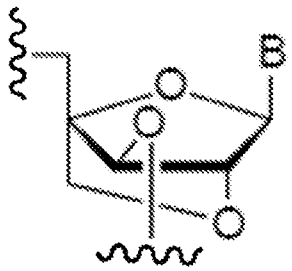


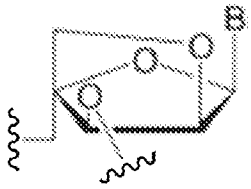
beta-D-thio-LNA



beta-D-amino-LNA

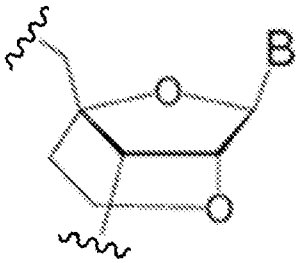
where R^e is substituted or unsubstituted C_{1-6} alkyl or H



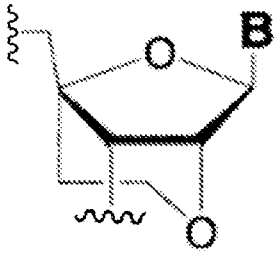


xylo-LNA [c]

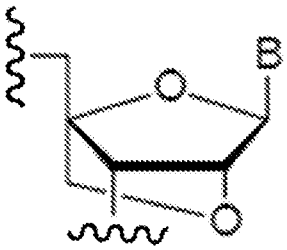
alpha-L-LNA



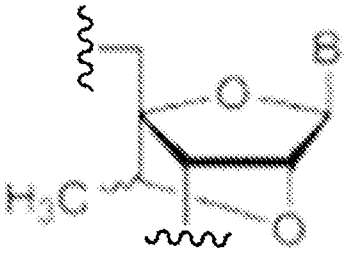
ENA



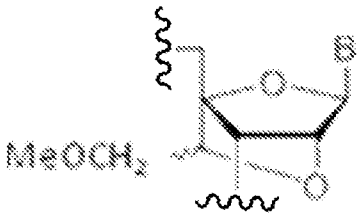
beta-D-ENA



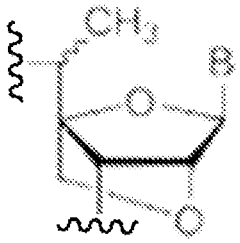
methylphosphonate-LNA



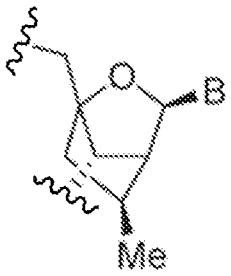
(*R*, *S*)-cEt



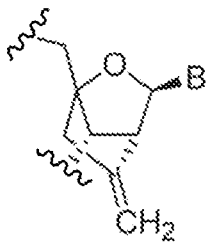
(*R*, *S*)-cMOE



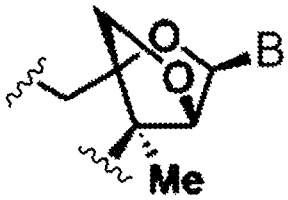
(*R*, *S*)-5'-Me-LNA



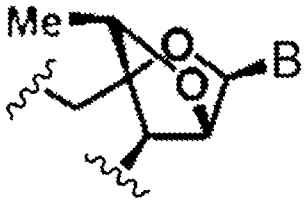
S-Me cLNA



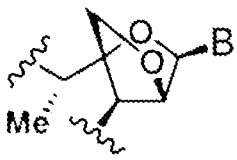
Methylene-cLNA



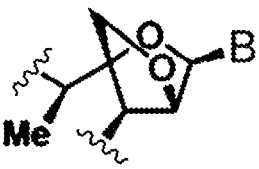
3'-Me-alpha-L-LNA



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



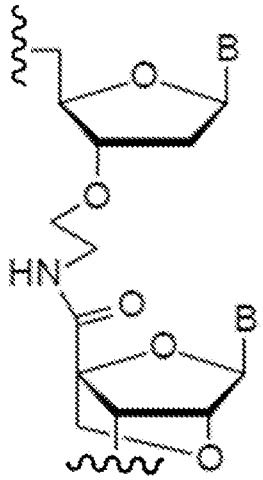
S-5'-Me-alpha-L-LNA



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

[00934] 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)-$N(R_l)$-$(CH_2)_2$-$N(R_m)(R_n)$, where each R_l, R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl.

[00935] 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).

[00936] 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).

[00937] 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.

[00938] 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.

[00939] 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).

[00940] 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.

[00941] 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.

[00942] 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).

[00943] 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.

[00944] 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.

[00945] 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).

[00946] 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).

[00947] 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.

[00948] 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).

[00949] 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.

[00950] 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.

[00951] 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.

[00952] In some embodiments, a C9orf72 oligonucleotide can comprise any sugar described

herein or known in the art. In some embodiments, a C9orf72 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 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.

Biological applications

[00953] As described herein, provided compositions and methods are capable of improving knockdown of RNA, including knockdown of C9orf72 RNA transcripts. In some embodiments, provided compositions and methods provide improved knockdown of C9orf72 transcripts (including but not limited to those comprising a repeat expansion) compared to a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[00954] In some embodiment, a C9orf72 oligonucleotide is capable of preferentially decreasing (knocking down) the expression, level and/or activity of a mutant or repeat expansion-containing C9orf72 gene or gene product (e.g., one comprising a hexanucleotide repeat expansion) relative to that of a wild-type or non-repeat expansion-containing C9orf72 gene or gene product (e.g., one lacking a hexanucleotide repeat expansion).

[00955] Preferential knockdown of repeat expansion-containing C9orf72 oligonucleotides is illustrated, for example, in Figure 4A and B. C9orf72 oligonucleotides WV-3688, WV-6408, WV-7658, WV-7659, WV-8011 and WV-8012 were all able to preferentially knock down the level of repeat expansion-containing C9orf72 RNA transcripts relative to the level of non-repeat expansion-containing C9orf72 RNA transcripts (e.g., total transcripts, most of which are normal transcripts which do not comprise a repeat expansion).

[00956] WV-3688, WV-6408, WV-7658, WV-7659, WV-8011, and WV-8012 all have the base sequence of CCUCACTCACCCACTCGCCA (for WV-3688) or CCTCACTCACCCACTCGCCA (the remainder), and have a sequence of:
mC*mCmUmCmA*C*T*C*A*C*C*C*A*C*T*mCmGmCmC*mA,
m5Ceo*m5CeoTeom5CeoAeo*C*T*C*A*C*C*C*A*C*T*m5CeoGeom5Ceom5Ceo*Aeo,
m5Ceo*Rm5CeoTeom5CeoAeo*RC*ST*SC*RA*SC*SC*RC*SA*SC*ST*Rm5CeoGeom5Ceom5Ceo*RAeo,
m5Ceo*Rm5CeoTeom5CeoAeo*RC*ST*SC*RA*SC*SC*SC*SA*SC*ST*Rm5CeoGeom5Ceom5Ceo*RAeo,

mC*Sm5CeoTeom5CeomA*SC*ST*SC*RA*SC*SC*SC*SA*SC*ST*SmC*SmG*SmC*SmC*SmA, mC*Sm5CeoTeom5CeomA*SC*ST*SC*RA*SC*SC*RC*SA*SC*ST*SmC*SmG*SmC*SmC*SmA, respectively. Total transcripts include V2, V3 and V1, both normal (healthy, without repeat expansions) and mutant (pathological, comprising a repeat expansion). Various transcripts are diagrammed in Figure 1. V1 is reportedly transcribed at very low levels (around 1% of the total C9orf72 transcripts) and does not contribute significantly to the levels of transcripts comprising hexanucleotide repeat expansions or to the levels of transcripts detected in assays for V3 transcripts.

[00957] V1, V2 and V3 are naturally produced pre-mRNA variants of the C9orf72 transcript produced by alternative pre-mRNA splicing. DeJesus-Hernandez et al. 2011. In variants 1 and 3 the expanded GGGGCC repeat is located in an intron between two alternatively spliced exons, whereas in variant 2 the repeat is located in the promoter region and thus not present in the transcript. V1 is C9orf72 Variant 1 transcript, which represents the shortest transcript and encodes the shorter C9orf72 protein (isoform b), see NM_145005.5. V2 is C9orf72 Variant 2 transcript, which differs in the 5' UTR and 3' coding region and UTR compared to variant 1. The resulting C9orf72 protein (isoform a) is longer compared to isoform 1. Variants 2 and 3 encode the same C9orf72 protein; see NM_018325.3. V3 is C9orf72 Variant 3 transcript, which differs in the 5' UTR and 3' coding region and UTR compared to variant 1. The resulting C9orf72 protein (isoform a) is longer compared to isoform 1; Variants 2 and 3 encode the same protein, see NM_001256054.1. Transcript variants 1 and 3 are predicted to encode for a 481 amino acid long protein encoded by C9ORF72 exons 2–11 (NP_060795.1; isoform a), whereas variant 2 is predicted to encode a shorter 222 amino acid protein encoded by exons 2–5 (NP_659442.2; isoform b). It is noted that, according to some reports, the V1, V2 and V3 transcripts are not equally abundant; reportedly, V2 is the major transcript, representing 90% of total transcripts, V3 representing 9%, and V1 representing 1%. Therefore, without being bound by any particular theory, this disclosure suggests that a decrease in total transcripts mediated by some C9orf72 oligonucleotides includes representation of knockdown of repeat expansion-containing transcripts. The data show that many C9orf72 oligonucleotides were thus capable of mediating preferential knockdown of repeat expansion-containing C9orf72 transcripts relative to non-repeat expansion-containing C9orf72 transcripts. For example, WV-6408 achieved 80% : 35% knockdown of repeat associated transcripts (V3) : total (mostly normal) C9 mRNA. WV-3537 and WV-3174 were also capable of mediating some preferential knockdown of repeat expansion-containing transcripts. In contrast, C9orf72 oligonucleotides WV-3662 and WV-3536, representing the sequences of SEQ ID NO: 0553 of WO2015054676 and the complement of SEQ ID NO: 0057 of WO2016168592, representively, were not capable of mediating preferential knockdown of repeat expansion-containing C9orf72 transcripts relative to non-repeat expansion-containing C9orf72 transcripts (Figures 4A and B).

[00958] In these experiments, patient derived ALS neurons (detailed in Example 9) were used for screening. Negative control oligonucleotide WV-2376 does not target C9orf72. Control oligonucleotide WV-3542 is described in Table 1A. In Figures 4C and 4D, oligonucleotides were tested at 1 and 10 μM.

[00959] Figures 5 and 6 present example data demonstrating the in vivo capability of C9orf72 oligonucleotides to mediate preferential knockdown of repeat expansion-containing C9orf72 transcripts in the C9-BAC mouse spinal cord and cortex, respectively. Presented data were those of: WV-6408, WV-8009, WV-8010, WV-8011, and WV-8012. Figures 5A and 6A show knockdown of total transcripts (including repeat expansion-containing and non-repeat expansion-containing transcripts). Figures 5B and 6B show knockdown of V3 (repeat expansion-containing) transcripts. Figures 5C and 6C show knockdown of Intron/AS transcripts (with probes targeting a region 3' to the repeat transcript expansion, the detected area includes both sense and antisense transcripts of the intronic region). Additional experimental details are provided in Example 9. Additional information related to preferential knockdown of repeat expansion-containing C9orf72 transcripts is presented herein.

[00960] In some embodiments, a C9orf72 oligonucleotide can preferentially knockdown or decrease the expression, level and/or activity of mutant (e.g., repeat expansion containing) V3 C9orf72 transcripts relative to the total C9orf72 transcripts.

[00961] In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, activity and/or level of a DPR protein translated from a repeat expansion.

[00962] In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the expression, activity and/or level of a C9orf72 gene product. In some embodiments, a C9orf72 gene product is a protein, such as a dipeptide repeat (DPR) protein. In some embodiments, DPRs can be produced by RAN translation in any of the six reading frames of a repeat-containing C9orf72 transcript. In some embodiments, a dipeptide repeat protein is produced via RNA (repeat-associated and non-ATG-dependent translation) of either the sense or the antisense strand of a hexanucleotide repeat region. DPR proteins are described, for example, in Zu et al. 2011 Proc. Natl. Acad. Sci. USA 108: 260-265; Zu et al. Proc. Natl. Acad. Sci. U S A. 2013 Dec 17;110(51):E4968-77; Lopez-Gonzalez et al., 2016, Neuron 92, 1–9; May et al. Acta Neuropathol (2014) 128:485–503; and Freibaum et al. 2017 Front. Mol. Neurosci. 10, Article 35; and Westergard et al., 2016, Cell Reports 17, 645–652. In some embodiments, a C9orf72 dipeptide repeat is or comprises any of: poly-(proline-alanine) (poly-PA or) or poly-(alanine-proline) or (poly-AP); poly-(proline-arginine) (poly-PR) or poly-(arginine-proline) (poly-RP); or poly-(proline-glycine) (poly-PG) or poly-(glycine-proline (poly-GP). Poly-GA is reportedly abundantly expressed in the C9orf72 brains, followed by poly-GP and poly-GR, while poly-PA and poly-PR resulting from translation of the antisense transcript are rare. Reportedly, Poly-GA and the other DPR species are transmitted between cells and how DPR uptake affects the receiving cells. Zhou et al. detected cell-to-cell

transmission of all hydrophobic DPR species and show that poly-GA boosts repeat RNA levels and DPR expression, suggesting DPR transmission may trigger a vicious cycle; treating cells with anti-GA antibodies reduced intracellular aggregation of DPRs. Zhou et al. 2017. EMBO Mol. Med. 9(5):687-702. Chang et al. reported that Glycine-Alanine Dipeptide Repeat proteins form toxic amyloids possessing cell-to-cell transmission properties. Chang et al. 2016. J. Biol. Chem. 291: 4903-4911.

[00963] In some embodiments, a DPR protein is a polyGP. As non-limiting examples, the amino acid sequence of a DPR protein is or comprises any of: GAGAGAGAGAGAGAGAGAGAWSGRARGRARGGAAVAVPAPA-AAEAQAVASG, GPGPGPGPGPGPGPGPGPGRGRGGPGGGPGAGLRLRCLRPRRRRRRR-WRVGE, or GRGRGRGRGRGRGRGRGRGVVGAGPGAGPGRGCGCGACARGGGGAGG-GEWVSEEAASWRVAVWGSAAGKRRG (from a sense frame); or PRPRPRPRPR-PRPRPRPRPLARDS, GPGPGPGPGPGPGPGPGP, or PAPAPAPAPAPAPAPAPAPSARLLSS-RACYRLRLFPSLFSSG (from an antisense frame).

[00964] As shown in Figure 10 and detailed in Example 13, C9orf72 oligonucleotides WV-6408, WV-8009, WV-8010, WV-8011, and WV-8012 all reduced the level of polyGP (pGP, a dipeptide repeat protein) in the hippocampus of C9-BAC mice. In addition, C9orf72 oligonucleotides WV-8549 and WV-8551 also reduced polyGP levels in the mouse hippocampus (data not shown).

[00965] C9orf72 gene products also include foci, which comprise a complex of a C9orf72 RNA or a portion thereof (e.g., an excised intron) bound by multiple RNA-binding proteins. Foci are described in, for example, Mori et al. 2013 Acta Neuropath. 125: 413-423. In some embodiments, a C9orf72 oligonucleotide is capable of mediating a decrease in the number of cells comprising a focus, and/or the number of foci per cell.

[00966] As non-limiting example data, administration of C9orf72 oligonucleotides WV-7658 and WV-7659 in mouse demonstrated a 51.8% and 62.2% decrease in the number of foci counted per 100 motor neuron nuclei [compared to PBS (negative control)] in the spinal cord anterior horn (location of the lower motor neurons); and 58.3% and 70.9% decrease, respectively, in the number of cells with more than 5 foci / cell; and a 49.1% and 55.0% decrease, respectively, in the number of foci per 100 motor neurons.

[00967] Without wishing to be bound by any particular theory, the present disclosure suggests that a significant knockdown of V3 C9orf72 transcript and/or decrease in the expression, activity and/or level of a DPR protein and/or a decrease in the number of cells comprising a focus, and/or the number of foci per cell can lead to or be associated with a significant inhibition of cellular pathology, with the underlying biology rationale that the expanded hexanucleotide repeat allele leads to longer resident time of the pre-spliced C9orf72 transcripts and the spliced intron, which makes them more vulnerable to intronic targeting oligonucleotides. Without wishing to be bound by any particular theory, the present

disclosure suggests that an about 50% knockdown of V3 C9orf72 transcript can lead to or be associated with an about 90% inhibition of cellular pathology.

[00968] An improvement mediated by a C9orf72 oligonucleotide can be an improvement of any desired biological functions, including but not limited to treatment and/or prevention of a C9orf72-related disorder or a symptom thereof. In some embodiments, a C9orf72-related disorder is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), corticobasal degeneration syndrome (CBD), atypical Parkinsonian syndrome, olivopontocerebellar degeneration (OPCD), primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), Huntington's disease (HD) phenocopy, Alzheimer's disease (AD), bipolar disorder, schizophrenia, or other non-motor disorders. In some embodiments, a symptom of a C9orf72-related disorder is selected from: agitation, anxiety, blunted emotions, changes in food preference, decreased energy and/or motivation, dementia, depression, difficulty in breathing, difficulty in swallowing, difficulty in projecting the voice, difficulty with respiration, distractibility, fasciculation and/or cramping of muscles, impaired balance, impaired motor function, inappropriate social behavior, lack of empathy, loss of memory, mood swings, muscle twitching, muscle weakness, neglect of personal hygiene, repetitive or compulsive behavior, shortness of breath, slurring of speech, unsteady gait, vision abnormality, weakness in the extremities.

[00969] In some embodiments, a symptom of a C9orf72-related disorder is semantic dementia, decrease in language comprehension, or difficulty in using correct or precise language. In some embodiments, a c9orf72-related disoder or a symptom thereof is corticobasal degeneration syndrome (CBD), shakiness, lack of coordination, muscle rigidity and/or spasm, progressive supranuclear palsy (PSP), a walking and/or balance problem, frequent falls, muscle stiffness, muscle stiffness in the neck and/or upper body, loss of physical function, and/or abnormal eye movement.

[00970] In some embodiments, FTD is behavioral variant frontotemporal dementia (bvFTD). In some embodiments, in bvFTD, reportedly, the most significant initial symptoms are associated with personality and behavior. In some embodiments, a c9orf72 oligonucleotide is capable of reducing the extent or rate at which a subject experiences disinhibition, which presents as a loss of restraint in personal relations and social life, as assessed according to methods well-known in the art.

[00971] In some embodiments, the present disclosure provides a method of treating a disease by administering a composition comprising a first plurality of oligonucleotides sharing a common base sequence comprising a common base sequence, which nucleotide sequence is complementary to a target sequence in the target C9orf72 transcript,

the improvement that comprises using as the oligonucleotide composition a stereocontrolled oligonucleotide composition characterized in that, when it is contacted with the C9orf72 transcript in an oligonucleotide or a knockdown system, RNase H-mediated knockdown of the C9orf72 transcript is

improved relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[00972] Evaluation and testing of efficacy of C9orf72 oligonucleotides

[00973] Various techniques and tools, including but not limited to many known in the art, can be used for evaluation and testing of C9orf72 oligonucleotides.

[00974] In some embodiments, evaluation and testing of efficacy of C9orf72 oligonucleotides can be performed by quantifying a change or improvement in the level, activity, expression, allele-specific expression and/or intracellular distribution of a C9orf72 target nucleic acid or a corresponding gene product following delivery of a C9orf72 oligonucleotide. In some embodiments, delivery can be via a transfection agent or without a transfection agent (e.g., gymnotic).

[00975] In some embodiments, evaluation and testing of efficacy of C9orf72 oligonucleotides can be performed by quantifying a change in the level, activity, expression and/or intracellular of a C9orf72 gene product (including but not limited to a transcript, DPR or focus) following introduction of a C9orf72 oligonucleotide. C9orf72 gene products include RNA produced from a C9orf72 gene or locus.

[00976] In some embodiments, the present disclosure provides a method of identifying and/or characterizing an oligonucleotide composition, the method comprising steps of:

providing at least one composition comprising a first plurality of oligonucleotides; and

assessing delivery relative to a reference composition.

[00977] In some embodiments, the present disclosure provides a method of identifying and/or characterizing an oligonucleotide composition, the method comprising steps of:

providing at least one composition comprising a first plurality of oligonucleotides; and

assessing cellular uptake relative to a reference composition.

[00978] In some embodiments, properties of a provided oligonucleotide compositions are compared to a reference oligonucleotide composition.

[00979] In some embodiments, a reference oligonucleotide composition is a stereorandom oligonucleotide composition. In some embodiments, a reference oligonucleotide composition is a stereorandom composition of oligonucleotides of which all internucleotidic linkages are phosphorothioate. In some embodiments, a reference oligonucleotide composition is a DNA oligonucleotide composition with all phosphate linkages.

[00980] In some embodiments, a reference composition is a composition of oligonucleotides having the same base sequence and the same chemical modifications. In some embodiments, a reference composition is a composition of oligonucleotides having the same base sequence and the same pattern of chemical modifications. In some embodiments, a reference composition is a chirally un-controlled (or stereorandom) composition of oligonucleotides having the same base sequence and chemical

modifications.

[00981] In some embodiments, a reference composition is a composition of oligonucleotides having the same base sequence but different chemical modifications, including but not limited to chemical modifications described herein. In some embodiments, a reference composition is a composition of oligonucleotides having the same base sequence but different patterns of internucleotidic linkages and/or stereochemistry of internucleotidic linkages and/or chemical modifications.

[00982] Various methods are known in the art for the detection of C9orf72 gene products, the expression, level and/or activity of which might be altered after introduction or administration of a C9orf72 oligonucleotide. As non-limiting examples: C9orf72 transcripts and their knockdown can be quantified with qPCR, C9orf72 protein levels can be determined via Western blot, RNA foci by FISH (fluorescence in situ hybridization), DPRs by Western blot, ELISA, or mass spectrometry. Commercially available C9orf72 antibodies include anti-C9orf72 antibody GT779 (1:2000; GeneTex, Irvine, California). In addition, functional assays can be performed on motor neurons (MN) expressing wild-type and/or mutant C9orf72 by Electrophysiology and NMJ formation.

[00983] In some embodiments, evaluation and testing of efficacy of C9orf72 oligonucleotides can be performed in vitro in a cell. In some embodiments, the cell is a cell which expresses C9orf72. In some embodiments, a cell is a SH-SY5Y (human neuroblastoma) cell engineered to express C9orf72. In some embodiments, a cell is a SH-SY5Y cell engineering to express C9orf72, as described in WO 2016/167780. In some embodiments, a cell is a patient-derived cell, patient-derived fibroblast, iPSC or iPSN. In some embodiments, a cell is an iPSC derived neuron or motor neuron. Various cells suitable for testing of a C9orf72 oligonucleotide include patient-derived fibroblasts, iPSCs and iPSNs and described in, for example, Donelly et al. 2013 Neuron 80, 415-428; Sareen et al. 2013 Sci. Trans. Med. 5: 208ra149; Swartz et al. STEM CELLS TRANSLATIONAL MEDICINE 2016;5:1–12; and Almeida et al. 2013 Acta Neuropathol. 126: 385-399. In some embodiments, a cell is a BAC transgenic mouse-derived cell, including without limitation, a mouse embryonic fibroblast or cortical primary neuron. In some embodiments, evaluation and testing involves a population of cells. In some embodiments, a population of cells is a population of iCell Neurons (also referenced as iNeurons), an iPS cell-derived mixed population of human cerebral cortical neurons that exhibit native electrical and biochemical activity, commercially available from Cellular Dynamics International, Madison, Wisconsin. Additional cells, including Spinal Cord Motor Neurons, Midbrain, Dopaminergic Neurons, Glutamatergic Neurons, GABAergic Neurons, Mixed Cortical Neurons, Medium Spiny Striatal GABAergic Neurons, Parvalbumin-Enriched Cortical GABAergic Neurons, Layer V Cortical Glutamatergic Neurons, are commercially available from BrainXell, Madison, Wisconsin.

[00984] In some embodiments, evaluation of a C9orf72 oligonucleotide can be performed in an

animal. In some embodiments, an animal is a mouse. C9orf72 mouse models and experimental procedures using them are described in Hukema et al. 2014 Acta Neuropath. Comm. 2: 166; Ferguson et al. 2016 J. Anat. 226: 871-891; Lagier-Tourenne et al. Proc. Natl. Acad. Sci. USA. 2013 Nov 19;110(47):E4530-9; Koppers et al. Ann. Neurol. 2015;78:426–438; Kramer et al. 2016 Science 353: 708; Liu et al., 2016, Neuron 90, 521–534; Peters et al., 2015, Neuron 88, 902–909; Picher-Martel et al. Acta Neuropathologica Communications (2016) 4:70. A C9-BAC mouse model is described herein (see Example 9).

[00985] In some embodiments, target nucleic acid levels can be quantitated by any method known in the art, many of which can be accomplished with kits and materials which are commercially available, and which methods are well known and routine in the art. Such methods include, e.g., Northern blot analysis, competitive polymerase chain reaction (PCR), or quantitative real-time PCR. RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. Probes and primers are designed to hybridize to a C9orf72 nucleic acid. Methods for designing real-time PCR probes and primers are well known in the art.

[00986] In some embodiments, evaluation and testing of efficacy of C9orf72 oligonucleotides can be performed using a luciferase assay. A non-limiting example of such an assay is detailed in Example 3, below. In some embodiments, a luciferase assay employs a construct comprising the luciferase gene (or an efficacious portion thereof) linked to a portion of the sense C9orf72 transcript, such as nt 1-374 or nt 158-900 (both of which comprise a hexanucleotide repeat expansion). In some embodiments, nt 1-374 comprises exon 1a and the intron between exons 1a and 1b. In some embodiments, a luciferase assay employs a construct comprising the luciferase gene (or an efficacious portion thereof) linked to a portion of the antisense C9orf72 transcript, such as nt 900 to 1 (which comprises a hexanucleotide repeat expansion). In some embodiments, a luciferase assay is performed in a transfect COS-7 cell.

[00987] In some embodiments, a C9orf72 protein level can be evaluated or quantitated in any method known in the art, including, but not limited to, enzyme-linked immunosorbent assay (ELISA), Western blot analysis (immunoblotting), immunocytochemistry, fluorescence-activated cell sorting (FACS), immunohistochemistry, immunoprecipitation, protein activity assays (for example, caspase activity assays), and quantitative protein assays. Antibodies useful for the detection of mouse, rat, monkey, and human C9orf72 are commercially available; additional antibodies to C9orf72 can be generated via methods known in the art.

[00988] An assay for detecting levels of an oligonucleotide or other nucleic acid is described herein (e.g., in Example 14). This assay can be used to detect, as non-limiting examples, a C9orf72 oligonucleotide or any other nucleic acid of interest, including nucleic acids or other oligonucleotides which do not target C9orf72 and nucleic acids.

[00989] Evaluation and testing of efficacy of C9orf72 oligonucleotides can be performed in vitro or in vivo by determining the change in number of repeat RNA foci (or RNA foci) in cells following delivery of the C9orf72 oligonucleotide. A repeat RNA focus is a structure formed when a RNA comprising a hexanucleotide repeat sequesters RNA-binding proteins, and is a measure and/or cause of RNA-mediated toxicity. In some embodiments, a RNA focus can be a sense or an antisense RNA focus. When a C9orf72 oligonucleotide is administered in vivo to an animal, the presence and/or number of RNA foci can be determined or examined in the brain of the animal, or a portion thereof, such as, without limitation, the cerebellum, cerebral cortex, hippocampus, thalamus, medulla, or any other portion of the brain. The number of foci per cell (e.g., up to 5 or greater than 5) or average thereof and/or the number of cells comprising a focus can be determined after delivery of a C9orf72 oligonucleotide. A decrease in any or all of these numbers indicates the efficacy of a C9orf72 oligonucleotide. RNA foci can be detected by an method known in the art, including, but not limited to FISH (fluorescence in situ hybridization); a non-limiting example of FISH is presented in Example 14.

[00990] Evaluation and testing of efficacy of C9orf72 oligonucleotides can be performed in vitro by determining the change in haploinsufficiency in cells following delivery of the C9orf72 oligonucleotide. Haploinsufficiency occurs, for example, when a hexanucleotide repeat RNA acts as a negative effector on C9orf72 transcription and/or expression of a C9orf72 gene, thus decreasing the overall amount of C9orf72 transcript or gene product. A decrease in haploinsufficiency indicates the efficacy of a C9orf72 oligonucleotide.

[00991] In some embodiments, a C9orf72 oligonucleotide does not significantly decrease the expression, activity and/or level of the C9orf72 protein. In some embodiments, a C9orf72 oligonucleotide decreases the expression, activity and/or level of a C9orf72 repeat expansion or a gene product thereof, but does not significantly decrease the expression, activity and/or level of the C9orf72 protein.

[00992] In some embodiments, a C9orf72 oligonucleotide (a) decreases the expression, activity and/or level of a C9orf72 repeat expansion or a gene product thereof, and (b) does not decrease the expression, activity and/or level of C9orf72 to a degree sufficient to cause a disease condition. Various disease conditions related to insufficient production of C9orf72 include improper endosomal trafficking, a robust immune phenotype characterized by myeloid expansion, T cell activation, increased plasma cells, elevated autoantibodies, immune-mediated glomerulonephropathy, and/or an auto-immune response, as described in, for example, Farg et al. 2014 Human Mol. Gen. 23: 3579-3595; and Atanasio et al. Sci Rep. 2016 Mar 16;6:23204. doi: 10.1038/srep23204.

[00993] Evaluation and testing of efficacy of C9orf72 oligonucleotides can be performed in vivo. In some embodiments, C9orf72 oligonucleotides can be evaluated and/or tested in animals. In some

embodiments, C9orf72 oligos can be evaluated and/or tested in humans and/or other animals to mediate a change or improvement in the level, activity, expression, allele-specific expression and/or intracellular distribution and/or to prevent, treat, ameliorate or slow the progress of a C9orf72-related disorder or at least one symptom of a C9orf72-related disorder. In some embodiments, such in vivo evaluation and/or testing can determine, after introduction of a C9orf72 oligonucleotide, phenotypic changes, such as, improved motor function and respiration. In some embodiments, a motor function can be measured by a determination of changes in any of various tests known in the art including: balance beam, grip strength, hindpaw footprint testing (e.g., in an animal), open field performance, pole climb, and rotarod. In some embodiments, respiration can measured by a determination of changes in any of various tests known in the art including: compliance measurements, invasive resistance, and whole body plethysmograph.

[00994] In some embodiments, the testing of the efficacy of a C9orf72 oligonucleotide be accomplished by contacting a motor neuron cell from a subject with a neurological disease with the C9orf72 oligonucleotide and determining whether the motor neuron cell degenerates. If the motor neuron cell does not degenerate, the C9orf72 oligonucleotide may be capable of reducing or inhibiting motor neuron degeneration. The motor neuron cell may be derived from a pluripotent stem cell. The pluripotent stem cell may have been reprogrammed from a cell from the subject. The cell from the subject may be a somatic cell, for example. The somatic cell may be a fibroblast, a lymphocyte, or a keratinocyte, for example. The assessment of whether a motor neuron cell degenerates or not may be based on a comparison to a control. In some embodiments, the control level may be a predetermined or reference value, which is employed as a benchmark against which to assess the measured and/or visual result. The predetermined or reference value may be a level in a sample (e.g. motor neuron cell) from a subject not suffering from a neurological disease or from a sample from a subject suffering from a neurological disease but wherein the motor neuron cell is not contacted with the C9orf72 oligonucleotide. The predetermined or reference value may be a level in a sample from a subject suffering from a neurological disease. In any of these screening methods, the cell from the subject having the neurological disease may comprise the (GGGGCC)n hexanucleotide expansion in C9orf72.

[00995] The efficacy of C9orf72 can also be tested in suitable test animals, such as those described in, as non-limiting examples: Peters et al. 2015 Neuron. 88(5):902-9; O'Rourke et al. 2015 Neuron. 88(5): 892–901; and Liu et al. 2016 Neuron. 90(3):521-34. In some embodiments, a test animal is a C9-BAC mouse. The efficacy of C9orf72 can also be tested in C9-BAC transgenic mice with 450 repeat expansions, which were also described in Jiang et al. 2016 Neuron 90, 1-16.

[00996] In some embodiments, in a test animal, levels of various C9orf72 transcripts can be determined, as can be C9orf72 protein level, RNA foci, and levels of DPRs (dipeptide repeat proteins). Tests can be performed on C9orf72 oligonucleotides and in comparison with reference oligonucleotides.

Several C9orf72 oligonucleotides disclosed herein are capable of reducing the percentage of cells comprising RNAi foci and the average number of foci per cell (data shown below and data not shown). Several C9orf72 oligonucleotides disclosed herein are capable of reducing the level of DPRs such as polyGP. As shown in Figure 10, C9orf72 oligonucleotides WV-6408, WV-8009, WV-8010, WV-8011, and WV-8012 all reduced the level of polyGP (pGP, a dipeptide repeat protein) in the hippocampus of C9-BAC mice. In addition, C9orf72 oligonucleotides WV-8549 and WV-8551 also reduced polyGP levels in the mouse hippocampus (data not shown).

[00997] In some embodiments, a c9orf72 oligonucleotide is capable of reducing the extent or rate of neurodegeneration caused by ALS, FTD or other c9orf72-related disorder. In some embodiments, in addition to an improvement, or at least reduction in the extent or rate of deterioration of any nervous system tissue, in behavioral symptoms, therapeutic efficacy of a c9orf72 oligonucleotide in a subject or other animal can also be monitored with brain scans, e.g., CAT scan, functional MRI, or PET scan, or other methods known in the art.

[00998] Various assays for analysis of C9orf72 oligonucleotides are described herein, for example in Example 9, 13, and 14, and include, inter alia, Reporter assay (Luciferase Assay), e.g., performed in an ALS neuron, and measuring, for example, analysis of V3/intron expression, activity and/or level; stability assay; TLR9 assay; Complement assay; PD (Pharmacodynamics) (C9-BAC, icv or Intracerebroventricular injection), e.g., PD and/or efficacy tested in C9orf72-BAC (C9-BAC) mouse model; in vivo procedures, including but not limited to injection into a lateral ventricle or other areas of the central nervous system (including but not limited to cortex and spinal cord) of a test animal, such as a mouse; analysis of number of foci and/or number of cells comprising foci: PolyGP (or pGP or DPR assay).

[00999] In some embodiments, selection criteria are used to evaluate the data resulting from the various assays and to select particularly desirable C9orf72 oligonucleotides. In some embodiments, at least one selection criterion is used. In some embodiments, two or more selection criteria are used. In some embodiments, selection criteria for a Luciferase assay (e.g., V3/intron knockdown) is at least partial knockdown of the V3 introns and/or at least partial knockdown of the intron transcript. In some embodiments, selection criteria for a Luciferase assay (e.g., V3/intron knockdown) is 50% KD (knockdown) of the V3 introns and 50% KD of the intron transcript. In some embodiments, selection criteria include a determination of IC_{50}. In some embodiments, selection criteria include an IC_{50} of less than about 10 nM, less than about 5 nM or less than about 1 nM. In some embodiments, selection criteria for a stability assay is at least 50% stability [a level of at least 50% of the oligonucleotide is still remaining and/or detectable] at Day 1. In some embodiments, selection criteria for a stability assay is at least 50% stability at Day 2. In some embodiments, selection criteria for a stability assay is at least 50%

stability at Day 3. In some embodiments, selection criteria for a stability assay is at least 50% stability at Day 4. In some embodiments, selection criteria for a stability assay is at least 50% stability at Day 5. In some embodiments, selection criteria for a stability assay is 80% [at least 80% of the oligonucleotide remains] at Day 5. In some embodiments, selection criteria is at least partial knockdown in number of foci and/or number of cells comprising foci. In some embodiments, selection criteria is at least 50% KD (knockdown) in number of foci and/or number of cells comprising foci. In some embodiments, selection criteria include lack of activation in a TLR9 assay. In some embodiments, selection criteria include lack of activation in a complement assay. In some embodiments, selection criteria include knockdown in a lateral ventricle or other area of the central nervous system (including but not limited to cortex and spinal cord) of a test animal, such as a mouse. In some embodiments, selection criteria include knockdown by at least 50% in a lateral ventricle or other area of the central nervous system (including but not limited to cortex and spinal cord) of a test animal, such as a mouse. In some embodiments, selection criteria include a knockdown in the expression, activity and/or level of DPR protein. In some embodiments, selection criteria include a knockdown in the expression, activity and/or level of DPR protein. In some embodiments, selection criteria include a knockdown in the expression, activity and/or level of DPR protein by at least 50%. In some embodiments, selection criteria include a knockdown in the expression, activity and/or level of the DPR protein PolyGP by at least 50%.

[001000] Oligonucleotides which have been evaluated and tested for efficacy in knocking down C9orf72 have various uses, including administration for use in treatment or prevention of a C9orf72-related disorder or a symptom thereof.

[001001] **Assay for detecting target nucleic acids of interest**

[001002] In some embodiments, the present disclosure pertains to a hybridization assay for detecting and/or quantifying a target nucleic acid (e.g., a target oligonucleotide), wherein the assay utilizes a capture probe, which is at least partially complementary to the target nucleic acid, and a detection probe; wherein the detection probe or a complex comprising the capture probe, the detection probe and the target nucleic acid is capable of being detected. Such an assay can be used to detect a C9orf72 oligonucleotide (e.g., in a tissue or fluid sample), or used to detect any target nucleic acid (to any target or sequence) in any sample. In some embodiments, the capture probe comprises a primary amine, which is capable of reacting to an amino-reactive solid support, thereby immobilizing the probe on the solid support. In some embodiments, the amino-reactive solid support comprises maleic anhydride. Immobilization of the probe can be performed with click chemistry using an alkyne and an azide moiety on the probe and the solid support. For click chemistry, the alkyne or azide can be, for example, at the 5' or 3' end of the probe, and can optionally be attached via a linker. For the click chemistry, the solid support, for example, comprises an alkyne or an azide moiety. In some embodiments, click chemistry

includes that described in, as a non-limiting example, Kolb et al. 2011 Angew. Chem. Int. Ed. 40: 2004-2021.

[001003] In some embodiments, a probe or complex which is capable of being detected directly or indirectly is involved in producing a detectable signal. In some embodiments, a probe or complex is (a) capable of producing a detectable signal in the absence of another chemical component (as a non-limiting example, having a moiety capable of producing a detectable signal, such as a fluorescent dye or radiolabel), or (b) comprises a ligand, label or other component which, when bound by an appropriate second moiety, is capable of producing a detectable signal. In some embodiments, a probe or complex of type (b) comprises a label such as biotin, digoxigenin, hapten, ligand, etc., which can be bound by an appropriate second chemical entity such as an antibody which, when bound to the label, is capable of producing a signal, e.g., via a radiolabel, chemiluminesce, dye, alkaline phosphatase signal, peroxidase signal, etc.

[001004] In some embodiments, the capture probe is immobilized on a solid support. In some embodiments, the capture probe is hybridized, bound or ligated to the target nucleic acid, and the detection probe is also hybridized, bound or ligated to the target nucleic acid, and the complex is capable of being detected. Many variants of hybridization assays are known in the art. In some embodiments, in a hybridization assay, the capture and the detection probe are the same probe, and a single-stranded nuclease is used to degrade probe which is not bound (or not fully bound) to a target nucleic acid.

[001005] In some embodiments, the present disclosure pertains to a hybridization assay for detecting and/or quantifying a target nucleic acid (e.g., a target oligonucleotide), wherein a probe (e.g., a capture probe) is at least partially complementary to the target nucleic acid and comprises a primary amine, wherein the primary amine is capable of reacting to an amino-reactive solid support, thereby immobilizing the probe on the solid support. The primary amine can be, for example, at the 5' or 3' end of the probe, and can optionally be attached via a linker. In some embodiments, the amino-reactive solid support comprises maleic anhydride.

[001006] The target oligonucleotide can be, for example, a C9orf72 oligonucleotide or an oligonucleotide to any target of interest.

[001007] In some embodiments, the assay is a hybridization assay, sandwich hybridization assay, competitive hybridization assay, dual ligation hybridization assay, nuclease hybridization assay, or electrochemical or electrochemical hybridization assay.

[001008] In some embodiments, the assay is a sandwich hybridization assay, wherein a capture probe is bound to a solid support and is capable of annealing to a portion of the target oligonucleotide; wherein a detection probe is capable of being detected and is capable of annealing to another portion of the target oligonucleotide; and wherein the hybridization of both the capture probe and the detection

probe to the target oligonucleotide produces a complex which is capable of being detected.

[001009] In some embodiments, the assay is a nuclease hybridization assay and the capture probe is a cutting probe fully complementary to the target oligonucleotide, wherein a cutting probe which is bound by full-length target oligonucleotides is capable of being detected; and wherein a cutting probe which is free (not bound to a target oligonucleotide) or which is bound to a shortmer, metabolite or degradation product of a target oligonucleotide is degraded by S1 nuclease treatment and therefore does not produce a detectable signal.

[001010] In some embodiments, the assay is a hybridization-ligation assay, wherein the capture probe is a template probe, which is fully complementary to the target oligonucleotide and is intended to serve as a substrate for ligase-mediated ligation of the target oligonucleotide and a detection probe.

[001011] In some embodiments, the present disclosure pertains to a method of detecting and/or quantifying a target nucleic acid (e.g., a target oligonucleotide), for example, in a sample, e.g., a tissue or fluid, comprising the steps of: (1) providing a capture probe, wherein the capture probe is at least partially complementary to the target nucleic acid and comprises a primary amine, wherein the primary amine is capable of being bound by an amino-reactive solid support, thereby immobilizing the probe on the solid support; (2) immobilizing the capture probe to the solid support; (3) providing a detection probe, wherein the detection probe is at least partially complementary to the target nucleic acid (e.g., in a region of the target nucleic acid different from the region to which the capture probe binds) and is capable of directly or indirectly producing a signal; wherein steps (2) and (3) can be performed in either order; (4) bringing the tissue or fluid in contact with the capture probe and detection probe under conditions suitable for hybridization of the probes to the target nucleic acid; (5) removing detection probe not hybridized to the target nucleic acid; and (6) detecting for the signal directly or indirectly produced by the detection probe, wherein detection of the signal indicates the detection and/or quantification of the target nucleic acid.

[001012] In some embodiments, the target oligonucleotide is a C9orf72 oligonucleotide. In some embodiments, the target oligonucleotide is not a C9orf72 oligonucleotide. In some embodiments, a target nucleic acid is an oligonucleotide, an antisense oligonucleotide, a siRNA agent, a double-stranded siRNA agent, a single-stranded siRNA agent, or a nucleic acid associated with a disease (e.g., a gene or gene product which is expressed or over-expressed in a disease state, such as a transcript whose abundance is increased in cancer cells, or which nucleic acid comprises a mutation associated with a disease or disorder).

[001013] In some embodiments, the amino-reactive solid support comprises maleic anhydride.

[001014] Figure 11. Figure 11A shows an example hybridization ELISA assay for measuring target oligonucleotide (e.g., ASO) levels, e.g., in tissues and fluids, including but not limited to animal biopsies. Figure 11B shows example chemistry for binding a primary amine-labeled capture probe to an

amino-reactive solid support, such as a plate comprising maleic anhydride.

[001015] The target oligonucleotide is reannealed to the detection probe, and then combined with the capture probe, which is attached to an amino-reactive plate via a primary amine label. Dual hybridization (e.g., sandwich hybridization) occurs between the capture probe, detection probe and the target oligonucleotide; a gap (not shown in Figure 11A) is allowable between the capture probe and detection probe, leaving a single-stranded portion of the target oligonucleotide not bound to the capture or detection probe. The solid support (e.g., a plate surface) comprises maleic anhydride (e.g., a maleic anhydride activated plate), which spontaneously reacts with the primary amine label on the end of a capture probe (e.g., at pH 8 to 9), immobilizing the probe to the solid support. In some embodiments, a solid support is a plate, tube, filter, bead, polymeric bead, gold, particle, well, or multiwell plate.

[001016] As a non-limiting example, the following conditions can be used:

Coating: 500 nM in 2.5% Na2CO3 pH9.0 50 ul/well, 37 C, 2 hr

Sample/Detection probe: 300 nM Detect probe as diluent, 4 C, O/N

Streptavidin-AP: 1:2000 in PBST 50 ul/well, RT, 1-2 hr

Substrate AttoPhos: 100 ul/well, RT, 5 min read

[001017] For example: The target nucleic acid is preannealed to the detection probe, and then combined with the capture probe, which is attached to a plate via a click chemistry using an alkyne (azide) moiety on the probe and the solid support. Dual hybridization (e.g., sandwich hybridization) occurs between the capture probe, detection probe and the target nucleic acid; a gap is allowable between the capture probe and detection probe, leaving a single-stranded portion of the target oligonucleotide not bound to the capture or detection probe. The solid support (e.g., a plate surface) comprises alkyne (or azide) moiety, which reacts with the azide (or alkyne) moiety label on the end of a capture probe with click chemistry, immobilizing the probe to the solid support. In some embodiments, a solid support is a plate, tube, filter, bead, polymeric bead, gold, particle, well, or multiwell plate.

[001018] A non-limiting example of an assay is provided below:

[001019] Hybridization ELISA assay to measure target oligonucleotide level in tissues, including animal biopsies:

[001020] The reverse complement sequence of the target oligonucleotide can be divided into 2 segments, each represented by a capture or detection probe. The 5'- sequence (of the target oligonucleotide) can be 5-15 nt; the 3' sequence can be 5-15 nt. However, the 5'-probe sequence (hybridizing to the 3'-portion of the target oligonucleotide) should not overlap the 3' probe sequence when they are both hybridized to the target oligonucleotide. A gap between 5'- probe and 3'-probe is allowable. Each probe should have a melting temperature (Tm) at least 25 C, preferably > 45 C, even more preferably > 50 C. To achieve high Tm, modified nucleotides can be used, such as Locked Nucleic

Acids (LNA) or Peptide Nucleic Acids (PNA). Other nucleotides in the probe can be either DNA or RNA nucleotides or any other forms of modified nucleotides, such as those having a 2'-OMe, 2'-F, or 2'-MOE modification.

[001021] The 5'-probe can also be labeled with a detection moiety with a linker at the 5'-position. This probe is the Detection Probe.

[001022] The 5'-probe (hybridizing to the 3'-portion of the target oligonucleotide) can be labeled with a primary amine with a linker at the 5'-position. This probe is the Capture Probe. The linker is used to link the primary amine to the probe nucleotides. The linker can be a C6-, C12- linker, PEG, TEG or any nucleotide sequence not related to the oligonucleotide (such as oligo dT). A 5'-primary amine with a linker can be put on during synthesis or post synthesis.

[001023] The 3'-probe can also be labeled with primary amine with a linker sequences at 3'-position. This probe is the Capture Probe.

[001024] The 3'-probe (hybridizing to the 5'-portion of the target oligonucleotide) can be labeled with a detection moiety with a linker at the 3'-position. This probe is the Detection Probe. The detection moiety can be biotin, digoxigenin, HaloTag® ligand (Promega, Madison, Wisconsin), or any other hapten. The detection moiety can also be Sulfo-Tag (Meso Scale Diagnostics, Rockville, Maryland). The linker is used to link the detection moiety with the probe nucleotides. The linker can be a C6-, C12-linker, PEG, TEG or any nucleotide sequence not related to oligonucleotide (such as oligo dT). A 3'-detection moiety with a linker can be put on during synthesis or post synthesis.

[001025] The Capture Probes (with a primary amine either at the 5'- or 3'- end of probe) can be immobilized on a solid surface activated to react with a primary amine, such as Maleic Anhydride Activated Plates (Pierce; available from ThermoFisher, Waltham, Massachusetts) or N-oxysuccinimide (NOS) activated DNA-BIND plate (Corning Life Sciences, Tewksbury, Massachusetts). The plate can also be other kind of plates activated for amine conjugation, such as MSD plate (Meso Scale Diagnostics, Rockville, Maryland). The surface can be a solid support such as beads, gold particles, carboxylated polystyrene microparticles (MagPlex Microspheres, Luminex Corporation; available from ThermoFisher, Waltham, Massachusetts), or Dynabeads (Thermo Fisher Scientific, Waltham, Massachusetts), so that flow based assay platform can be used, such as Luminex or bead-array platform (BD™ Cytometric Bead Array – CBA, BD Biosciences, San Jose, California).

[001026] The biological samples containing the target oligonucleotide, such as tissue lysates or liquid biological fluids (plasma, blood, serum, CSF, urine, or other tissue or fluid), are mixed with the detection probe at a proper concentration of the oligonucleotide and detection probe, heat-denatured then put on surfaces coated with Capture Probes (plates or microparticles) to promote sequence specific hybridization either at room temperature or 4 C for a period of time (hybridization), in an appropriate

hybridization buffer. Excessive detection probes are removed by washing the surfaces (plates or beads). Then the surface is incubated with reagents which recognize the detection moieties, such as avidin/streptavidin for biotin, antibodies to DIG or haptens, or HaloTag to its ligand.

[001027] The detection reagents are usually labeled with an enzyme, such as horseradish peroxidase (HRP) or alkaline phosphatase (AP), or fluorophores or Sulfo-Tag. After extensive washes, enzyme labeled detection reagents are detected by adding respective substrates, such as TMB for HRP or AttoPhos for AP, and plates are read by plate reader in absorbance mode or fluorescence mode (fluorescent substrates). In some embodiments, a label comprises Fluorescein, B-Phycoerythrin, Rhodamine, Cyanine Dye, Allophycocyanin or a variant or derivative thereof.

[001028] Fluorophore labeled detection reagents can be used for flow-based detection platform, such as Luminex or Bead-array platform.

[001029] Sulfo-Tagged detection reagents can be read by MSD reader (Meso Scale Discovery) directly.

[001030] The oligonucleotide amount can be calculated using a standard curve of serial dilution of test articles run in the same assay.

[001031] Another non-limiting example of a hybridization assay is provided in Example 14.

[001032] Various assays for utility of oligonucleotides (including but not limited to C9orf72 oligonucleotides) are described herein and/or known in the art.

[001033] **Administration of provided oligonucleotides and compositions thereof**

[001034] In some embodiments, provided oligonucleotides are capable of directing a decrease in the expression and/or level of a target gene or its gene product.

[001035] In some embodiments, a target gene is a C9orf72 comprising a hexanucleotide repeat expansion.

[001036] In some embodiments, a provided oligonucleotide composition is administered at a dose and/or frequency lower than that of an otherwise comparable reference oligonucleotide composition with comparable effect in improving the knockdown of a target, including, as a non-limiting example, a C9orf72 transcript. In some embodiments, a stereocontrolled oligonucleotide composition is administered at a dose and/or frequency lower than that of an otherwise comparable stereorandom reference oligonucleotide composition with comparable effect in improving the knockdown of the target C9orf72 transcript.

[001037] In some embodiments, the present disclosure recognizes that properties, *e.g.*, improved knockdown activity, etc. of oligonucleotides and compositions thereof can be optimized by chemical

modifications and/or stereochemistry. In some embodiments, the present disclosure provides methods for optimizing oligonucleotide properties through chemical modifications and stereochemistry.

[001038] In some embodiments, the present disclosure provides a method of administering a oligonucleotide composition comprising a first plurality of oligonucleotides and having a common nucleotide sequence, the improvement that comprises:

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

[001039] In some embodiments, provided C9orf72 oligonucleotides, compositions and methods provide improved delivery. In some embodiments, provided oligonucleotides, compositions and methods provide improved cytoplasmatic delivery. In some embodiments, improved delivery is to a population of cells. In some embodiments, improved delivery is to a tissue. In some embodiments, improved delivery is to an organ. In some embodiments, improved delivery is to the central nervous system or a portion thereof, e.g., CNS. In some embodiments, improved delivery is to an organism. Example structural elements (*e.g.*, chemical modifications, stereochemistry, combinations thereof, etc.), oligonucleotides, compositions and methods that provide improved delivery are extensively described in this disclosure.

[001040] Various dosing regimens can be utilized to administer provided chirally controlled oligonucleotide compositions. In some embodiments, multiple unit doses are administered, separated by periods of time. In some embodiments, a given composition has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which are separated from one another by a time period of the same length; in some embodiments, a dosing regimen comprises a plurality of doses and at least two different time periods separating individual doses. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from the first dose amount. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second (or subsequent) dose amount that is same as or different from the first dose (or another prior dose) amount. In some embodiments, a dosing regimen comprises administering at least one unit dose for at least one day. In some embodiments, a dosing regimen comprises administering more than one dose over a time period of at least one day, and sometimes more than one day. In some embodiments, a dosing regimen comprises administering multiple doses over a time period of at least week. In some embodiments, the time period is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 or more (*e.g.*, about 45, 50, 55, 60,

65, 70, 75, 80, 85, 90, 95, 100 or more) weeks. In some embodiments, a dosing regimen comprises administering one dose per week f or more than one week. In some embodiments, a dosing regimen comprises administering one dose per week for 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 or more (*e.g.*, about 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more) weeks. In some embodiments, a dosing regimen comprises administering one dose every two weeks f or more than two week period. In some embodiments, a dosing regimen comprises administering one dose every two weeks over a time period of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 or more (*e.g.*, about 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more) weeks. In some embodiments, a dosing regimen comprises administering one dose per month for one month. In some embodiments, a dosing regimen comprises administering one dose per month f or more than one month. In some embodiments, a dosing regimen comprises administering one dose per month for 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more months. In some embodiments, a dosing regimen comprises administering one dose per week for about 10 weeks. In some embodiments, a dosing regimen comprises administering one dose per week for about 20 weeks. In some embodiments, a dosing regimen comprises administering one dose per week for about 30 weeks. In some embodiments, a dosing regimen comprises administering one dose per week for 26 weeks. In some embodiments, an oligonucleotide is administered according to a dosing regimen that differs from that utilized for a chirally uncontrolled (*e.g.*, stereorandom) oligonucleotide composition of the same sequence, and/or of a different chirally controlled oligonucleotide composition of the same sequence. In some embodiments, an oligonucleotide is administered according to a dosing regimen that is reduced as compared with that of a chirally uncontrolled (*e.g.*, stereorandom) oligonucleotide composition of the same sequence in that it achieves a lower level of total exposure over a given unit of time, involves one or more lower unit doses, and/or includes a smaller number of doses over a given unit of time. In some embodiments, an oligonucleotide is administered according to a dosing regimen that extends for a longer period of time than does that of a chirally uncontrolled (*e.g.*, stereorandom) oligonucleotide composition of the same sequence Without wishing to be limited by theory, Applicant notes that in some embodiments, the shorter dosing regimen, and/or longer time periods between doses, may be due to the improved stability, bioavailability, and/or efficacy of a chirally controlled oligonucleotide composition. In some embodiments, an oligonucleotide has a longer dosing regimen compared to the corresponding chirally uncontrolled oligonucleotide composition. In some embodiments, an oligonucleotide has a shorter time period between at least two doses compared to the corresponding chirally uncontrolled oligonucleotide composition. Without wishing to be limited by theory, Applicant notes that in some embodiments longer dosing regimen, and/or shorter time periods between doses, may be due to the improved safety of a chirally controlled

oligonucleotide composition.

[001041] In some embodiments, with their improved delivery (and other properties), provided compositions can be administered in lower dosages and/or with lower frequency to achieve biological effects, for example, clinical efficacy.

[001042] A single dose can contain various amounts of oligonucleotides. In some embodiments, a single dose can contain various amounts of a type of chirally controlled oligonucleotide, as desired suitable by the application. In some embodiments, a single dose contains about 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300 or more (*e.g.*, about 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000 or more) mg of a type of chirally controlled oligonucleotide. In some embodiments, a single dose contains about 1 mg of a type of chirally controlled oligonucleotide. In some embodiments, a single dose contains about 5 mg of a type of chirally controlled oligonucleotide. In some embodiments, a single dose contains about 10 mg of a type of chirally controlled oligonucleotide. In some embodiments, a single dose contains about 15 mg of a type of chirally controlled oligonucleotide. In some embodiments, a single dose contains about 20 mg of a type of chirally controlled oligonucleotide. In some embodiments, a single dose contains about 50 mg of a type of chirally controlled oligonucleotide. In some embodiments, a single dose contains about 100 mg of a type of chirally controlled oligonucleotide. In some embodiments, a single dose contains about 150 mg of a type of chirally controlled oligonucleotide. In some embodiments, a single dose contains about 200 mg of a type of chirally controlled oligonucleotide. In some embodiments, a single dose contains about 250 mg of a type of chirally controlled oligonucleotide. In some embodiments, a single dose contains about 300 mg of a type of chirally controlled oligonucleotide. In some embodiments, a chirally controlled oligonucleotide is administered at a lower amount in a single dose, and/or in total dose, than a chirally uncontrolled oligonucleotide. In some embodiments, a chirally controlled oligonucleotide is administered at a lower amount in a single dose, and/or in total dose, than a chirally uncontrolled oligonucleotide due to improved efficacy. In some embodiments, a chirally controlled oligonucleotide is administered at a higher amount in a single dose, and/or in total dose, than a chirally uncontrolled oligonucleotide. In some embodiments, a chirally controlled oligonucleotide is administered at a higher amount in a single dose, and/or in total dose, than a chirally uncontrolled oligonucleotide due to improved safety.

[001043] **Treatment of C9orf72-related disorders or a symptom thereof**

[001044] In some embodiments, provided oligonucleotides are capable of directing a decrease in the expression, level and/or activity of a C9orf72 target gene or a gene product thereof. In some embodiments, an C9orf72-related disorder is a disorder related to, caused and/or associated with abnormal or excessive activity, level and/or expression of, a deleterious mutation in, or abnormal tissue or

inter- or intracellular distribution of an C9orf72 gene or a gene product thereof. In some embodiments, a C9orf72-related disorder is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), corticobasal degeneration syndrome (CBD), atypical Parkinsonian syndrome, olivopontocerebellar degeneration (OPCD), primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), Huntington's disease (HD) phenocopy, Alzheimer's disease (AD), bipolar disorder, schizophrenia, or other non-motor disorders. Symptoms of a C9orf72-related disorder include those described herein and known in the art.

[001045] Without wishing to be bound by any particular theory or terminology, the present specification notes that, with the understanding of C9orf72-related diseases constantly evolving, the exact labeling of various c9orf72-related diseases is also reportedly evolving. In some embodiments, c9orf72 oligonucleotides are useful for decreasing levels of hexanucleotide repeat-containing mutant alleles of C9orf72 (at the protein and/or mRNA level) and/or decrease the level of dipeptide repeat proteins produced from hexanucleotide-repeat-containing mutant C9orf72 mRNA, wherein the oliognucleotides are useful for treating a C9orf72 related disease.

[001046] In some embodiments, a c9orf72-related disorder is FTD. In some embodiments, FTD is an abbreviation for frontotemporal dementia or frontotemporal degeneration. In some embodiments, frontotemporal degeneration (FTD) is a disease process that affects the frontal and temporal lobes of the brain. It causes a group of disorders characterized by changes in behavior, personality, language, and/or movement. Clinical diagnoses of FTD include any one or more of: behavioral variant FTD (bvFTD), primary progressive aphasia (PPA), and the movement disorders progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). In some embodiments, a patient suffering from or susceptible to PPA, PSP or CBD does not exhibit or identify with dementia. In some embodiments, frontotemporal dementia is equivalent to or characterized by the symptoms of bvFTD.

[001047] The present disclosure pertains to methods of using oligonucleotides disclosed herein which are capable of targeting C9orf72 and useful for treating and/or manufacturing a treatment for a C9orf72-related disorder. In some embodiments, a base sequence of an oligonucleotide can comprise or consist of a base sequence which has a specified maximum number of mismatches from a specified base sequence.

[001048] In some embodiments, the present disclosure pertains to the use of a composition of comprising a C9orf72 oligonucleotide for the manufacture of a medicament for treating a neurodegenerative disease.

[001049] In some embodiments, the present disclosure pertains to a method of treating or ameliorating an C9orf72-related disorder in a patient thereof, the method comprising the step of administering to the patient a therapeutically effective amount of an oligonucleotide to C9orf72.

[001050] In some embodiments, the present disclosure pertains to a method comprising administering to an animal a composition comprising a C9orf72 oligonucleotide.

[001051] In some embodiments, the animal is a subject, e.g., a human.

[001052] In some embodiments, a subject or patient suitable for treatment of a C9orf72-related disorder, such as administration of a C9orf72 oligonucleotide, can be identified or diagnosed by a health care professional. A C9orf72-related disease is one of several neurological diseases. In some embodiments, a diagnose of a subject as having a neurological disease can be performed by the assessment of one or more symptoms, e.g., a symptom of motor neuron degeneration. In some embodiments, to diagnose a neurological disease, a physical exam may be followed by a thorough neurological exam. In some embodiments, the neurological exam may assess motor and sensory skills, nerve function, hearing and speech, vision, coordination and balance, mental status, and changes in mood or behavior. Non-limiting symptoms of a disease associated with a neurological disease may be weakness in the arms, legs, feet, or ankles; slurring of speech; difficulty lifting the front part of the foot and toes; hand weakness or clumsiness; muscle paralysis; rigid muscles; involuntary jerking or writing movements (chorea); involuntary, sustained contracture of muscles (dystonia); bradykinesia; loss of automatic movements; impaired posture and balance; lack of flexibility; tingling parts in the body; electric shock sensations that occur with movement of the head; twitching in arm, shoulders, and tongue; difficulty swallowing; difficulty breathing; difficulty chewing; partial or complete loss of vision; double vision; slow or abnormal eye movements; tremor; unsteady gait; fatigue; loss of memory; dizziness; difficulty thinking or concentrating; difficulty reading or writing; misinterpretation of spatial relationships; disorientation; depression; anxiety; difficulty making decisions and judgments; loss of impulse control; difficulty in planning and performing familiar tasks; aggressiveness; irritability; social withdrawal; mood swings; dementia; change in sleeping habits; wandering; change in appetite.

[001053] In some embodiments, the composition prevents, treats, ameliorates, or slows progression of at least one symptom of a C9orf72-related disorder.

[001054] In some embodiments, an animal or human is suffering from a symptom of a C9orf72-related disorder.

[001055] In some embodiments, the present disclosure pertains to a method for introducing an oligonucleotide that decreases C9orf72 gene expression into a cell, the method comprising: contacting the cell with an oligonucleotide or a C9orf72 oligonucleotides.

[001056] In some embodiments, the present disclosure pertains to a method for decreasing C9orf72 gene expression in a mammal in need thereof, the method comprising: administering to the mammal a nucleic acid-lipid particle comprising an oligonucleotide to C9orf72.

[001057] In some embodiments, the present disclosure pertains to a method for the in vivo delivery

of an oligonucleotide that targets C9orf72 gene expression, the method comprising: administering to a mammal an oligonucleotide to C9orf72.

[001058] In some embodiments, the present disclosure pertains to a method for treating and/or ameliorating one or more symptoms associated with a C9orf72-related disorder in a mammal in need thereof, the method comprising: administering to the mammal a therapeutically effective amount of a nucleic acid-lipid particle comprising an oligonucleotide to C9orf72.

[001059] In some embodiments, the present disclosure pertains to a method of inhibiting C9orf72 expression in a cell, the method comprising: (a) contacting the cell with an oligonucleotide to C9orf72; and (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of an C9orf72 gene, thereby inhibiting expression of the C9orf72 gene in the cell.

[001060] In some embodiments, C9orf72 expression is inhibited by at least 30%.

[001061] In some embodiments, the present disclosure pertains to a method of treating a disorder mediated by C9orf72 expression comprising administering to a human in need of such treatment a therapeutically effective amount of an oligonucleotide to C9orf72.

[001062] In some embodiments, administration causes a decrease in the expression, activity and/or level of a C9orf72 transcript containing a repeat expansion or a gene product thereof.

[001063] In some embodiments, the present disclosure pertains to a method of treatment of a C9orf72-related disorder.

[001064] In some embodiments, the present disclosure pertains to a method comprising the steps of: Providing a system comprising two or more different splicing products of the same mRNA, wherein at least one splicing product is disease-associated and at least one splicing product is non-disease-associated; introducing into a system an oligonucleotide, wherein the oligonucleotide is complementary to a sequence which is present in the at least one disease-associated splicing product, but not present in the at least one non-disease-associated splicing product, wherein the oligonucleotide is capable of reducing the expression, level and/or activity of the disease-associated splicing product relative to the expression, level and/or activity of the non-disease-associated splicing product.

[001065] In some embodiments of the method, the oligonucleotide is complementary to an intron-exon junction present on the disease-associated splicing product but not present on the non-disease-associated splicing product.

[001066] In some embodiments of the method, the oligonucleotide comprises at least one chirally controlled internucleotidic linkage.

[001067] In some embodiments of the method, the oligonucleotide is a c9orf72 oligonucleotide and the system is a subject suffering from and/or susceptible a c9orfy2-related disorder.

[001068] In some embodiments, a subject is administered a second therapeutic agent or method.

[001069] In some embodiments, a subject is administered a c9orf72 oligonucleotide and one or more second therapeutic agent or method.

[001070] In some embodiments, a second therapeutic agent or method is capable of preventing, treating, ameliorating or slowing the progress of a neurological disease.

[001071] In some embodiments, a second therapeutic agent or method is capable of preventing, treating, ameliorating or slowing the progress of a C9orf72-related disorder.

[001072] In some embodiments, a second therapeutic agent or method is capable of preventing, treating, ameliorating or slowing the progress of a neurological disease selected from: an endosomal and/or lysosomal trafficking modulator, a glutamate receptor inhibitor, a PIKFYVE kinase inhibitor, and a potassium channel activator.

[001073] In some embodiments a second therapeutic agent or method comprises an antibody to a dipeptide repeat protein or an agent (e.g., an antibody or small molecule) which disrupts the formation of or decreases the abundance or number of RNA foci.

[001074] In some embodiments, a second therapeutic agent or method indirectly decreases the expression, activity and/or level of C9orf72, as non-limiting examples, by knocking down a gene or gene product which increases the expression, activity and/or level of C9orf72. In some embodiments, a second therapeutic agent or method knocks down SUPT4H1, the human Spt4 ortholog, knockdown of which decreased production of sense and antisense C9orf72 RNA foci, as well as DPR proteins. Kramer et al. 2016 Science 353: 708. In some embodiments, a second therapeutic agent or method is a nucleic acid, small molecule, gene therapy or other agent or method described in the literature, including, as a non-limiting example, Mis et al. Mol Neurobiol. 2017 Aug;54(6):4466-4476.

[001075] In some embodiments, a second therapeutic agent is physically conjugated to a C9orf72 oligonucleotide. In some embodiments, a C9orf72 oligonucleotide is physically conjugated to a second oligonucleotide which decreases (directly or indirectly) the expression, activity and/or level of C9orf72, or which is useful for treating a symptom of a C9orf72-related disorder. In some embodiments, a first C9orf72 oligonucleotide is physically conjugated to a second C9orf72 oligonucleotide, which can be identical to the first C9orf72 oligonucleotide or not identical, and which can target a different or the same or an overlapping sequence as the first C9orf72 oligonucleotide. In some embodiments, a C9orf72 oligonucleotide is conjugated or co-administered or incorporated into the same treatment regime as an oligonucleotide which knocks down SUPT4H1. In some embodiments, a C9orf72 oligonucleotide is conjugated or co-administered or incorporated into the same treatment regime as a second therapeutic agent which improves the expression, activity and/or level of another (non-C9orf72) gene or gene product which is associated with a C9orf72-related disorder such as ALS or FTD, such as: SOD1, TARDBP,

FUS/TLS, MAPT, TDP-43, SUPT4H1, or FUS/TLS.

[001076] In some embodiments, improving the expression, activity and/or level of such a gene or gene product includes, inter alia: decreasing the expression, activity and/or level of such a gene or gene product is such is too high in the disease state; increasing the expression, activity and/or level or such a gene or gene product is such is too low in the disease state; and/or decreasing the expression, activity and/or level of a mutant and/or disease-associated variant of such a gene or gene product. In some embodiments, a second therapeutic agent is an oligonucleotide. In some embodiments, a second therapeutic agent is an oligonucleotide physically conjugated to a C9orf72 oligonucleotide. In some embodiments, a second therapeutic agent comprises monomethyl fumarate (MMF), which reportedly activates Nrf2, and/or an omega-3 fatty acid. In some embodiments, a second therapeutic agent comprises monomethyl fumarate (MMF) and/or the omega-3 fatty acid, docosahexaenoic acid (DHA), which reportedly inhibits NF-κB. In some embodiments, a second therapeutic agent comprises a conjugate of monomethyl fumarate (MMF) and the omega-3 fatty acid, docosahexaenoic acid (DHA). In some embodiments, a second therapeutic agent is CAT-4001 (Catabasis Pharmaceuticals, Cambridge, MA, US).

[001077] In some embodiments, a second therapeutic agent is capable of preventing, treating, ameliorating or slowing the progress of a neurological disease selected from: an endosomal and/or lysosomal trafficking modulator, a glutamate receptor inhibitor, a PIKFYVE kinase inhibitor, and a potassium channel activator described in WO2016/210372. In some embodiments, a potassium channel activator is retigabine. In some embodiments, a glutamate receptor is on a motor neuron (MN) or spinal motor neuron. In some embodiments, a glutamate receptor is NMDA, AMPA, or kainite. In some embodiments, a glutamate receptor inhibitor is AP5 ((2R)-amino-5-phosphonovaleric acid; (2R)-amino-5-phosphonopentanoate), CNQX (6-cyano-7-nitroquinoxaline-2,3-dione), or NBQX (2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione).

[001078] In some embodiments, a second therapeutic agent is capable of decreasing the expression, level and/or activity of a gene (or a gene product thereof) associated with a c9orf72-related disoder, such as SOD1, TARDBP, FUS/TLS, MAPT, TDP-43, SUPT4H1, or FUS/TLS. In some embodiments, a second therapeutic agent is an agent which deceases the expression, level and/or activity of a gene (or a gene product thereof) associated with amyotrophic lateral sclerosis (ALS) or frontotemporal dementia (FTD), such as SOD1, TARDBP, FUS/TLS, MAPT, TDP-43, SUPT4H1, or FUS/TLS. In some embodiments, a second therapeutic agent is capable of controlling excessive oxidative stress. In some embodiments, a second therapeutic agent is Radicava® (edaravone). In some embodiments, a second therapeutic agent is ursodeoxycholic acid (UDCA). In some embodiments, a second therapeutic agent is capable of affecting neurons by reducing their activity through blocking Na+ entrance into the neurons,

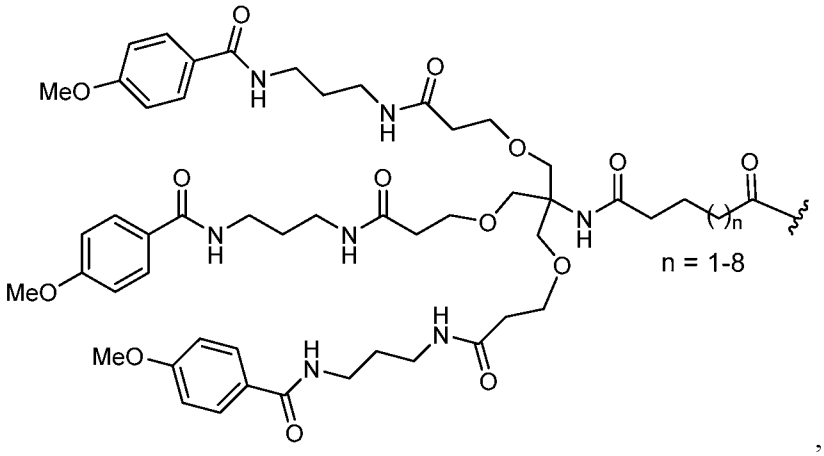
and blocking the release of the chemicals that cause the activity of the motor neurons. In some embodiments, a second therapeutic agent is riluzole. In some embodiments, a second therapeutic agent is capable of: reducing fatigue, easing muscle cramps, controlling spasticity, and/or reducing excess saliva and phlegm. In some embodiments, a second therapeutic agent is capable of reducing pain. In some embodiments, a second therapeutic agent is a nonsteroidal and/or anti-inflammatory drug and/or opioid. In some embodiments, a second therapeutic agent is capable of reducing depression, sleep disturbance, dysphagia, spasticity, difficulty swallowing saliva, and/or constipation. In some embodiments, a second therapeutic agent is baclofen or diazepam. In some embodiments, a second therapeutic agent is or comprises trihexyphenidyl, amitriptyline and/or glycopyrrolate. In some embodiments, a second therapeutic agent is a dsRNA or siRNA which comprises a strand which has a sequence which comprises at least 15 contiguous nt of the sequence of any oligonucleotide disclosed herein.

Pharmaceutical compositions

[001079] In some embodiments, the present disclosure provides pharmaceutical compositions comprising a provided compound, *e.g.*, a provided oligonucleotide, or a pharmaceutically acceptable salt thereof, and a pharmaceutical carrier. In some embodiments, an oligonucleotide is a C9orf72 oligonucleotide.

[001080] When used as therapeutics, a provided oligonucleotide or oligonucleotide composition described herein is administered as a pharmaceutical composition. In some embodiments, the pharmaceutical composition is suitable for administration of an oligonucleotide to an area of the body affected by a disorder, including but not limited to the central nervous system. In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of a provided oligonucleotides, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable inactive ingredient selected from pharmaceutically acceptable diluents, pharmaceutically acceptable excipients, and pharmaceutically acceptable carriers.

[001081] In some embodiments, a provided C9orf72 is conjugated to an additional chemical moiety suitable for use in delivery to the central nervous system, selected from: glucose, GluNAc (N-acetyl amine glucosamine) and anisamide, and a molecule of any of the structures of:



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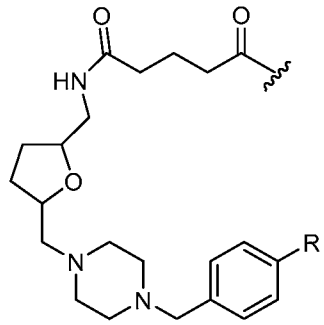
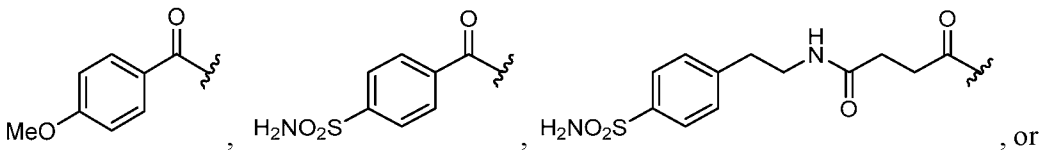
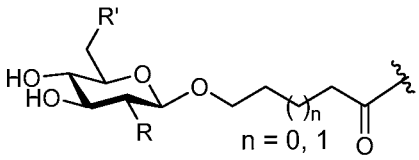


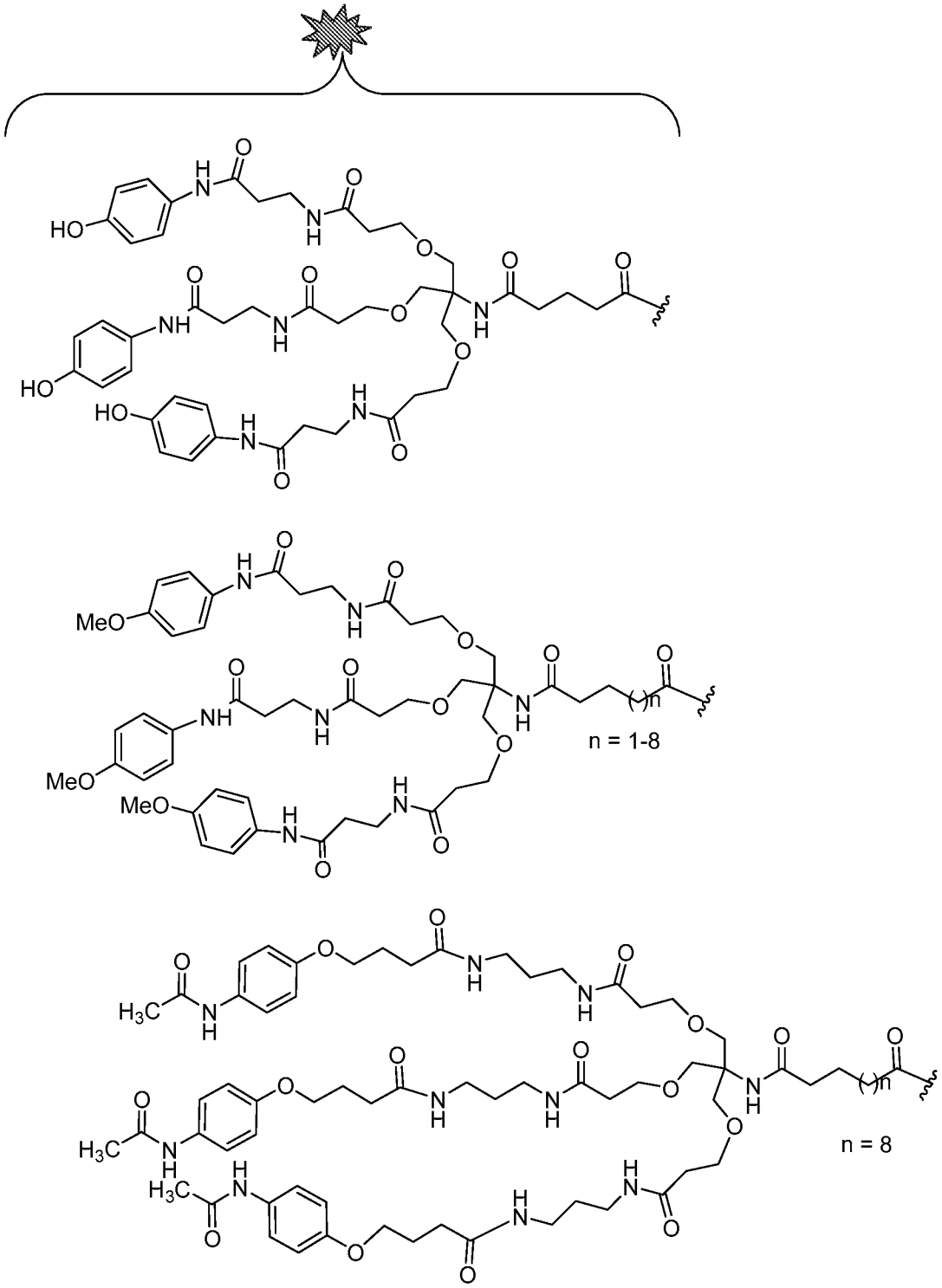
R = F, OMe, OH, NHAc, $NHCOCF_3$,



, or



R = NHAc, R' = OH; R = NHCOC6H4OMe(p-anisoyl), R'=OH
R = NHAc, R' = NHCOC6H4OMe(p-anisoyl); R = OH, R' = NHCOC6H4OMe(p-anisoyl),



which are described in more detail in Examples 1 and 2.

[001082] In some embodiments, an additional chemical moiety conjugated to an oligonucleotide is capable of targeting the oligonucleotide to a cell in the nervous system.

[001083] In some embodiments, an additional chemical moiety conjugated to a provided

oligonucleotide comprises anisamide or a derivative or analog thereof and is capable of targeting the provided oligonucleotide to a cell expressing a particular receptor, such as the sigma 1 receptor.

[001084] In some embodiments, a provided oligonucleotide is formulated for administration to a body cell and/or tissue expressing its target.

[001085] In some embodiments, an additional chemical moiety conjugated to a C9orf72 oligonucleotide is capable of targeting the C9orf72 oligonucleotide to a cell in the nervous system.

[001086] In some embodiments, an additional chemical moiety conjugated to a C9orf72 oligonucleotide comprises anisamide or a derivative or analog thereof and is capable of targeting the C9orf72 oligonucleotide to a cell expressing a particular receptor, such as the sigma 1 receptor.

[001087] In some embodiments, a provided C9orf72 oligonucleotide is formulated for administration to a body cell and/or tissue expressing C9orf72. In some embodiments, such a body cell and/or tissue is a neuron or a cell and/or tissue of the central nervous system. In some embodiments, broad distribution of oligonucleotides and compositions, described herein, within the central nervous system may be achieved with intraparenchymal administration, intrathecal administration, or intracerebroventricular administration.

[001088] In some embodiments, the pharmaceutical composition is formulated for intravenous injection, oral administration, buccal administration, inhalation, nasal administration, topical administration, ophthalmic administration or otic administration. In some embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a suspension, a gel, a colloid, a dispersion, a suspension, a solution, an emulsion, an ointment, a lotion, an eye drop or an ear drop.

[001089] In some embodiments, the present disclosure provides a pharmaceutical composition comprising chirally controlled oligonucleotide, or composition thereof, in admixture with a pharmaceutically acceptable excipient. One of skill in the art will recognize that the pharmaceutical compositions include the pharmaceutically acceptable salts of the chirally controlled oligonucleotide, or composition thereof, described above.

[001090] A variety of supramolecular nanocarriers can be used to deliver nucleic acids. Example nanocarriers include, but are not limited to liposomes, cationic polymer complexes and various polymeric. Complexation of nucleic acids with various polycations is another approach for intracellular delivery; this includes use of PEGlyated polycations, polyethyleneamine (PEI) complexes, cationic block co-polymers, and dendrimers. Several cationic nanocarriers, including PEI and polyamidoamine dendrimers help to release contents from endosomes. Other approaches include use of polymeric nanoparticles, microspheres, liposomes, dendrimers, biodegradable polymers, conjugates, prodrugs, inorganic colloids such as sulfur or iron, antibodies, implants, biodegradable implants, biodegradable microspheres,

osmotically controlled implants, lipid nanoparticles, emulsions, oily solutions, aqueous solutions, biodegradable polymers, poly(lactide-coglycolic acid), poly(lactic acid), liquid depot, polymer micelles, quantum dots and lipoplexes. In some embodiments, an oligonucleotide is conjugated to another molecular.

[001091] Additional nucleic acid delivery strategies are known in addition to the example delivery strategies described herein.

[001092] In therapeutic and/or diagnostic applications, the compounds of the disclosure can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington, The Science and Practice of Pharmacy, (20th ed. 2000).

[001093] Provided oligonucleotides, and compositions thereof, are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.01 to about 1000 mg, from about 0.5 to about 100 mg, from about 1 to about 50 mg per day, and from about 5 to about 100 mg per day are examples of dosages that may be used. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[001094] Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art, and may include, by way of example but not limitation, acetate, benzenesulfonate, besylate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, carnsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington, The Science and Practice of Pharmacy (20th ed. 2000). Preferred pharmaceutically acceptable salts include, for example, acetate, benzoate, bromide, carbonate, citrate, gluconate, hydrobromide, hydrochloride, maleate, mesylate, napsylate, pamoate (embonate), phosphate, salicylate, succinate, sulfate, or tartrate.

[001095] In some embodiments, a provided C9orf72 oligonucleotides is formulated in a pharmaceutical composition described in U.S. Applications No. 61/774759; 61/918, 175, filed 12/19/13; 61/918,927; 61/918,182; 61/918941; 62/025224; 62/046487; or International Applications No. PCT/US04/042911; PCT/EP2010/070412; or PCT/I B2014/059503.

[001096] Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for

example, in a timed- or sustained- low release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington, The Science and Practice of Pharmacy (20th ed. 2000). Suitable routes may include oral, buccal, by inhalation spray, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intra-articullar, intra-sternal, intra-synovial, intra-hepatic, intralesional, intracranial, intraperitoneal, intranasal, or intraocular injections or other modes of delivery.

[001097] For injection, the agents of the disclosure may be formulated and diluted in aqueous solutions, such as in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[001098] Use of pharmaceutically acceptable inert carriers to formulate the compounds herein disclosed for the practice of the disclosure into dosages suitable for systemic administration is within the scope of the disclosure. With proper choice of carrier and suitable manufacturing practice, the compositions of the present disclosure, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection.

[001099] The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the disclosure to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject (*e.g.*, patient) to be treated.

[001100] For nasal or inhalation delivery, the agents of the disclosure may also be formulated by methods known to those of skill in the art, and may include, for example, but not limited to, examples of solubilizing, diluting, or dispersing substances such as, saline, preservatives, such as benzyl alcohol, absorption promoters, and fluorocarbons.

[001101] In certain embodiments, oligonucleotides and compositions are delivered to the CNS. In certain embodiments, oligonucleotides and compositions are delivered to the cerebrospinal fluid. In certain embodiments, oligonucleotides and compositions are administered to the brain parenchyma. In certain embodiments, oligonucleotides and compositions are delivered to an animal/subject by intrathecal administration, or intracerebroventricular administration. Broad distribution of oligonucleotides and compositions, described herein, within the central nervous system may be achieved with intraparenchymal administration, intrathecal administration, or intracerebroventricular administration.

[001102] In certain embodiments, parenteral administration is by injection, by, *e.g.*, a syringe, a pump, etc. In certain embodiments, the injection is a bolus injection. In certain embodiments, the injection is administered directly to a tissue, such as striatum, caudate, cortex, hippocampus and

cerebellum.

[001103] In certain embodiments, methods of specifically localizing a pharmaceutical agent, such as by bolus injection, decreases median effective concentration (EC50) by a factor of 20, 25, 30, 35, 40, 45 or 50. In certain embodiments, the pharmaceutical agent in an antisense compound as further described herein. In certain embodiments, the targeted tissue is brain tissue. In certain embodiments the targeted tissue is striatal tissue. In certain embodiments, decreasing EC50 is desirable because it reduces the dose required to achieve a pharmacological result in a patient in need thereof.

[001104] In certain embodiments, an antisense oligonucleotide is delivered by injection or infusion once every month, every two months, every 90 days, every 3 months, every 6 months, twice a year or once a year.

[001105] Pharmaceutical compositions suitable for use in the present disclosure include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[001106] In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of an active compound into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

[001107] Pharmaceutical preparations for oral use can be obtained by combining an active compound with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[001108] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[001109] Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol.

The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, an active compound may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

[001110] A composition can be obtained by combining an active compound with a lipid. In some embodiments, the lipid is conjugated to an active compound. In some embodiments, the lipid is not conjugated to an active compound. In some embodiments, a lipid comprises a C_{10}-C_{40} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises a C_{10}-C_{40} linear, saturated or partially unsaturated, aliphatic chain, optionally substituted with one or more C_{1-4} aliphatic group. In some embodiments, the lipid is selected from the group consisting of: lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, docosahexaenoic acid (cis-DHA), turbinaric acid and dilinoleyl. In some embodiments, an active compound is any oligonucleotide or other nucleic acid described herein. In some embodiments, an active compound is a nucleic acid of a sequence comprising or consisting of any sequence of any nucleic acid listed in Table 1A. In some embodiments, a composition comprises a lipid and an an active compound, and further comprises another component selected from: another lipid, and a targeting compound or moiety. In some embodiments, a lipid includes, without limitation: an amino lipid; an amphipathic lipid; an anionic lipid; an apolipoprotein; a cationic lipid; a low molecular weight cationic lipid; a cationic lipid such as CLinDMA and DLinDMA; an ionizable cationic lipid; a cloaking component; a helper lipid; a lipopeptide; a neutral lipid; a neutral zwitterionic lipid; a hydrophobic small molecule; a hydrophobic vitamin; a PEG-lipid; an uncharged lipid modified with one or more hydrophilic polymers; phospholipid; a phospholipid such as 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; a stealth lipid; a sterol; a cholesterol; and a targeting lipid; and any other lipid described herein or reported in the art. In some embodiments, a composition comprises a lipid and a portion of another lipid capable of mediating at least one function of another lipid. In some embodiments, a targeting compound or moiety is capable of targeting a compound (*e.g.*, a composition comprising a lipid and a active compound) to a particular cell or tissue or subset of cells or tissues. In some embodiments, a targeting moiety is designed to take advantage of cell- or tissue-specific expression of particular targets, receptors, proteins, or other subcellular components; In some embodiments, a targeting moiety is a ligand (*e.g.*, a small molecule, antibody, peptide, protein, carbohydrate, aptamer, etc.) that targets a composition to a cell or tissue, and/or binds to a target, receptor, protein, or other subcellular component.

[001111] Certain example lipids for use in preparation of a composition for delivery of an active compound allow (*e.g.*, do not prevent or interfere with) the function of an active compound. Non-limiting example lipids include: lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid,

alpha-linolenic acid, gamma-linolenic acid, docosahexaenoic acid (cis-DHA), turbinaric acid and dilinoleyl.

[001112] As described in the present disclosure, lipid conjugation, such as conjugation with fatty acids, may improve one or more properties of oligonucleotides.

[001113] In some embodiments, a composition for delivery of an active compound is capable of targeting an active compound to particular cells or tissues, as desired. In some embodiments, a composition for delivery of an active compound is capable of targeting an active compound to a muscle cell or tissue. In some embodiments, the present disclosure pertains to compositions and methods related to delivery of active compounds, wherein the compositions comprise an active compound a lipid. In various embodiments to a muscle cell or tissue, the lipid is selected from: lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, docosahexaenoic acid (cis-DHA), turbinaric acid and dilinoleyl.

[001114] Depending upon the particular disorder to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may be administered together with C9orf oligonucleotides of this disclosure.

[001115] In some embodiments, a second therapeutic agent administered with a first C9orf72 oligonucleotide is a second, different, C9orf72 oligonucleotide.

[001116] In some embodiments, C9orf72 oligonucleotides disclosed herein can be used for a method for the prevention and/or treatment of a C9orf72-related disorder or a symptom thereof, or for the manufacture of medicament for use in such a method.

EXEMPLIFICATION

[001117] Certain examples of provided technologies (compounds (oligonucleotides, reagents, etc.), compositions, methods (methods of preparation, use, assessment, etc.)) were presented below.

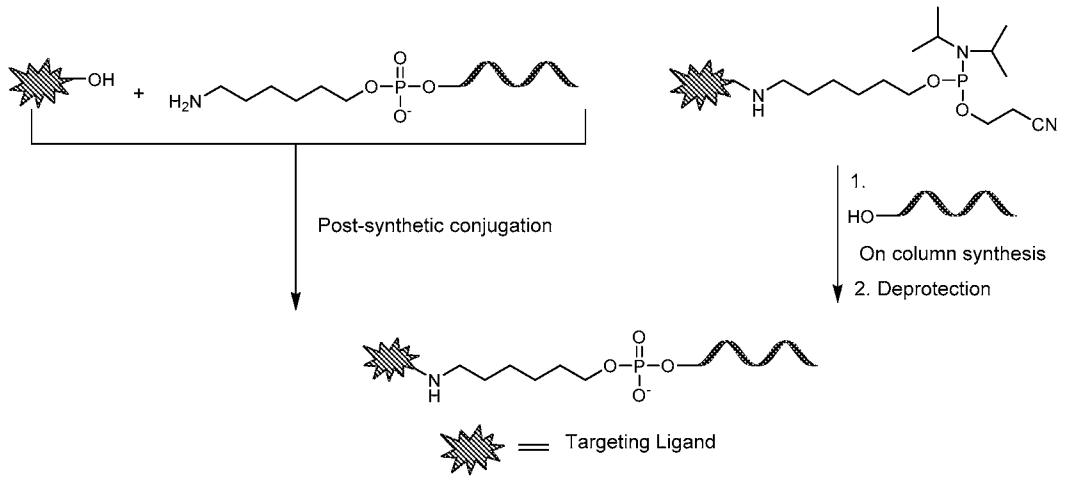
[001118] Various technologies for preparing oligonucleotides and oligonucleotide compositions (both stereorandom and chirally controlled) are known and can be utilized in accordance with the present disclosure, including, for example, those in WO/2010/064146, WO/2011/005761, WO/2013/012758, WO/2014/010250, US2013/0178612, WO/2014/012081, WO/2015/107425, WO/2017/015555, and WO/2017/062862, the methods and reagents of each of which are incorporated herein by reference.

EXAMPLE 1.

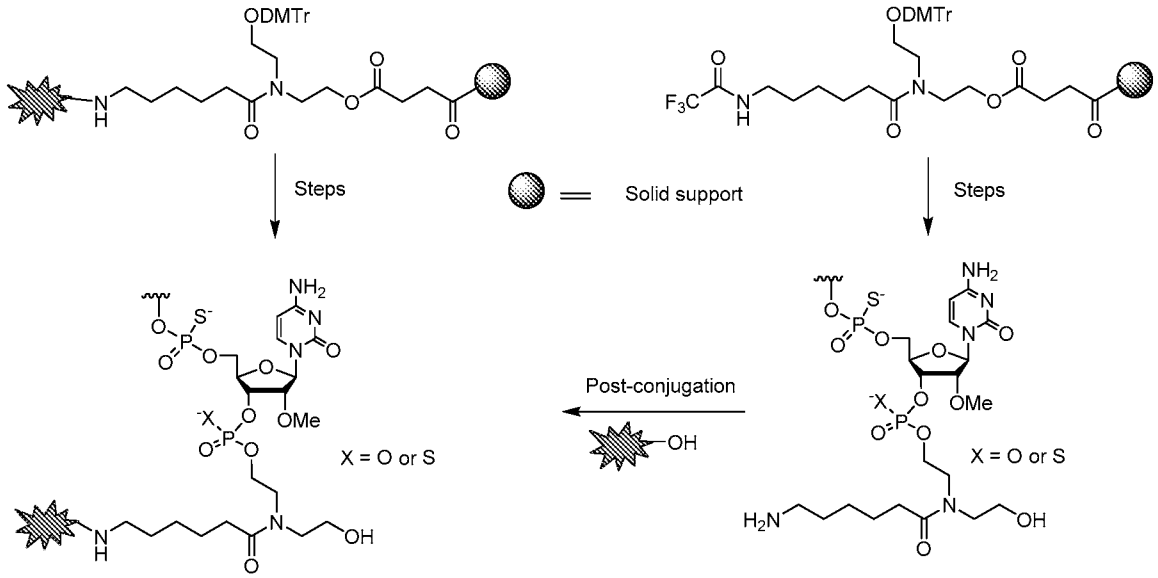
Conjugation of Oligonucleotides.

In some embodiments, the present disclosure provides methods for conjugation of oligonucleotides, for example, for better delivery to CNS. Examples 1 and 2 show conjugation of oligonucleotides for CNS delivery.

In some embodiments, provided oligonucleotides comprise chemical moieties connected to the 5'-end optionally through linker moieties. In some embodiments, provided oligonucleotides comprises chemical moieties connected to the 5'-end −OH optionally through a linker. In some embodiments, the present disclosure provides the following 5' cConjugation strategies:

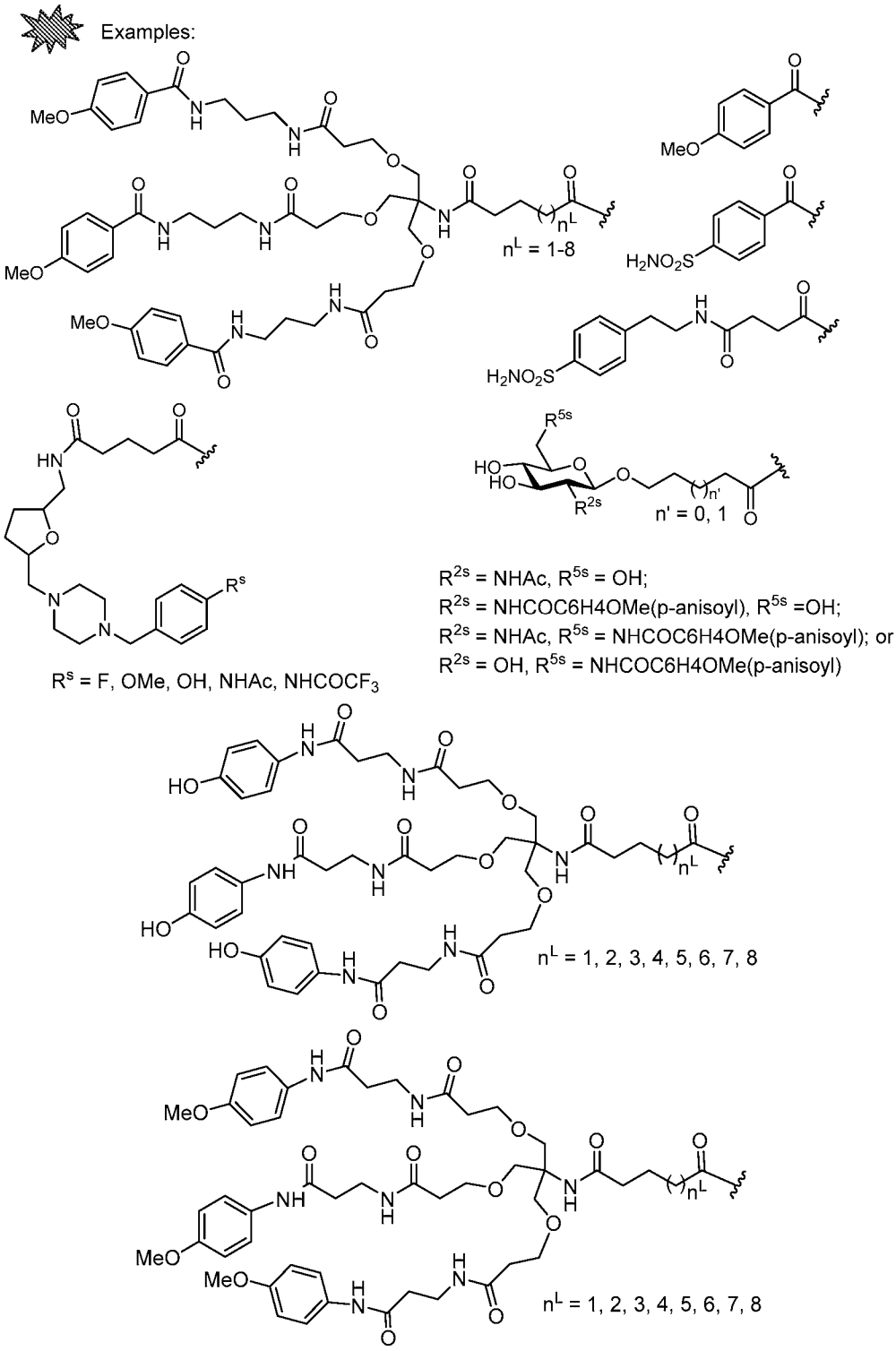


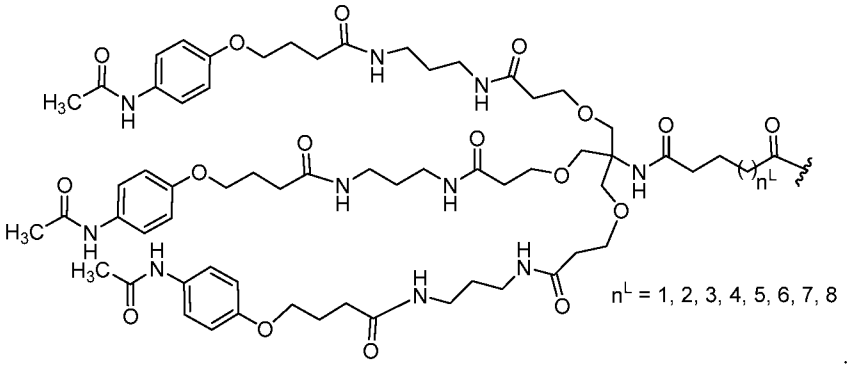
In some embodiments, provided oligonucleotides comprise chemical moieties connected to the 5'-end optionally through linker moieties. In some embodiments, the present disclosure provides the following 3' cConjugation strategies:



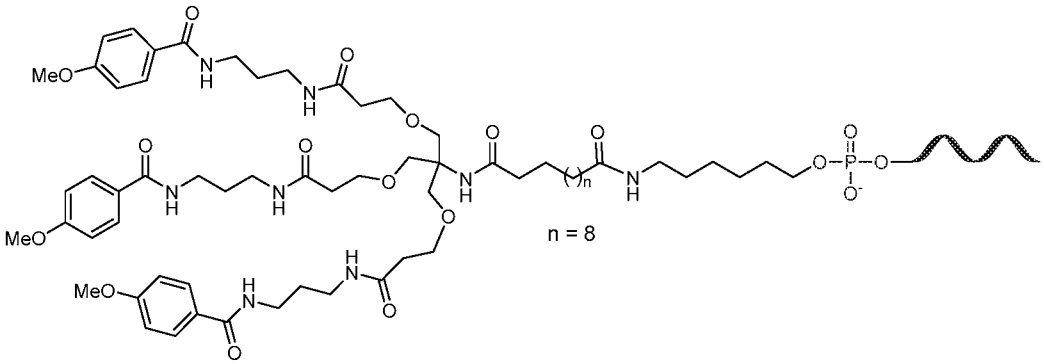
Various chemical moieties, e.g., ligand for cell receptors, can be utilized in accordance with the present disclosure, for example, those described in Juliano et al., J. Am. Chem. Soc. 2010, 132, 8848; Banerjee R et al., Int J Cancer. 2004, 112, 693; J. Med. Chem., 2017, 60 (10), pp 4161–4172; etc. In some embodiments, a chemical moiety is selected from:

[001119]

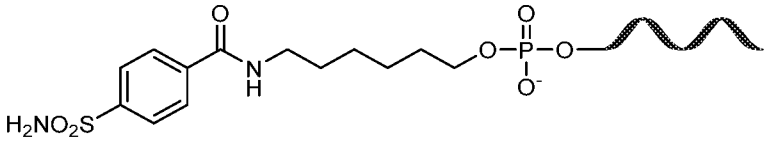

Examples:
MeO
n^L = 1-8
H_2NO_2S
R^{5s}
HO
R^{2s}
n' = 0, 1
R^{2s} = NHAc, R^{5s} = OH;
R^{2s} = NHCOC6H4OMe(p-anisoyl), R^{5s} =OH;
R^{2s} = NHAc, R^{5s} = NHCOC6H4OMe(p-anisoyl); or
R^{2s} = OH, R^{5s} = NHCOC6H4OMe(p-anisoyl)
R^s
R^s = F, OMe, OH, NHAc, NHCOCF3
n^L = 1, 2, 3, 4, 5, 6, 7, 8
n^L = 1, 2, 3, 4, 5, 6, 7, 8



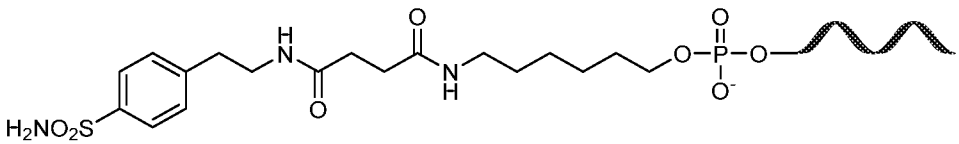
Conjugates of various oligonucleotides



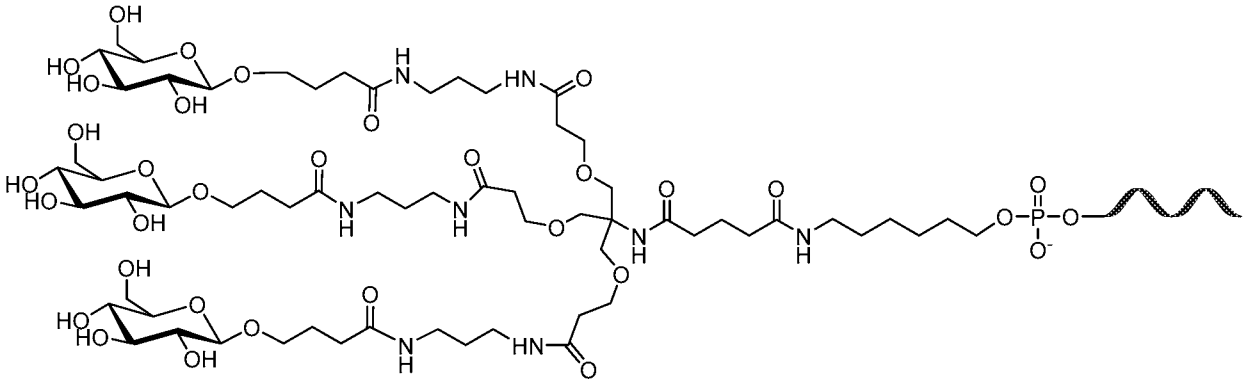
WV-9063 (C9orf72, intron), WV-9381(C9orf72, intron), WV-7560 (Malat1), WV-8447 (exon 1a), WV-8819 (a non-C9orf72 target), WV-9066 (a non-C9orf72 target), WV-9065 (a non-C9orf72 target)



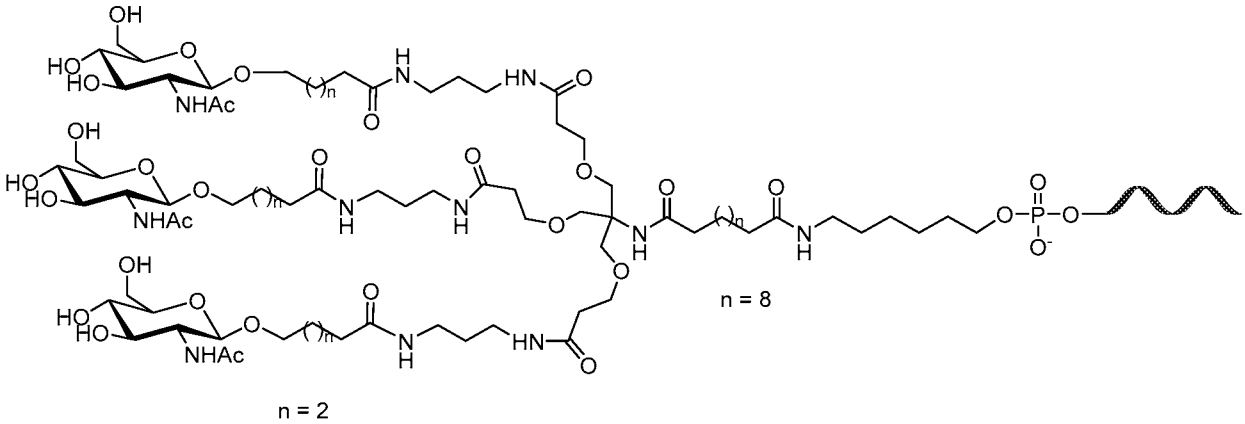
WV-7558 (Malat1)



WV-7559 (Malat1)

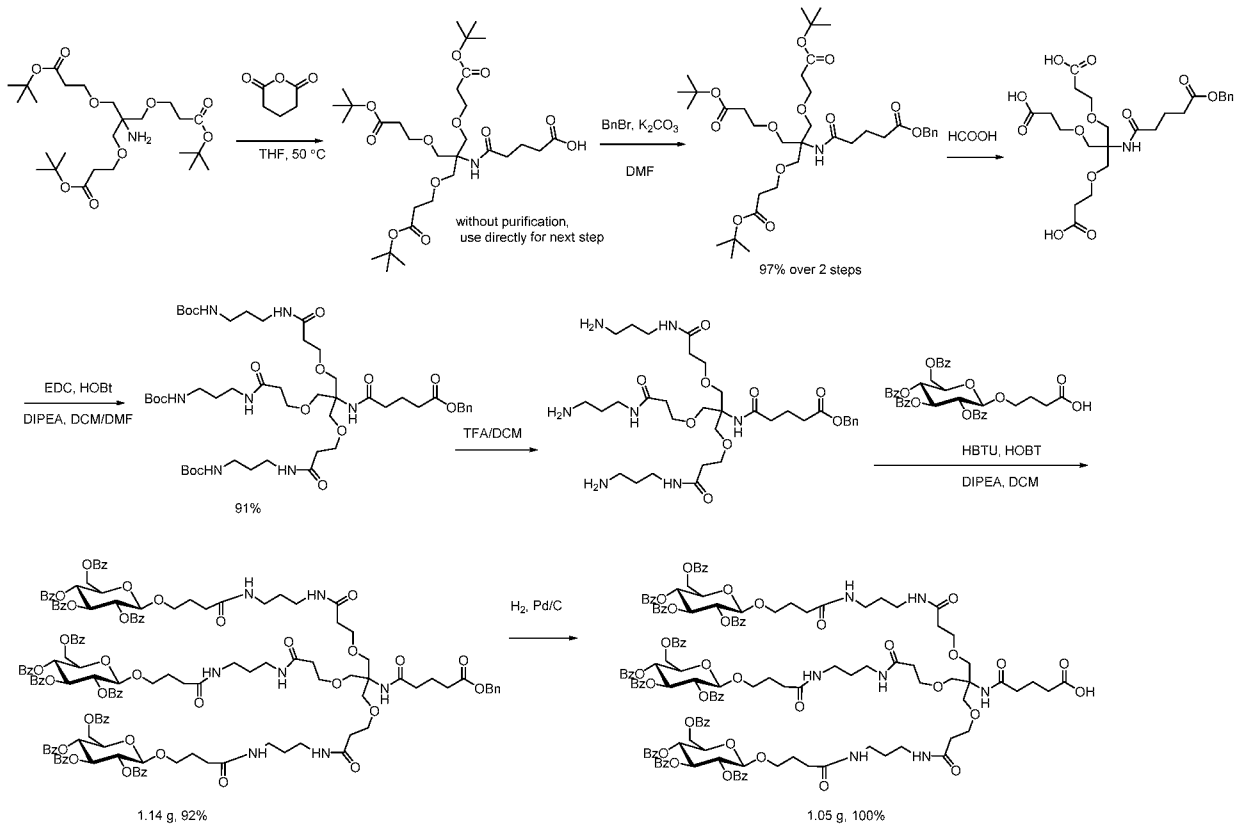


WV-8448 (Malat1), WV-8446 (exon 1a)



WV-8896 (Malat1), WV-8445 (exon 1a)

Synthesis of 4,10,17-trioxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-13-oxa-5,9,16-triazahenicosan-21-oic acid



Step 1: A solution of di-tert-butyl 3,3'-((2-amino-2-((3-(tert-butoxy)-3-oxopropoxy)methyl)propane-1,3-diyl)bis(oxy))dipropanoate **1** (4.0 g, 7.91 mmol) and dihydro-2H-pyran-2,6(3H)-dione (0.903 g, 7.91 mmol) in THF (40 mL) was stirred at 50 °C for 3 hrs and at rt for 3 hrs. LC-MS showed desired product. Solvent was evaporated to give acid **2**, which was directly used for next step without purification.

Step 2: To a solution of 5-((9-((3-(tert-butoxy)-3-oxopropoxy)methyl)-2,2,16,16-tetramethyl-4,14-dioxo-3,7,11,15-tetraoxaheptadecan-9-yl)amino)-5-oxopentanoic acid **2** (4.90 g, 7.91 mmol) and (bromomethyl)benzene (1.623 g, 9.49 mmol) in DMF was added anhydrous K_2CO_3 (3.27 g, 23.73 mmol). The mixture was stirred at 40 °C for 4 hrs and at room temperature for overnight. Solvent was evaporated under reduced pressure. The reaction mixture was diluted with EtOAc, washed with water, dried over anhydrous sodium sulfate, concentrated under reduced pressure to give a residue, which was purified by ISCO eluting with 10% EtOAc in hexane to 50% EtOAc in hexane to give di-tert-butyl 3,3'-((2-(5-(benzyloxy)-5-oxopentanamido)-2-((3-(tert-butoxy)-3-oxopropoxy)methyl)propane-1,3-diyl)bis(oxy))dipropanoate **3** (5.43 g, 7.65 mmol, 97 % yield) as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.28 (m, 5H), 6.10 (s, 1H), 5.12 (s, 2H), 3.70 (s, 6 H), 3.64 (t, J = 8.0 Hz, 6H), 2.50 – 2.38 (m, 8H), 2.22 (t, J = 7.3 Hz, 2H), 1.95 (p, J = 7.4 Hz, 2H), 1.45 (s, 27H); MS, 710.5 $(M+H)^+$.

Step 3: A solution of di-tert-butyl 3,3'-((2-(5-(benzyloxy)-5-oxopentanamido)-2-((3-(tert-butoxy)-3-oxopropoxy)methyl)propane-1,3-diyl)bis(oxy))dipropanoate **3** (5.43 g, 7.65 mmol) in formic acid (50 mL) was stirred at room temperature for 48 hrs. LC-MS showed the reaction was not complete. Solvent

was evaporated under reduced pressure. The crude product was re-dissolved in formic acid (50 mL) and was stirred at room temperature for 6 hrs. LC-MS showed the reaction was complete. Solvent was evaporated under reduced pressure, co-evaporated with toluene (3X) under reduced pressure, and dried under vacuum to give 3,3'-((2-(5-(benzyloxy)-5-oxopentanamido)-2-((2-carboxyethoxy)methyl)propane-1,3-diyl)bis(oxy))dipropanoic acid **4** (4.22 g, 7.79 mmol, 102 % yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.11 (s, 3H), 7.41 – 7.27 (m, 5H), 6.97 (s, 1H), 5.07 (s, 2H), 3.55 (t, J = 6.4 Hz, 6H), 3.53 (s, 6 H), 2.40 (t, J = 6.3 Hz, 6H), 2.37 – 2.26 (m, 2H), 2.08 (t, J = 7.3 Hz, 2H), 1.70 (p, J = 7.4 Hz, 2H); MS, 542.3 $(M+H)^+$.

Step 4: A solution of 3,3'-((2-(5-(benzyloxy)-5-oxopentanamido)-2-((2-carboxyethoxy)methyl)propane-1,3-diyl)bis(oxy))dipropanoic acid **4** (4.10 g, 7.57 mmol) and HOBt (4.60 g, 34.1 mmol) in DCM (60 mL) and DMF (15 mL) at 0 °C was added *tert*-butyl (3-aminopropyl)carbamate (5.94 g, 34.1 mmol), EDAC HCl salt (6.53 g, 34.1 mmol) and DIPEA (10.55 ml, 60.6 mmol). The reaction mixture was stirred at 0 °C for 15 minutes and at room temperature for 20 hrs. LC-MS showed the reaction was not complete. EDAC HCl salt (2.0 g) and tert-butyl (3-aminopropyl)carbamate (1.0 g) was added into the reaction mixture. The reaction mixture was stirred at room temperature for 4 hrs. Solvent was evaporated to give a residue, which was dissolved in EtOAc (300 mL), washed with water (1X), saturated sodium bicarbonate (2X), 10% citric acid (2X) and water, dried over sodium sulfate, and concentrated to give a residue which was purified by ISCO (80 g gold cartridge) eluting with DCM to 30% MeOH in DCM to give benzyl 15,15-bis(13,13-dimethyl-5,11-dioxo-2,12-dioxa-6,10-diazatetradecyl)-2,2-dimethyl-4,10,17-trioxo-3,13-dioxa-5,9,16-triazahenicosan-21-oate **5** (6.99 g, 6.92 mmol, 91 % yield) as a white solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.38 – 7.33 (m, 5H), 6.89 (brs, 3H), 6.44 (s, 1 H), 5.23 (brs, 3H), 5.12 (s, 2H), 3.71 – 3.62 (m, 12H), 3.29 (q, J = 6.2 Hz, 6H), 3.14 (q, J = 6.5 Hz, 6H), 2.43 (dt, J = 27.0, 6.7 Hz, 8H), 2.24 (t, J = 7.2 Hz, 2H), 1.96 (p, J = 7.5 Hz, 2H), 1.64 – 1.59 (m, 6H), 1.43 (d, J = 5.8 Hz, 27H); MS (ESI): 1011.5 (M+H)+.

Step 5: To a solution of benzyl 15,15-bis(13,13-dimethyl-5,11-dioxo-2,12-dioxa-6,10-diazatetradecyl)-2,2-dimethyl-4,10,17-trioxo-3,13-dioxa-5,9,16-triazahenicosan-21-oate (0.326 g, 0.46 mmol) in DCM (5 mL) was added TFA (2 mL). The reaction mixture was stirred at room temperature for 4 hrs. LC-MS showed the reaction was completed. Solvent was evaporated under reduced pressure to give benzyl 5-((1,19-diamino-10-((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate as a colorless oil. Directly use for next step without purification.

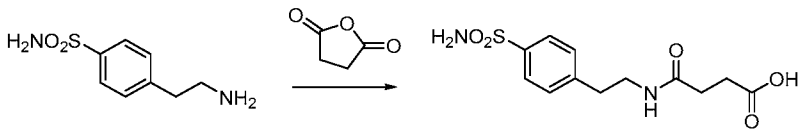
Step 6: To a solution of 5-(((2R,3R,4R,5R,6R)-3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanoic acid (1.10 g, 1.61 mmol), HBTU (0.558 g, 1.47 mmol), HOBT (0.062 g, 0.46 mmol) and DIPEA (1.2 mL, 6.9 mmol) in DCM (6 mL) followed by benzyl 5-((1,19-diamino-10-

((3-((3-aminopropyl)amino)-3-oxopropoxy)methyl)-5,15-dioxo-8,12-dioxa-4,16-diazanonadecan-10-yl)amino)-5-oxopentanoate in acetonitrile (5 mL). The mixture was stirred at room temperature for 3 hrs. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO (40 g gold column) eluting with DCM to 20% MeOH in DCM to give 4,10,17-trioxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-13-oxa-5,9,16-triazahenicosan-21-oic benzyl ester (1.14 g, 92 % yield) as a white solid. MS (ESI): 1353.7 $(M/2+H)^+$.

Step 7: To a solution of 4,10,17-trioxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-13-oxa-5,9,16-triazahenicosan-21-oic benzyl ester (1.09 g, 0.400 mmol) in EtOAc (50 mL) was added 10% Pd-C (200 mg) and methanol (2 mL). The reaction mixture was stirred at room temperature for 3 hrs. LC-MS showed the reaction was complete, diluted with EtOAc, and filtered through celite, washed with 20% MeOH in EtOAc, concentrated under reduced pressure to give 4,10,17-trioxo-15,15-bis((3-oxo-3-((3-(4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butanamido)propyl)amino)propoxy)methyl)-1-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzoyloxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-13-oxa-5,9,16-triazahenicosan-21-oic acid (1.06 g, 100%) as a white solid. MS (ESI): 1308.1 $(M+H)^+$.

EXAMPLE 2

Synthesis of 4-oxo-4-((4-sulfamoylphenethyl)amino)butanoic acid

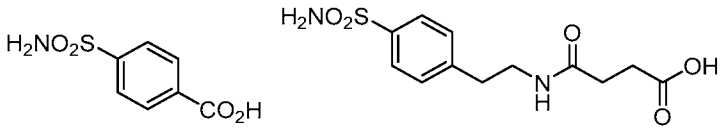


To solid reagents 4-(2-aminoethyl)benzenesulfonamide (2.00 g, 9.99 mmol) and dihydrofuran-2,5-dione (0.999 g, 9.99 mmol) was added THF (30 mL). The reaction mixture was stirred at 60 °C for 7 hrs. Solvent was evaporated under reduced pressure to give 4-oxo-4-((4-sulfamoylphenethyl)amino)butanoic acid (3.00 g, 9.99 mmol, 100 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.09 (s, 1H), 7.96 (t, J = 5.6 Hz, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.29 (s, 2H), 3.26 (q, J = 6.8 Hz, 2H), 2.76 (t, J = 7.2 Hz, 2H), 2.40 (t, J = 6.9 Hz, 2H), 2.27 (t, J = 6.9 Hz, 2H); MS (ESI), 301.1 $(M+H)^+$.

General procedure for conjugation of sulfonamides with WV-7557

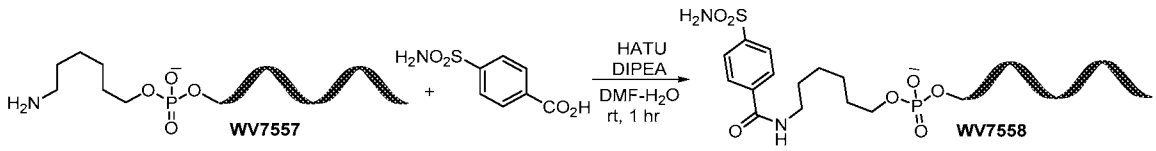
(Synthesis of WV-7558 and 7559)

Procedure: Synthesis of WV-7558 and WV-7559 follows same procedure as described below. To a solution of sulfonamide (5 equivalents), in 2 ml DMF was added HATU (4.5 equivalents) and DIPEA (25 equivalents). This mixture was stirred well for 2 minutes (Scheme 1 and 2).



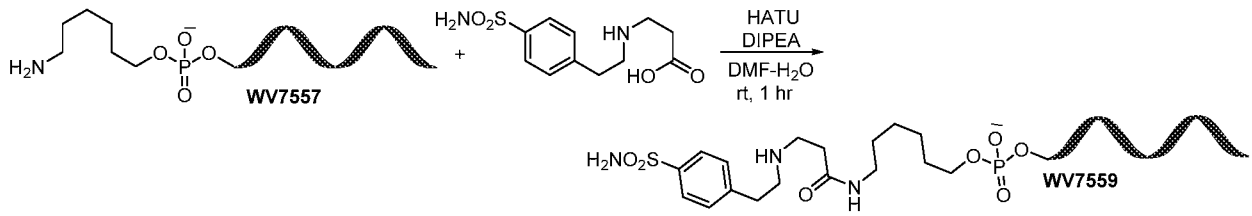
To this solution was added, a solution of WV-7557 (1 equivalent) in water and shaken well for 60 minutes. The solvent was removed under vacuum and crude product was purified by RP column (C18) chromatography to obtain the product. The purified product was desalted over a C-18 cartridge using sodium acetate solution.

Synthesis of WV-7558: Following the general procedure outlined above, 4-sulfamoyl benzoic acid (11 mg, 54.5 µmol), HATU (18.6 mg, 49 µmol) and DIPEA (35 mg, 272 µmol) were stirred for 2 minutes in 2 ml DMF (Scheme 1). This activated HATU intermediate was added into a solution of WV-7557 (75 mg, 10.9 µmol) in 0.75 ml water. The reaction vial was shaken for 60 minutes. Solvent was removed under reduced pressure, purification and desalting was performed as described above. Amount of product obtained is 20 mg. Molecular weight of the product calculated: 7063; Deconvoluted mass obtained: 7065



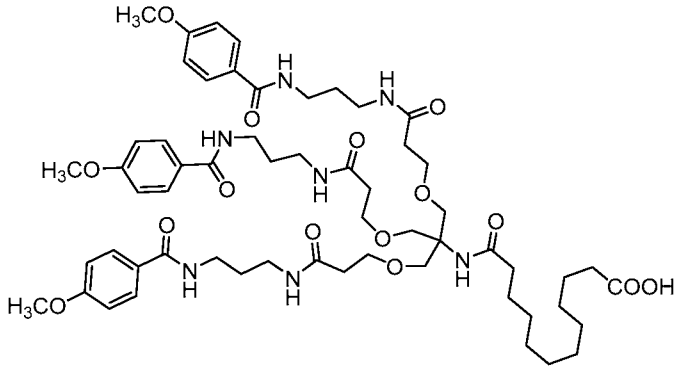
Scheme 1

Synthesis of WV-7559: Following the general procedure outlined above, 4-sulfamoyl benzoic acid (16.3 mg, 54.5 µmol), HATU (18.6 mg, 49 µmol) and DIPEA (35 mg, 272 µmol) were stirred for 2 minutes in 2 ml DMF (Scheme 2). This activated HATU intermediate was added into a solution of WV-7557 (75 mg, 10.9 µmol) in 0.75 ml water. The reaction vial was shaken for 60 minutes. Solvent was removed under reduced pressure, purification and desalting was performed as described above. Amount of product obtained is 13 mg. Molecular weight of the product calculated: 7162; Deconvoluted mass obtained: 7165.



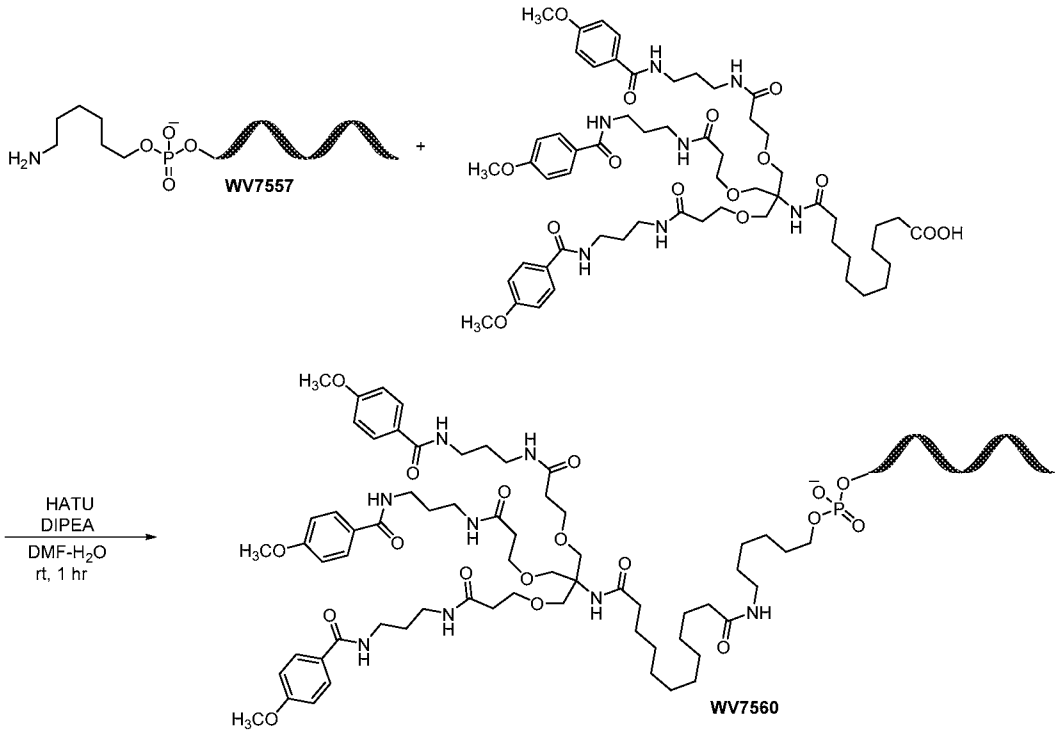
Scheme 2

General procedure for conjugation of tri antennary anisamide with WV-7557 and WV 8444: Synthesis of WV-7560 and WV 8447



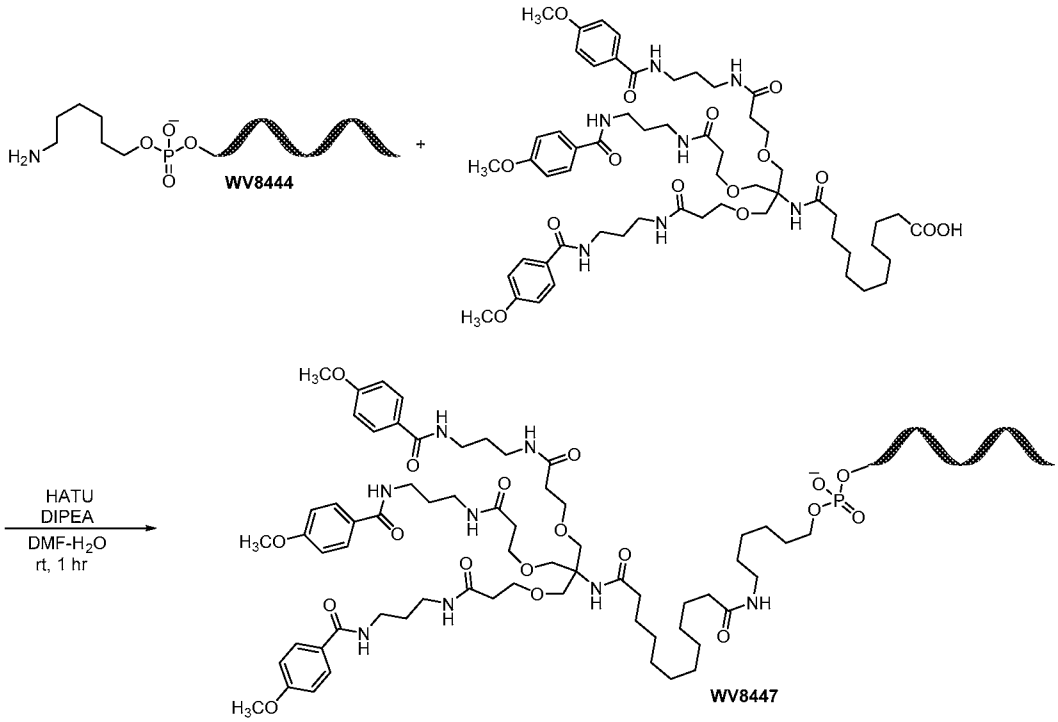
General Procedure: To a solution of triantennary anisamide (2 equivalents), in 2 ml DMF was added HATU (1.8 equivalents) and DIPEA (10 equivalents). This mixture was stirred well for 2 minutes. To this solution was added a solution of WV-7557 (1 equivalent) in water and shaken well for 60 minutes. The solvent was removed under vacuum and crude product was purified by RP column (C8) chromatography to obtain the product. The purified product was desalted over a C-18 cartridge using sodium acetate solution.

Synthesis of WV-7560: To a solution of triantennary anisamide (11 mg, 9.8 μmol), in 2 ml DMF was added HATU (3.34 mg, 8.82 μmol) and DIPEA (6.3 mg, 9 μl, 49 μmol). This mixture was stirred well for 2 minutes (**Scheme 3**). To this solution was added a solution of WV-7557 (33.7 mg, 4.9 μmol) in 0.88 ml water and shaken well for 60 minutes. The solvent was removed under vacuum and crude product was purified by RP column (C8) chromatography to obtain the product WV-7560 (25 mg). The purified product was desalted over a C-18 cartridge using sodium acetate solution. Molecular weight of product calculated:7982; De-convoluted mass obtained: 7987.



Scheme 3

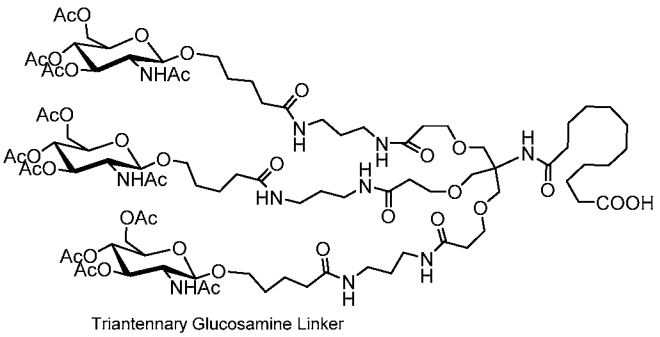
Synthesis of WV-8447: To a solution of triantennary anisamide (13 mg, 11.6 μmol), in 2 ml DMF was added HATU (4 mg, 10.4 μmol) and DIPEA (7.5 mg, 10.3 μl, 58 μmol). This mixture was stirred well for 2 minutes (**Scheme 4**). To this solution was added a solution of WV-8444 (40 mg, 5.8 μmol) in 1 ml water and shaken well for 60 minutes. The solvent was removed under vacuum and the crude product was purified by RP column (C8) chromatography to obtain the product WV-8447. The purified product was desalted over a C-18 cartridge using sodium acetate solution. Molecular weight of product calculated:7970; De-convoluted mass obtained: 7975.

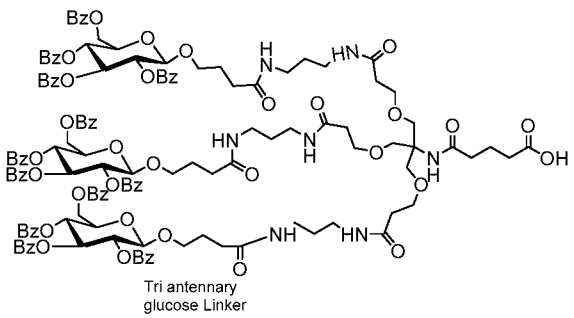


Scheme 4

General Procedure for conjugation of Triantennary Glucosamine/Glucose derivative with WV-7557 or WV-8444

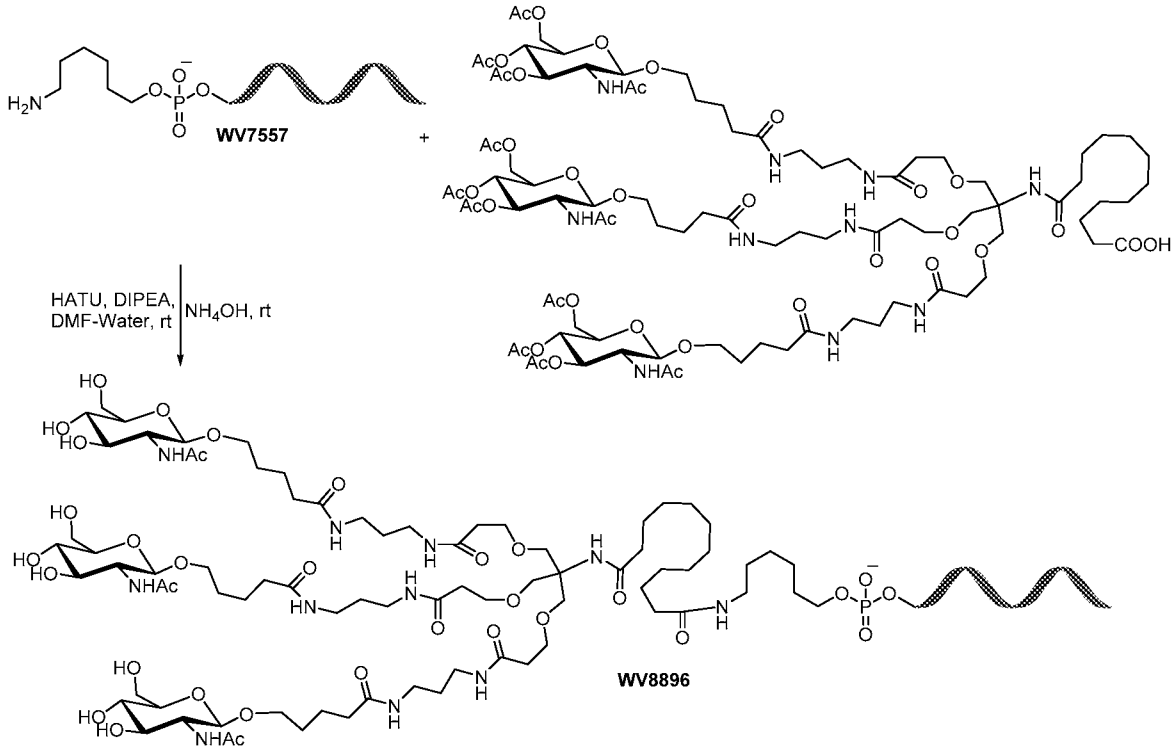
To a solution of triantennary glucosamine or glucose derivative (2 equivalents), in 2 ml DMF was added HATU (1.8 equivalents) and DIPEA (10 equivalents). This mixture was stirred well for 2 minutes. To this solution was added a solution of WV-7557 or WV-8444 (1 equivalent) in water and shaken well for 60 minutes. The solvent was removed under vacuum and crude product was treated with 30% NH_4OH solution at room temperature for 24 hours. The solvent was removed under vacuum and the crude product was purified by RP column (C8) chromatography to obtain the product. The purified product was desalted over a C-18 cartridge using sodium acetate solution.





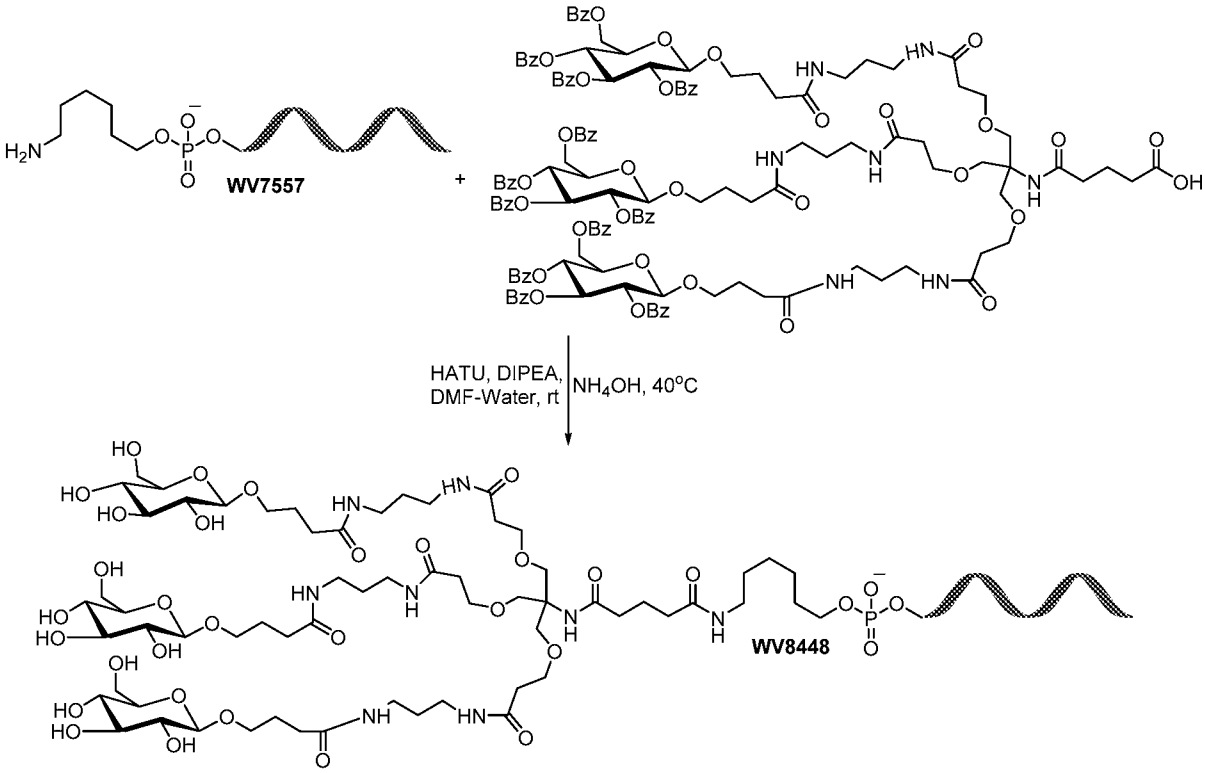
Synthesis of WV-8896: Following the general procedure shown above, Glucosamine derivative (23.3 mg, 11.6 μmol), HATU (4 mg, 10.44 μmol) and DIPEA (7.5 mg, 58 μmol) was stirred in 2 ml DMF

(**Scheme 5**). To this solution was added 40 mg (5.8 μmol) of WV-7557 in 1 ml water. Reaction mixture was stirred for 60 minutes to obtain the desired product. This product was treated with NH_4OH as described above. Amount of product obtained is 20 mg. Molecular weight calculated: 8496; Deconvoluted mass obtained: 8494



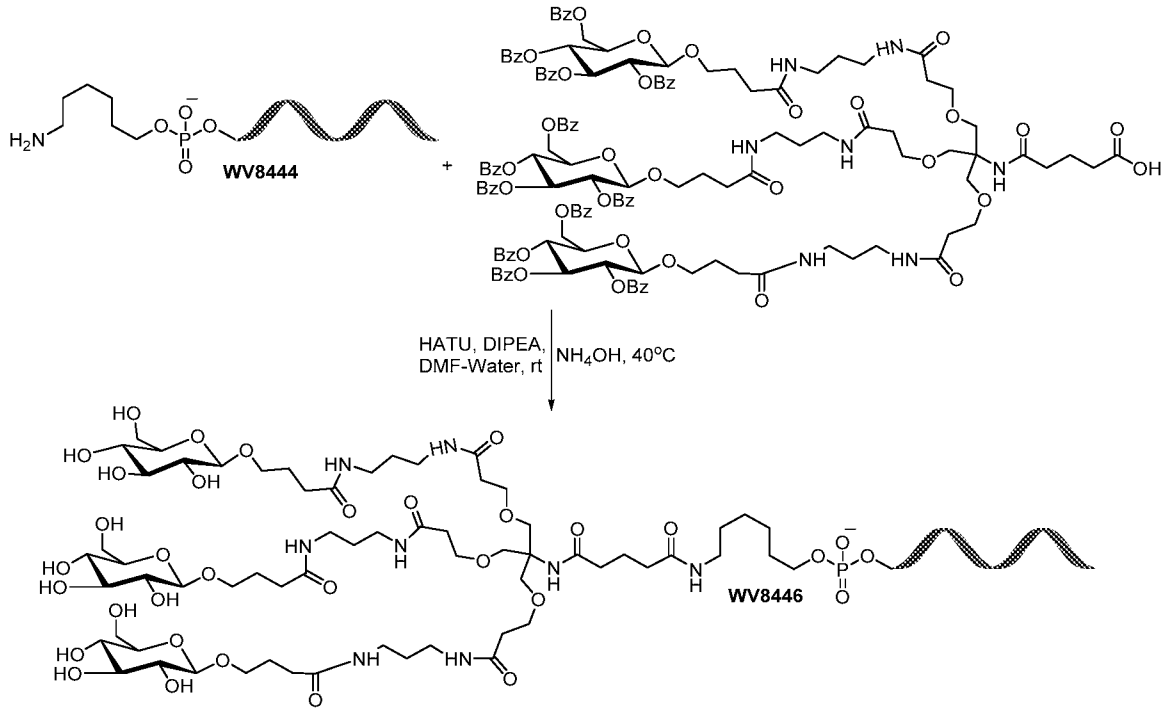
Scheme 5

Synthesis of WV-8448: Following the general procedure shown above, Glucose derivative (57 mg, 21.8 μmol), HATU (7.5mg, 19.6 μmol) and DIPEA (14.6 mg, 109 μmol) was stirred in 2 ml DMF (**Scheme 6**). To this solution was added 75 mg (10.9 μmol) of WV-7557 in 1 ml water. Reaction mixture was stirred for 60 minutes to obtain the desired product. This product was heated at 40°C with NH_4OH as described above to obtain the product. Molecular weight calculated: 8227; Deconvoluted mass obtained: 8233.



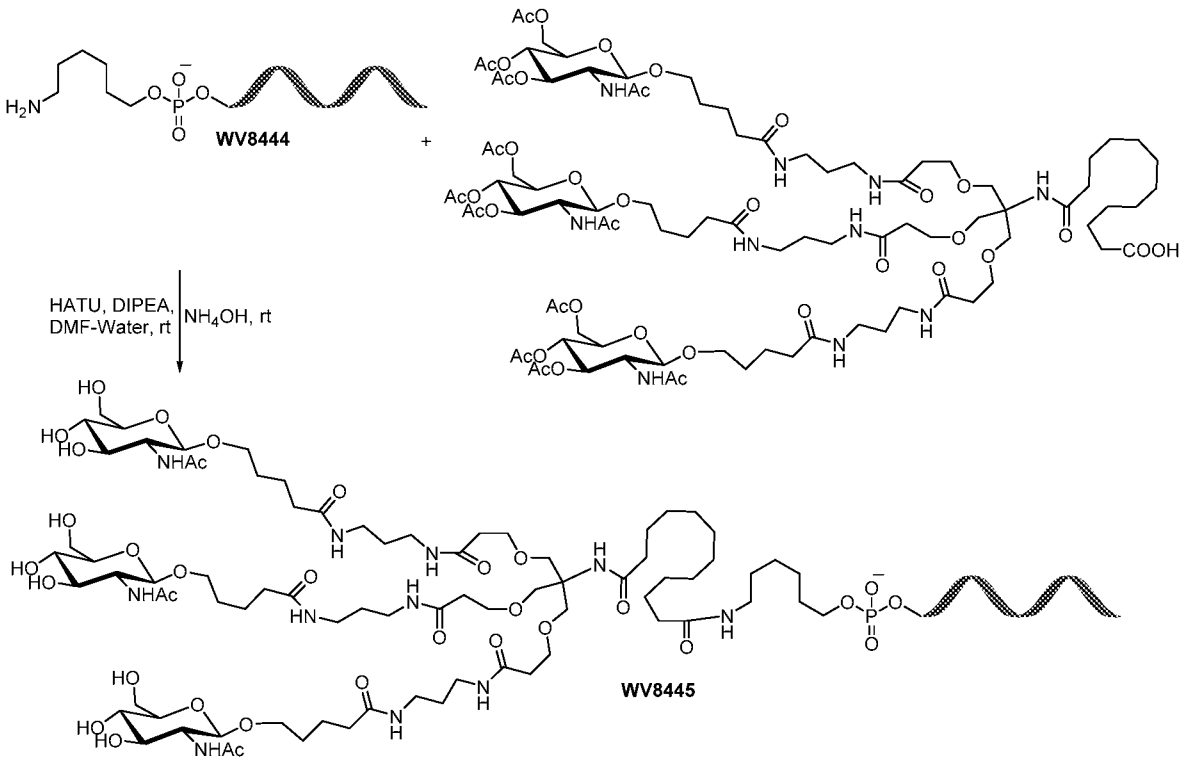
Scheme 6

Synthesis of WV-8446: Following the general procedure shown above, Glucose derivative (30mg, 11.6 μmol), HATU (4mg, 10.4 μmol) and DIPEA (7.5 mg, 58 μmol) was stirred in 2 ml DMF (**Scheme 7**). To this solution was added 40 mg (5.8 μmol) of WV 8444 in 1 ml water. Reaction mixture was stirred for 60 minutes to obtain the desired product. This product was heated at 40°C with NH_4OH as described above to obtain the product. Molecular weight calculated: 8214; Deconvoluted mass obtained: 8218.



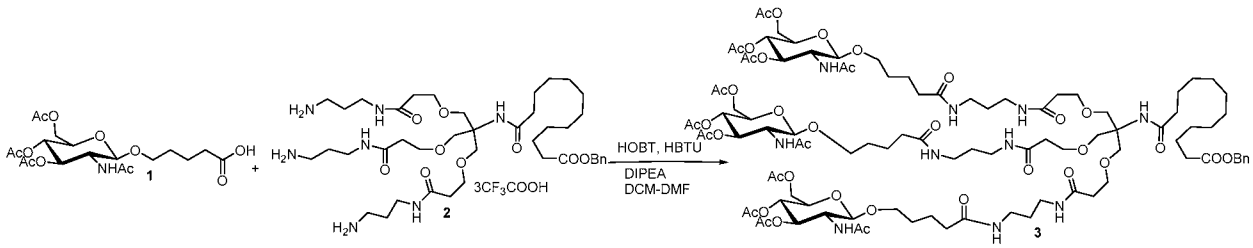
Scheme 7

Synthesis of WV-8445: Following the general procedure shown above, Glucosamine derivative (24mg, 12 μmol), HATU (4mg, 10.4 μmol) and DIPEA (7.5 mg, 58 μmol) was stirred in 2 ml DMF (**Scheme 8**). To this solution was added 40 mg (5.8 μmol) of WV 8444 in 1 ml water. Reaction mixture was stirred for 60 minutes to obtain the desired product. This product was heated at 40°C with NH_4OH as described above to obtain the product. Molecular weight calculated:8477; Deconvoluted mass obtained: 8484.



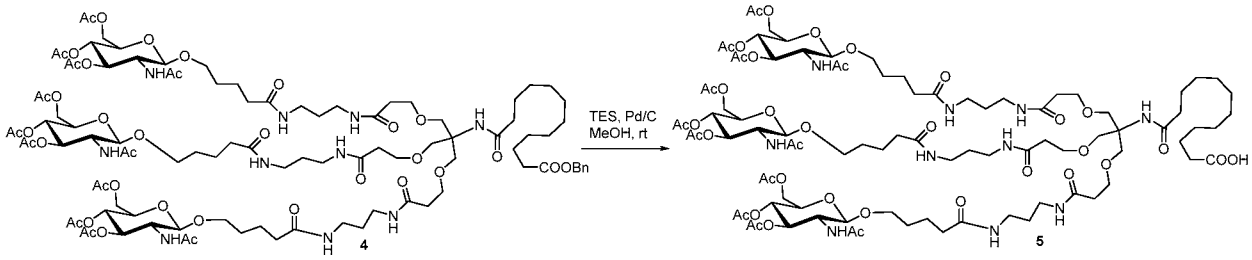
Scheme 8

Synthesis of GlucNAc Linker.



GlucNAc acid[1] **1** (1.88 g, 4.2 mmol) and HOBT (0.73 g, 5.4 mmol) was stirred in anhydrous DMF-DCM mixture (11+15 ml) under nitrogen at room temperature for 10 minutes. HBTU (2.05 g, 5.4 mmol) was added followed by DIPEA (2.17 g, 16.8 mmol) at 10 °C. To this solution was added tri-amine salt[2] **2** (1.38 g, 1.2 mmol) and stirred overnight. Solvent was removed under vacuum and the residue was dissolved in ethyl acetate (200 ml). To this solution was added 100 ml of a mixture of sat. ammonium chloride, sat. sodium chloride, sat. sodium bicarbonate and water (1:1:1:1). The ethyl acetate layer was turbid initially. After thoroughly shaking the layers got separated. Aqueous layer was extracted with ethyl acetate (x2). Combined organic fractions were washed with brine and dried over anhydrous sodium sulfate. Solvent removal under reduced pressure afforded 490 mg of crude product. This product was purified by CC on an ISCO machine. The eluent was DCM-Methanol (0-20% methanol in DCM).

Amount of product obtained was 1.26 g (50%). LC-MS (+ mode): 1768 (M- 1GlucNAc), 1438 (M-2 GlucNAc), 1108 (M-3 GlucNAc), 1049 (M/2 +1).



Procedure: To a solution of benzyl ester **4** (0.25 g, 0.119 mmol) in 7 ml dry methanol, under an atmosphere of argon, was added 1.5 ml (9.4 mmol) Triethylsilane (TES) drop wise. A vigorous reaction sets in and the RM was stirred for 3 hours. LC-MS analysis of the product indicates completion of reaction. The RM was filtered over celite and solvent was removed under vacuum. The crude product was triturated (X3) with ether-methanol (3:1) mixture and dried under vacuum. This product **5** was used for next reaction without further purification. 1H NMR (500 MHz, DMSO-D6): δ 7.90 (3H, d, *J=10 Hz*), 7.80 (t, 3H), 7.70 (t, 3H), 5.03 (t, 3H), 4.77 (t, 3H), 4.54 (3H, d, *J=10 Hz*), 4.14 (3H, dd, J_1*=9 Hz,* J_2*=5Hz*), 3.97-3.93 (m, 3H), 3.79-3.74 (m, 3H), 3.69-3.61 (m, 6H), 3.51-3.47 (m, 3H), 3.40-3.35 (m, 3H), 3.31(d, 3H, *J=9Hz*), 2.98 (m, 12H), 2.23 (t, 3H), 2.13 (t, 3H), 2.01-1.99 (m, 3H), 1.97(s, 9H), 1.92(s, 9H), 1.86(s, 9H), 1.71(s, 9H), 1.49-1.32 (m, 22H), 1.18 (br s, 12H).

Ref 1 and 2: US Patent WO 2014/025805 A1; dated 13 February 2014.

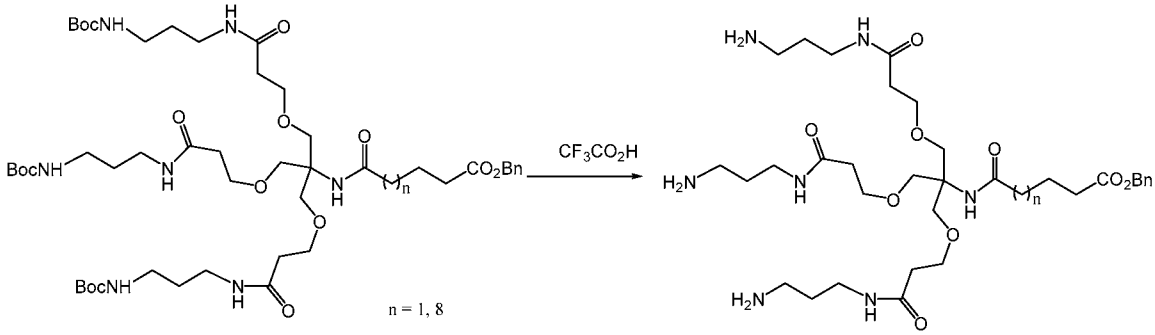
References:

Juliano et al. *J. Am. Chem. Soc.* 2010, 132, 8848

Banerjee R et al. *Int. J. Cancer.* 2004, 112, 693

He et al. *J. Med. Chem.*, 2017, *60* (10), pp 4161–4172

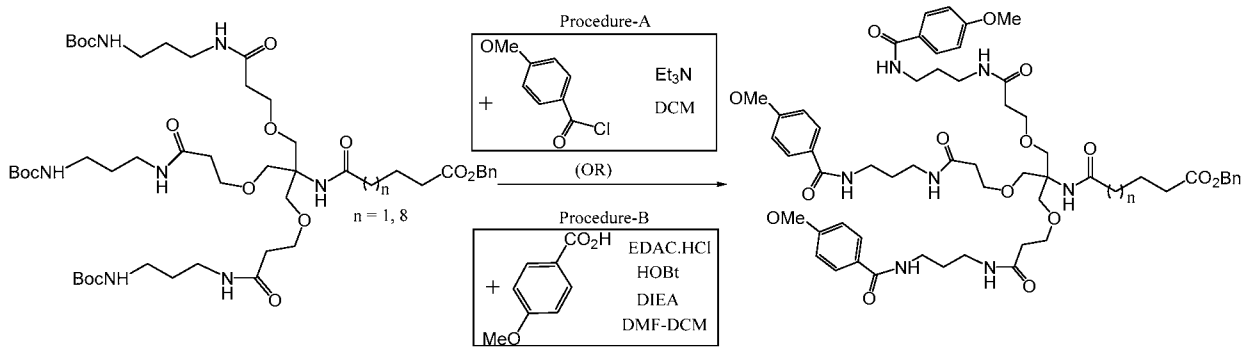
General Procedure for the deprotection of Amine:



15.2 g of NHBoc amine was dissolved in dry DCM (100 ml) then TFA (50 ml) was added dropwise at RT. Reaction mixture was stirred at RT overnight. Solvents were removed under reduced pressure then

co-evaporated with toluene (2 x 50 mL) then used for the next step without any further purification. NMR in CD_3OD confirmed the NHBoc deprotection.

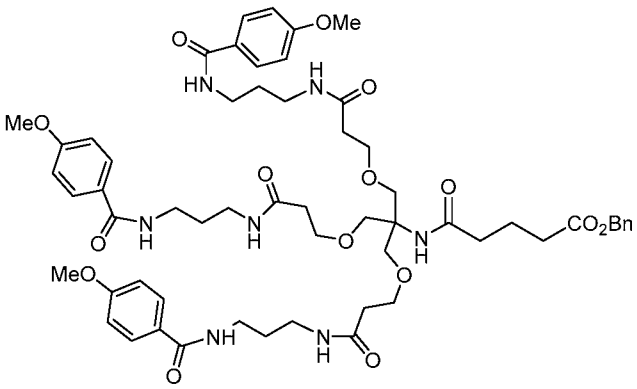
General procedure for the anisamide formation:



Procedure-A: The crude amine from the previous step was dissolved in a mixture of DCM (100 ml) and Et_3N (10 equ.) at RT. During this process, the reaction mixture was cooled with a water bath. Then *4*-Methoxybenzoyl chloride (4 equ) was added dropwise to the reaction mixture under argon atmosphere at RT, stirring continued for 3 h. Reaction mixture was diluted with water and extracted with DCM. Organic layer was extracted with aq. $NaHCO_3$, 1N HCl, brine then dried with magnesium sulfate evaporated to dryness. The crude product was purified by silica column chromatography using DCM-MeOH as eluent.

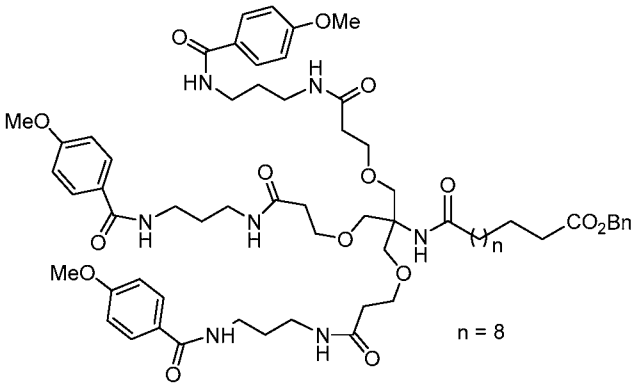
Procedure-B: The crude amine (0.27 equ), acid and HOBt (1 equ) were dissolved in a mixture of DCM and DMF (2:1) in an appropriate sized RBF under argon. EDAC.HCl (1.25 equ) was added portion wise to the reaction mixture under constant stirring. After 15 mins, the reaction mixture was cooled to ~10 ^oC then DIEA (2.7 equ) was added over a period of 5 mins. Slowly warmed the reaction mixture to ambient temperature and stirred under argon for overnight. TLC indicated completion of the reaction TLC condition, DCM: MeOH (9.5:0.5). Solvents were removed under reduced pressure, then water was added to the residue, and a gummy solid separated out. The clear solution was decanted, and the solid residue was dissolved in EtOAc and washed successively with water, 10% aqueous citric acid, aq. $NaHCO_3$, followed by saturated brine. The organic layer was separated and dried over magnesium sulfate. Solvent was removed under reduced pressure then the crude product was purified with silica column to get the pure product.

Anisamide:



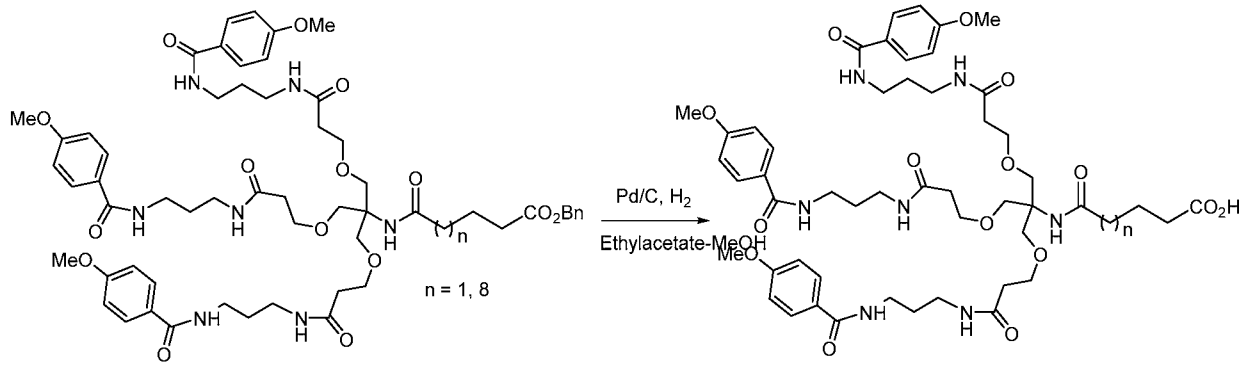
Anizamide was obtained from the amine in 32% yield over 2 steps using the above procedure-B: 1H NMR ($CDCl_3$): δ = 7.74 (d, 6H), 7.44 (t, 2H), 7.34 (t, 1H), 7.26 (m, 5H), 7.05 (m, 3H), 6.83 (d, 6H), 6.46 (s, 1H), 5.01 (s, 2H), 3.75 (s, 9H), 3.57 (m, 12H), 3.37 (m, 6H), 3.25 (m, 6H), 2.31 (m, 8H), 2.11 (m, 2H), 1.84 (m, 2H), 1.62 (m, 6H) ppm.

Anisamide:



Anizamide was obtained from the amine in 57% yield over 2 steps using the above procedure-A: 1H NMR ($CDCl_3$): δ = 7.75 (m, 3H), 7.73 (d, 6H), 7.43 (t, 3H), 7.25 (m, 5H), 6.80 (d, 6H), 6.51 (brs, 1H), 5.01 (s, 2H), 3.72 (s, 9H), 3.58 (m, 6H), 3.21 (m, 12H), 2.33 (t, 3H), 2.25 (t, 2H), 2.02 (t, 2H), 1.64 (q, 6H), 1.52 (p, 2H), 1.41 (q, 2H), 1.12 (m, 12H) ppm.

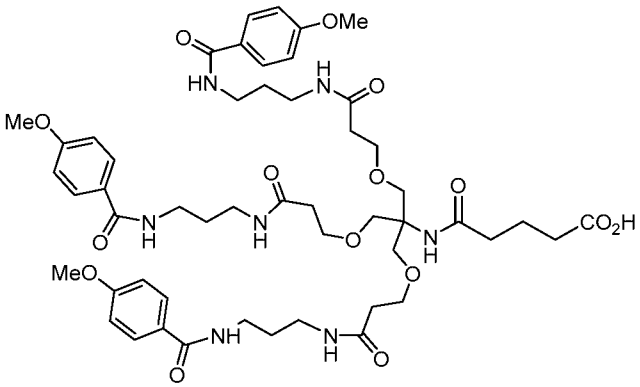
General procedure for the debenzylation:



The benzyl ester (10 g) was dissolved in a mixture of ethyl acetate (100 ml) and methanol (25 ml) then

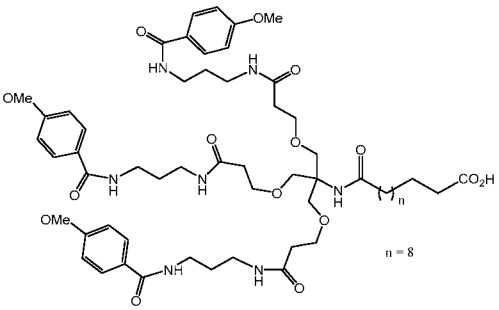
Pd/C, 1 g (10% palladium content) was added under argon atmosphere then the reaction mixture was vacuumed and flushed with hydrogen and stirred at RT under H2 atmosphere for 3 h. TLC indicated completion of the reaction, filtered through pad of celite and washed with methanol, evaporated to dryness to yield a foamy white solid.

Acid:



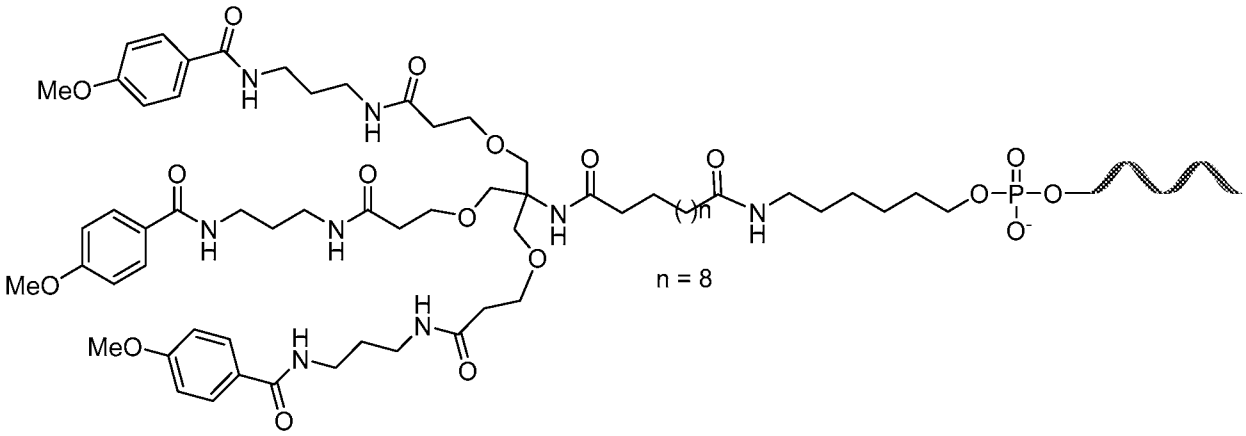
Yield 98%, 1H NMR (CD_3OD): δ = 8.35 (t, 1H), 8.01 (t, 1H), 7.82 (d, 6H), 7.27 (d, 1H), 6.99 (d, 6H), 3.85 (s, 9H), 3.68 (m, 12H), 3.41 (m, 6H), 3.29 (m, 6H), 2.42 (m, 6H), 2.31 (q, 2H), 2.21 (td, 2H), 1.80 (m, 8H) ppm.

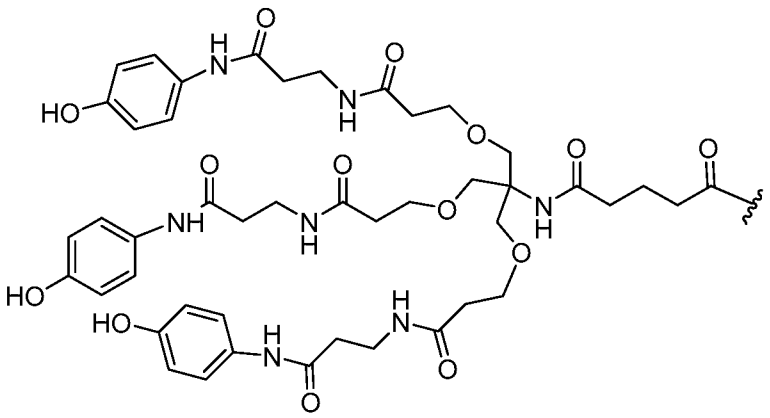
Acid:

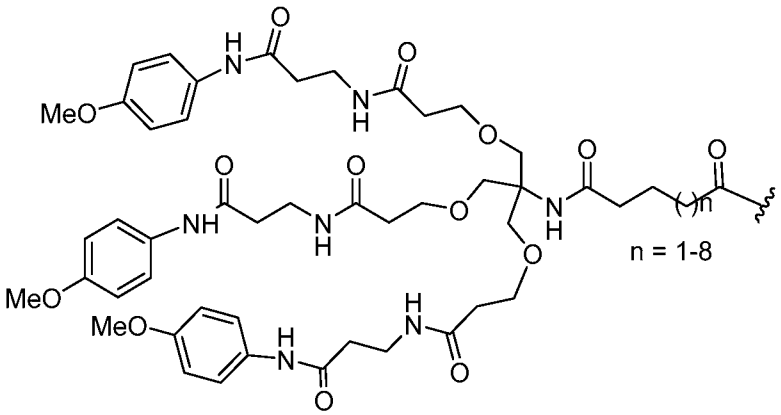


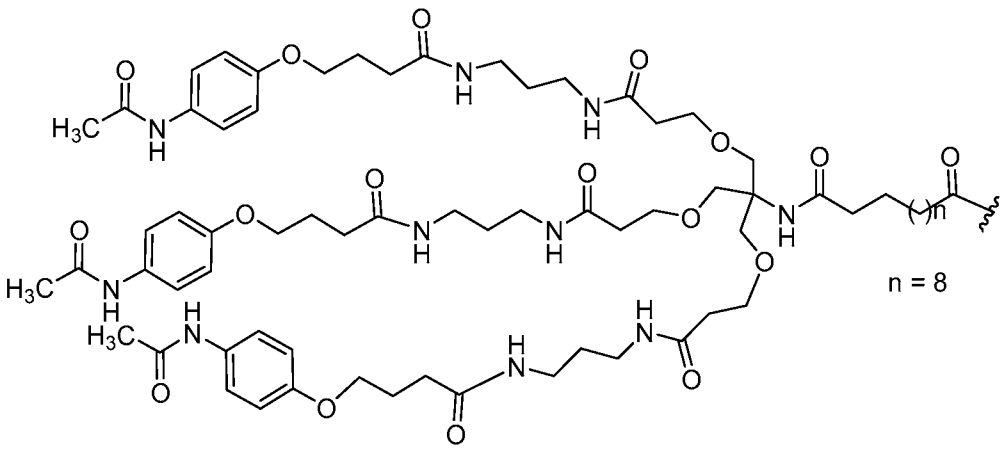
Yield 94%, 1H NMR (CD_3OD): δ = 8.36 (t, 2H), 8.02 (t, 2H), 7.82 (d, 6H), 7.23 (d, 1H), 6.98 (d, 6H), 3.85 (s, 9H), 3.70 (s, 6H), 3.67 (t, 6H), 3.41 (q, 4H), 3.28 (m, 8H), 2.42 (t, 6H), 2.27 (t, 2H), 2.13 (t, 2H), 1.79 (p, 6H), 1.54 (dp, 4H), 1.25 (m, 12H) ppm.

Additional compositions, including oligonucleotides comprising analogues of anisamide, are presented below:


MeO
n = 8


HO


MeO
n = 1-8


H3C
n = 8

EXAMPLE 3.

Activity of various C9orf72 oligonucleotides in Dual-luciferase reporter assay

[001120] Tables 2A to 2C present data pertaining to the activities of various C9orf72 oligonucleotides in a Dual-luciferase reporter assay

[001121] Each data point in Tables 2A to C is % of Renilla signal compared to WV-993, a control oligonucleotide which does not target C9orf72. In these tables, an ASO is a C9orf72 oligonucleotide.

[001122] Numbers are replicates performed simultaneously. The numbers represent the amount of residual gene expression. For example, WV-3677 replicate 1 (in the first row in Table 2A) shows 1.522608% residual gene expression, representing 98.477392% knockdown.

[001123] Constructs: C9orf72 nt 1-374 (Table 2A), C9orf72 nt 158-900 (Table 2B) or C9orf72 nt 900-1 (Table 2C) sequences were separately cloned into the NotI site of the psiCHECK-2 vector (Promega Corporation, Madison, WI), which is in the middle of the 3'UTR of the hRluc gene. The new construct thus comprises a portion of the wild-type C9orf72 which does not contain a hexanucleotide repeat expansion.

[001124] Sequences used for making these constructs are presented below:

C9, 1-374 (Exon 1a and part of intron 1)

ACGTAACCTACGGTGTCCCGCTAGGAAAGAGAGGTGCGTCAAACAGCGACAAGTTCCGCCCACGTAAAAG
ATGACGCTTG
GTGTGTCAGCCGTCCCTGCTGCCCGGTTGCTTCTCTTTTGGGGGCGGGGTCTAGCAAGAGCAGGTGTGGG
TTTAGGAGGT
GTGTGTTTTTGTTTTTCCCACCCTCTCTCCCCACTACTTGCTCTCACAGTACTCGCTGAGGGTGAACAAG
AAAAGACCTG
ATAAAGATTAACCAGAAGAAAACAAGGAGGGAAACAACCGCAGCCTGTAGCAAGCTCTGGAACTCAGGAG
TCGCGCGCTA
GGGGCCGGGGCCGGGGCCGGGGCGTGGTCGGGGCGGGCCCGGGGGCGGGCCCGG

C9, 158-900 (intron 1)

GTGTGTGTTTTTGTTTTTCCCACCCTCTCTCCCCACTACTTGCTCTCACAGTACTCGCTGAGGGTGAACA
AGAAAAGACC
TGATAAAGATTAACCAGAAGAAAACAAGGAGGGAAACAACCGCAGCCTGTAGCAAGCTCTGGAACTCAGG
AGTCGCGCGC
TAGGGGCCGGGGCCGGGGCCGGGGCGTGGTCGGGGCGGGCCCGGGGGCGGGCCCGGGGCGGGGCTGCGGT
TGCGGTGCCT

GCGCCCGCGGCGGCGGAGGCGCAGGCGGTGGCGAGTGGGTGAGTGAGGAGGCGGCATCCTGGCGGGTGGC
TGTTTGGGGT
TCGGCTGCCGGGAAGAGGCGCGGGTAGAAGCGGGGGCTCTCCTCAGAGCTCGACGCATTTTTACTTTCCC
TCTCATTTCT
CTGACCGAAGCTGGGTGTCGGGCTTTCGCCTCTAGCGACTGGTGGAATTGCCTGCATCCGGGCCCCGGGC
TTCCCGGCGG
CGGCGGCGGCGGCGGCGGCGCAGGGACAAGGGATGGGGATCTGGCCTCTTCCTTGCTTTCCCGCCCTCAG
TACCCGAGCT
GTCTCCTTCCCGGGGACCCGCTGGGAGCGCTGCCGCTGCGGGCTCGAGAAAAGGGAGCCTCGGGTACTGA
GAGGCCTCGC
CTGGGGGAAGGCCGGAGGGTGGGCGGCGCGCGGCTTCTGCGGACCAAGTCGGGGTTCGCTAGGAACCCGA
GACGGTCCCT
GCCGGCGAGGAGATCATGCGGG

C9, 900-1 (antisense RNA)

CCCGCATGATCTCCTCGCCGGCAGGGACCGTCTCGGGTTCCTAGCGAACCCCGACTTGGTCCGCAGAAGC
CGCGCGCCGCCCACCCTCCGGCCTTCCCCCA
GGCGAGGCCTCTCAGTACCCGAGGCTCCCTTTTCTCGAGCCCGCAGCGGCAGCGCTCCCAGCGGGTCCCC
GGGAAGGAGACAGCTCGGGTACTGAGGGC
GGGAAAGCAAGGAAGAGGCCAGATCCCCATCCCTTGTCCCTGCGCCGCCGCCGCCGCCGCCGCCGGG
AAGCCCGGGGCCCGGATGCAGGCAATT
CCACCAGTCGCTAGAGGCGAAAGCCCGACACCCAGCTTCGGTCAGAGAAATGAGAGGGAAAGTAAAAATG
CGTCGAGCTCTGAGGAGAGCCCCCGCTT
CTACCCGCGCCTCTTCCCGGCAGCCGAACCCCAAACAGCCACCCGCCAGGATGCCGCCTCCTCACTCACC
CACTCGCCACCGCCTGCGCCTCCGCCGCCGC
GGGCGCAGGCACCGCAACCGCAGCCCCGCCCCGGGCCCGCCCCCGGGCCCGCCCCGACCACGCCCCGGCC
CCGGCCCCGGCCCCTAGCGCGCGACTCCT
GAGTTCCAGAGCTTGCTACAGGCTGCGGTTGTTTCCCTCCTTGTTTTCTTCTGGTTAATCTTTATCAGGT
CTTTTCTTGTTCACCCTCAGCGAGTACTGTGAGAGCAA
GTAGTGGGGAGAGAGGGTGGGAAAAACAAAAACACACACCTCCTAAACCCACACCTGCTCTTGCTAGACC
CCGCCCCCAAAAGAGAAGCAACCGGGCAG
CAGGGACGGCTGACACACCAAGCGTCATCTTTTACGTGGGCGGAACTTGTCGCTGTTTGACGCACCTCTC
TTTCCTAGCGGGACACCGTAGGTTACGT

[001125] Each of the constructs expresses two Luminescent proteins: Firefly luciferase from hluc

gene and Renilla luciferase from hRluc gene.

[001126] The construct (20ng) and tested oligonucleotides (different doses) were cotransfected with Lipofectamine 2000 into Cos 7 cells for 48 hours and the Firefly and Renilla signal were read with a plate reader.

[001127] An efficacious C9orf72 oligonucleotide targeting the inserted sequences should decrease the Renilla signal without affecting the Firefly signal. The data analysis normalizes the Renilla with Firefly signal and compares the efficacy of the tested oligonucleotide to the control oligonucleotide. In Tables 2A and 2B, the numbers represent the percentage of remaining renilla signal. For example, for WV-3677, 1.5% residual level was detected in a replicate and 2.4% in another replicate at 30nM (representing 98.5% and 97.6% knockdown, respectively).

Table 2A. Exon 1a targeting C9orf72 oligonucleotides (tested using the construct comprising C9orf72 1-374)

oligo-nucleotide ID	oligonucleotide (30nM)		oligonucleotide (15nM)	
WV-3677	1.5	2.4	2.8	2.8
WV-3678	8.0	11.4	13.5	15.9
WV-3679	5.3	6.8	9.2	7.0
WV-3680	26.2	24.6	26.4	27.4
WV-3681	16.2	17.0	19.3	17.3
WV-3682	26.6	31.3	23.6	27.1
WV-3683	12.0	18.5	6.5	7.2
WV-3684	30.9	45.1	23.2	23.0
WV-3685	9.4	41.5	9.9	9.8
WV-3686	19.7	22.9	24.0	15.4
WV-6928	7.1	6.1	10.3	11.3
WV-6929	13.9	19.2	21.7	26.8
WV-6930	5.5	6.6	9.4	10.3
WV-6931	4.1	6.2	7.3	7.3
WV-6932	12.1	10.4	9.4	12.2
WV-6933	6.5	8.1	12.9	14.8
WV-6934	12.6	13.8	25.6	26.9
WV-6935	7.0	11.5	16.0	17.2
WV-6936	22.3	20.7	16.9	16.4
WV-6937	6.6	8.1	8.3	9.8
WV-6938	6.6	8.5	21.5	21.8
WV-6939	10.4	14.4	28.3	25.4
WV-6940	5.7	5.1	6.5	6.5
WV-6941	9.4	14.1	19.5	24.6
WV-6942	10.1	12.6	18.0	20.9
WV-6943	20.6	25.9	32.0	39.2

WV-6944	24.2	23.2	24.6	29.0
WV-6945	24.6	26.0	43.3	41.3
WV-6946	25.4	33.9	40.7	49.2
WV-6947	20.5	24.0	43.7	44.7
WV-6948	30.7	25.7	38.9	43.3
WV-6949	18.1	21.0	34.9	43.6
WV-3677	2.8	3.4	3.8	3.3

Table 2B. Intron1 Targeting C9orf72 oligonucleotides (using construct comprising C9orf72 158-900)

oligonucleotide ID	oligonucleotide (30nM)		oligonucleotide (15nM)	
WV-3687	10.3	15.5	33.1	19.5
WV-3688	11.7	11.1	10.2	11.8
WV-3689	3.6	12.6	8.6	8.2
WV-3690	4.7	9.3	5.4	4.8
WV-3691	25.0	24.3	29.3	29.3
WV-3692	20.9	22.9	27.7	25.5
WV-3693	50.6	36.0	31.0	29.3
WV-3694	18.9	35.3	45.7	45.5
WV-3695	29.2	63.7	55.9	55.2
WV-3696	32.0	73.0	32.3	27.9
WV-3697	18.5	81.8	36.4	38.2
WV-3698	9.5	28.1	33.4	31.1
WV-3699	9.0	40.5	27.8	20.7
WV-3700	37.2	57.3	44.0	35.6
WV-3701	42.6	39.8	44.9	31.7
WV-3702	45.3	14.4	38.5	30.0
WV-3703	48.2	29.8	20.5	15.0
WV-3704	10.4	47.6	12.3	9.5
WV-3705	23.8	21.8	47.1	50.0
WV-3706	35.9	32.5	45.5	39.1
WV-3707	60.9	86.4	73.3	74.1
WV-3708	68.4	76.7	96.9	79.3
WV-3709	89.3	107.7	138.6	113.7
WV-3710	107.8	96.3	121.8	117.5
WV-6471	9.6	14.6	46.5	89.5
WV-6472	8.9	10.0	25.5	77.0
WV-6473	8.6	9.2	24.8	60.3
WV-6474	13.6	8.1	12.8	11.8
WV-6475	25.4	17.2	33.0	26.0
WV-6476	47.8	30.9	24.5	17.9
WV-6477	55.9	93.4	20.9	21.4

WV-6478	40.2	79.3	35.7	33.1
WV-6479	35.5	68.7	27.2	20.6
WV-6480	40.2	59.6	22.2	13.4
WV-6481	40.7	65.7	27.9	26.5
WV-6482	18.9	36.4	39.0	16.0
WV-6483	17.9	23.6	29.4	20.8
WV-6484	21.1	22.6	27.6	18.6
WV-6485	19.0	30.7	32.2	32.7
WV-6486	23.6	15.5	17.6	15.3
WV-6487	24.0	22.5	18.6	20.3
WV-6488	16.1	20.2	18.3	13.5
WV-6489	21.6	34.8	17.4	15.1
WV-3688	16.9	15.3	13.5	11.8
WV-3687	15.5	15.8	24.8	24.1
WV-3536	47.3	57.0	60.2	85.7
WV-6408	3.5	5.7	7.7	7.6
WV-6950	10.3	15.4	23.7	18.7
WV-6951	11.1	9.5	12.0	12.6
WV-6952	7.0	6.2	9.8	11.2
WV-6953	23.2	27.2	41.3	42.2
WV-6954	20.8	19.2	34.8	28.0
WV-6955	9.6	11.0	14.2	11.8
WV-6956	14.4	14.4	21.1	22.0
WV-6957	27.6	26.5	45.9	36.5
WV-6958	23.4	26.4	22.4	22.4
WV-6959	12.7	13.9	17.8	18.0
WV-6960	10.0	10.7	9.8	8.7
WV-6961	22.9	23.4	19.3	18.4
WV-6962	20.1	20.9	17.3	16.0
WV-6963	17.2	21.0	24.7	22.6
WV-6964	24.3	25.6	19.6	19.0
WV-6965	18.6	18.4	20.0	16.4
WV-6966	22.0	22.0	28.7	30.1
WV-6967	36.9	33.0	19.1	19.5
WV-6968	31.4	31.1	18.6	19.7
WV-6969	8.9	9.1	4.7	5.1
WV-6970	19.0	19.0	8.4	7.8
WV-6971	15.8	16.6	16.6	14.0
WV-6972	13.7	15.8	14.5	12.7
WV-6973	39.0	43.9	26.9	20.7
WV-6974	12.8	16.3	9.8	9.6
WV-6975	22.3	23.6	17.1	15.9
WV-6976	9.3	11.7	7.4	7.9

WV-6977	26.3	33.9	13.3	12.6
WV-6978	20.1	20.0	11.0	8.7
WV-6979	22.5	19.9	15.8	14.4
WV-6980	20.0	24.3	17.4	17.2
WV-6981	22.7	22.9	22.2	20.3
WV-6982	13.3	17.9	14.7	13.1
WV-6983	35.9	35.2	17.2	18.2
WV-6984	47.4	67.2	34.1	34.8
WV-6985	13.0	13.8	15.3	15.9
WV-6986	13.8	14.2	15.0	14.8
WV-6987	19.2	19.9	22.5	22.6
WV-6988	18.3	20.4	16.2	17.2
WV-6989	12.5	12.5	12.0	9.4
WV-6990	16.7	26.1	30.0	25.9
WV-6991	26.4	24.2	28.0	29.2
WV-6992	34.7	34.6	44.2	44.6
WV-6993	26.8	29.9	38.1	38.8
WV-6994	14.3	16.2	17.2	16.7
WV-6995	11.5	13.7	13.1	13.9
WV-6996	11.3	9.4	14.8	13.5
WV-6997	8.4	9.9	16.7	20.1
WV-6998	14.4	16.9	25.4	24.0
WV-6999	21.2	23.9	29.8	28.0
WV-7000	23.4	19.1	26.5	27.2
WV-7001	9.3	10.0	9.2	10.0
WV-7002	7.1	9.5	7.0	8.8
WV-7003	28.5	29.0	14.2	13.1
WV-7004	11.3	13.1	11.9	11.3
WV-7005	20.3	19.6	15.3	13.5
WV-7006	16.1	20.3	13.2	12.3
WV-7007	11.5	12.0	10.8	11.3
WV-7008	24.3	21.6	34.7	34.2
WV-7009	18.7	21.6	30.6	32.3
WV-7010	25.1	27.9	29.3	26.2
WV-7011	19.8	23.5	22.6	23.6
WV-7012	31.4	38.5	26.4	23.7
WV-6408	5.2	4.6	7.6	10.5

Table 2C. Antisense Transcript Targeting C9orf72 oligonucleotides (tested using the construct with C9orf72 900-1)		
oligonucleotide ID	**oligonucleotide (30nM)**	**oligonucleotide (15nM)**

WV-3719	31.1	25.4	13.9	14.7
WV-3720	41.9	46.3	24.8	21.4
WV-3721	30.2	36.3	22.6	23.7
WV-3722	20.3	26.0	19.3	16.6
WV-3723	14.1	13.7	9.8	10.0
WV-3724	31.6	33.5	18.6	19.0
WV-3725	64.1	89.0	27.5	32.6
WV-3726	206.7	49.4	50.0	48.5
WV-3727	58.2	47.2	50.2	46.3
WV-3728	39.6	33.7	69.2	58.6
WV-3729	34.1	25.6	49.1	50.2
WV-3730	14.0	20.5	17.6	14.2
WV-3731	21.5	27.8	21.2	32.3
WV-3732	13.1	16.1	22.1	16.8
WV-3733	13.7	20.0	24.1	19.7
WV-3734	9.0	14.7	17.7	25.4
WV-3735	21.2	28.5	47.7	21.2
WV-3736	10.0	17.1	17.7	48.4
WV-3737	11.9	8.4	13.3	14.2
WV-3738	42.0	36.6	39.8	65.7
WV-3739	16.6	12.5	16.1	20.5
WV-3740	43.9	40.0	58.2	67.3
WV-3741	30.6	46.4	23.6	32.1
WV-3742	38.1	38.4	50.2	60.1
WV-3743	23.4	25.2	19.1	16.9
WV-3744	42.6	44.2	66.4	69.3
WV-3745	13.4	10.8	15.0	21.1
WV-3746	183.3	142.7	92.3	106.2
WV-3747	148.5	135.5	93.0	80.1
WV-3748	88.1	78.2	73.0	64.4
WV-3749	90.8	99.5	72.3	62.7
WV-3750	102.3	105.0	77.1	77.6
WV-3751	169.9	150.3	88.4	76.0
WV-3752	115.1	80.1	74.2	53.5

EXAMPLE 4.

Ability of C9orf72 oligonucleotides to knock down C9orf72 transcripts in vitro

Various C9orf72 oligonucleotides were tested for their ability to knockdown C9orf72 transcripts in vitro. The tested oligonucleotides had any of 20 different sequences (seq 1 to 20), and each sequence was tested in each of three different formats (e.g., 2'-O-Methyl full PS, 2'-O-Methyl PS/PO, or MOE full PS). The exact sequences and modifications for each C9orf72 oligonucleotide is presented in Table 1A.

Table 3A. C9orf72 oligonucleotides tested in this experiment

	Group A	Group B	Group C
	2'-O-Methyl full PS	2'-O-Methyl PS/PO	MOE full PS
mRNA seq 1	WV-3561	WV-3657	WV-5905
mRNA seq 2	WV-3562	WV-3658	WV-5906
mRNA seq 3	WV-3563	WV-3659	WV-5907
mRNA seq 4	WV-3564	WV-3660	WV-5908
mRNA seq 5	WV-3565	WV-3661	WV-5909
mRNA seq 6	WV-3566	WV-3662	WV-5910
mRNA seq 7	WV-3567	WV-3663	WV-5911
mRNA seq 8	WV-3568	WV-3664	WV-5912
mRNA seq 9	WV-3569	WV-3665	WV-5913
mRNA seq 10	WV-3570	WV-3666	WV-5914
mRNA seq 11	WV-3571	WV-3667	WV-5915
mRNA seq 12	WV-3572	WV-3668	WV-5916
mRNA seq 13	WV-3573	WV-3669	WV-5917
mRNA seq 14	WV-3574	WV-3670	WV-5918
mRNA seq 15	WV-3575	WV-3671	WV-5919
mRNA seq 16	WV-3576	WV-3672	WV-5920
mRNA seq 17	WV-3577	WV-3673	WV-5921
mRNA seq 18	WV-3578	WV-3674	WV-5922
mRNA seq 19	WV-3579	WV-3675	WV-5923
mRNA seq 20	WV-3580	WV-3676	WV-5924

C9orf72 oligonucleotides were tested in iCell neurons, at 48hours, at a concentration of 10uM. Results are presented below. Numbers represent amount of residual C9orf72 transcripts (measured were a total of all C9orf72 transcripts) remaining after gymnotic introduction of the oligonucleotides or controls into the cells. For example, for Water, in Group A, 0.992 indicates 99.2% retention of C9orf72 transcript level, or essentially no knockdown relative to the control. For WV-3675, representing mRNA sequence 19 Group B, 0.316 indicates 31.6% residual C9orf72 transcript level, or 68.4% knockdown. Unless noted otherwise, other data representing residual transcript level is presented in this same or a similar format.

Table 3B. Activity of C9orf72 oligonucleotides tested in this experiment

	Group A	Group B	Group C
	2'-O-Methyl full PS	2'-O-Methyl PS/PO	MOE full PS
mRNA seq 1	1.169	0.648	1.087
mRNA seq 2	0.782	1.121	0.877
mRNA seq 3	0.597	0.886	0.514
mRNA seq 4	0.572	0.710	0.448
mRNA seq 5	0.593	0.898	0.497
mRNA seq 6	0.478	0.311	0.228
mRNA seq 7	0.402	0.305	0.247
mRNA seq 8	0.850	1.017	0.624

mRNA seq 9	0.923	1.061	0.607
mRNA seq 10	0.963	1.025	0.717
mRNA seq 11	0.963	0.481	0.747
mRNA seq 12	1.068	1.210	0.865
mRNA seq 13	0.886	0.425	0.678
mRNA seq 14	0.976	0.943	0.742
mRNA seq 15	0.886	0.963	0.732
mRNA seq 16	0.892	0.963	0.563
mRNA seq 17	0.782	0.963	0.463
mRNA seq 18	0.473	0.747	0.624
mRNA seq 19	0.660	0.316	0.669
mRNA seq 20	0.678	0.651	0.763
control	1.032	1.017	0.774
Water	0.992	0.985	1.026
WV-3537			0.624

EXAMPLE 5.

Activities of various C9orf72 oligonucleotides in various assays

Tables 4A to D show activity of C9orf72 oligonucleotides in knocking down C9orf72 transcripts (Table 4A, all transcripts; Table 4B, only V3 transcripts; Table 4C, Intron/AS transcripts; and Table 4D, only Exon 1a transcripts) in vitro in iPSC neurons. Table 4C shows knockdown of Intron/AS transcripts (with probes targeting a region 3' to the repeat transcript expansion, the detected area includes both sense and antisense transcripts of the intronic region). Relative-fold change in C9orf72 / HPRT1 is shown. Three replicate experiments are shown for the various C9orf72 oligonucleotides, at a concentration of 1 μM (Column A) or 10 μM (Column B). Numbers represent residual transcript level (all C9orf72 transcripts). For example, with WV-7601, three replicates were done at a concentration of 1 μM (Group A), showing 82.6%, 86.8% and 77.6% residual C9orf72 transcript level (all C9orf72 transcripts), corresponding to 17.4%, 13.2% and 22.3% knockdown, respectively. For WV-7601, three replicates were also performed at a concentration of 10 μM (Group B), showing 76.0%, 68.5%, and 75.0% residual C9orf72 transcript level (all C9orf72 transcripts), corresponding to 24.0%, 31.5%, and 25.0% knockdown, respectively. Delivery of oligonucleotides was gymnotic and cells were tested after 1 week. Controls used included WV-5302 and WV-6493, which target Malat1. Malat1 and C9orf72 oligonucleotides were also tested against Malat1; Malat1 oligonucleotides were efficacious in knocking down Malat1, but C9orf72 oligonucleotides were not efficacious in knocking down Malat1 (data not shown). Controls also include WV-2549 and WV-6028, which target a gene target which is not C9orf72.

Table 4A. Activity of C9orf72 oligonucleotides (residual level of all C9orf72 transcripts)

	A (1 μM)	**B (10 μM)**
WV-7601	0.826	0.760

	0.868	0.685
	0.776	0.750
WV-7657	0.832	0.622
	0.844	0.676
	0.886	0.719
WV-7658	0.917	0.798
	0.850	0.676
	0.880	0.704
WV-7659	0.882	0.740
	0.946	0.631
	0.852	0.626
WV-8005	0.795	0.622
	0.768	0.568
	0.763	0.609
WV-8006	0.952	0.681
	0.835	0.662
	0.774	0.700
WV-8007	0.727	0.605
	0.697	0.568
	0.702	0.545
WV-8008	0.747	0.502
	0.637	0.601
	0.717	0.584
WV-8009	0.722	0.593
	0.732	0.605
	0.779	0.553
WV-8010	0.688	0.572
	0.742	0.626
	0.835	0.622
WV-8011	0.650	0.486
	0.702	0.486
	0.655	0.483
WV-8012	0.707	0.489
	0.687	0.496
	0.655	0.496
WV-2549	0.939	0.900
	0.920	0.888
	0.907	
WV-6028	0.972	1.006
	0.992	0.932
	0.972	0.985
WV-3688	0.852	0.731
	0.840	0.711
	0.876	0.806
WV-6408	0.773	0.624
	0.835	0.641
	0.945	0.558
WV-3662	0.423	
	0.429	0.109

		0.086
WV-7118	0.405	0.240
	0.380	0.240
	0.380	0.237
WV-6936	0.937	1.044
	0.862	0.974
	0.924	0.915
WV-7027	0.963	0.928
	0.868	0.981
	0.937	0.994
WV-5302	0.880	0.947
	0.874	1.029
	0.937	1.022
WV-6493	0.990	0.981
	0.833	1.001
	0.990	1.044
WV-2376	1.018	0.987
	0.911	0.693
	0.970	0.764
WV-3542	0.892	0.994
	0.892	0.967
	1.004	1.022

Table 4B. Activity of C9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

	A (1 μM)	**B (10 μM)**
WV-7603	0.631	0.455
	0.725	0.442
	0.740	0.445
WV-7604	0.572	0.436
	0.622	0.407
	0.601	0.362
WV-7605	0.667	0.340
	0.695	0.354
	0.648	0.374
WV-7606	0.676	0.298
	0.495	0.286
	0.576	0.247
WV-7601	0.475	0.286
	0.557	0.278
	0.530	0.247
WV-7657	0.618	0.424
	0.676	0.364
	0.549	0.407
WV-7658	0.568	0.326
	0.542	0.321
	0.572	0.304
WV-7659	0.558	0.333
	0.539	0.315
	0.582	0.296

WV-8005	0.366	0.123
	0.327	0.124
	0.392	0.147
WV-8006	0.409	0.158
	0.438	0.171
	0.473	0.157
WV-8007	0.182	0.056
	0.196	0.056
	0.238	0.050
WV-8008	0.197	0.048
	0.183	0.045
	0.172	0.043
WV-8009	0.412	0.150
	0.379	0.129
	0.406	0.110
WV-8010	0.339	0.137
	0.344	0.138
	0.368	0.128
WV-8011	0.229	0.059
	0.244	0.067
	0.263	0.055
WV-8012	0.212	0.046
	0.244	0.050
	0.217	0.057
WV-2549	0.827	0.821
	0.936	0.905
	0.983	
WV-6028	0.943	1.018
	0.990	0.983
	0.905	1.011
WV-3688	0.735	0.502
	0.730	0.472
	0.715	0.538
WV-6408	0.505	0.341
	0.557	0.343
	0.644	0.343
WV-3662	0.357	
	0.408	0.071
		0.028
WV-7118	0.369	0.153
	0.404	0.159
	0.352	0.148
WV-6936	0.843	0.562
	0.792	0.649
	0.808	0.589
WV-7027	0.792	0.602
	0.819	0.731
	0.941	0.778
WV-5302	1.066	1.062

	1.059	1.055
	1.066	1.077
WV-6493	1.044	1.026
	1.030	1.085
	0.995	1.115
WV-2376	0.981	1.108
	0.968	0.887
	0.995	0.828
WV-3542	1.030	1.041
	1.009	0.991
	1.016	1.070

Table 4C. Activity of C9orf72 oligonucleotides (residual level of Intron/AS C9orf72 transcripts)

	A (1 μM)	**B (10 μM)**
WV-7603	0.557	0.654
	0.767	0.705
	0.799	0.654
WV-7604	0.386	0.375
	0.538	0.329
	0.535	0.299
WV-7605	0.851	0.585
	0.845	0.561
	0.663	0.610
WV-7606	0.783	0.408
	0.178	0.623
	0.343	0.520
WV-7601	0.303	0.260
	0.260	0.271
	0.265	0.311
WV-7657	0.715	0.606
	0.756	0.513
	0.405	0.434
WV-7658	0.520	0.345
	0.502	0.277
	0.677	0.370
WV-7659	0.372	0.417
	0.458	0.397
	0.359	0.479
WV-8005	0.471	0.346
	0.613	0.425
	0.626	0.654
WV-8006	0.410	0.355
	0.474	0.663
	0.471	0.411
WV-8007	0.621	0.531
	0.512	0.475
	0.548	0.307
WV-8008	0.439	0.645
	0.311	0.485

	0.564	0.495
WV-8009	0.580	0.593
	0.685	0.479
	0.592	0.706
WV-8010	0.461	0.394
	0.252	0.431
	0.407	0.341
WV-8011	0.514	0.415
	0.594	0.774
	0.972	0.774
WV-8012	0.594	1.050
	0.650	0.633
	0.606	0.651
WV-2549	0.435	1.198
	1.282	1.174
	1.318	
WV-6028	1.715	2.001
	1.049	2.604
	0.846	1.058
WV-3688	0.795	0.703
	0.687	0.836
	0.554	0.764
WV-6408	1.071	1.029
	0.741	1.036
	0.789	0.940
WV-3662	1.273	
	1.180	0.802
		1.376
WV-7118	1.356	1.094
	0.712	1.248
	1.156	0.876
WV-6936	1.291	1.375
	1.064	1.310
	1.443	1.944
WV-7027	0.507	0.727
	0.992	1.494
	0.768	1.777
WV-5302	1.230	2.157
	0.737	0.795
	1.101	0.840
WV-6493	0.562	1.463
	0.586	0.727
	0.536	0.784
WV-2376	0.784	1.985
	1.579	0.387
	0.594	0.426
WV-3542	1.494	1.515
	1.283	1.944
	1.704	2.361

Table 4D. Activity of C9orf72 oligonucleotides (residual level of Exon 1a C9orf72 transcripts)

	A (1 μM)	B (10 μM)
WV-7603	1.006	1.127
	1.042	1.051
	0.965	0.981
WV-7604	0.823	1.059
	0.823	0.848
	0.737	0.738
WV-7605	1.282	1.059
	1.205	1.023
	1.049	1.096
WV-7606	0.907	0.995
	0.524	1.008
	0.687	1.044
WV-7601	0.707	1.044
	0.795	0.909
	0.726	0.848
WV-7657	0.985	0.854
	0.888	0.728
	0.551	0.733
WV-7658	0.979	1.104
	0.829	0.786
	1.124	1.183
WV-7659	1.160	1.582
	1.090	1.119
	0.904	1.088
WV-8005	0.923	1.199
	0.996	1.119
	0.936	1.330
WV-8006	1.121	1.088
	1.010	1.216
	0.792	0.981
WV-8007	1.168	1.582
	0.904	1.358
	0.873	1.058
WV-8008	1.090	1.755
	0.820	1.560
	1.136	1.684
WV-8009	0.892	1.233
	0.917	1.001
	0.843	0.884
WV-8010	0.755	0.896
	0.666	1.111
	1.010	1.037
WV-8011	1.028	1.084
	1.049	1.153
	1.086	1.138
WV-8012	0.986	1.298

	0.933	1.138
	0.926	1.254
WV-2549	0.946	1.084
	1.132	1.047
	1.071	
WV-6028	1.197	1.194
	0.959	1.334
	1.086	1.054
WV-3688	1.013	1.122
	0.852	0.977
	0.795	0.943
WV-6408	1.101	1.254
	1.049	1.316
	1.172	1.245
WV-3662	0.939	
	1.028	0.886
		1.271
WV-7118	1.070	1.171
	1.026	1.020
	1.077	1.013
WV-6936	1.077	0.408
	0.945	0.773
	1.115	0.677
WV-7027	1.123	0.978
	1.221	1.204
	1.246	1.171
WV-5302	1.281	1.524
	1.026	1.116
	1.034	0.965
WV-6493	1.100	1.255
	0.971	1.282
	0.912	1.238
WV-2376	1.171	1.462
	1.255	0.747
	0.951	0.817
WV-3542	1.383	1.657
	1.412	1.680
	1.588	2.011

EXAMPLE 6.

Activities of various C9orf72 oligonucleotides in various assays

Tables 5A to D show activity of various C9orf72 oligonucleotides in knocking down C9orf72 transcripts (Table 5A, all transcripts; Table 5B, only V3 transcripts; Table 5C, Intron/AS; and Table 5D, only Exon 1a transcripts). Relative-fold change in C9orf72 / HPRT1 is shown. Three replicate experiments are shown for the various C9orf72 oligonucleotides, at a concentration of 1 μM (Column A) or 10 μM (Column B). As with Tables 5A to D, numbers represent residual transcript level. Delivery of

oligonucleotides was gymnotic and cells were tested after 1 week.

Table 5A. Activity of C9orf72 oligonucleotides (residual level of all C9orf72 transcripts)

	A (1 μM)	B (10 μM)
WV-8122	1.031	0.928
	0.975	0.802
	0.942	0.718
WV-8311	1.090	0.915
	0.948	0.744
	0.962	0.819
WV-8315	0.923	0.600
	0.935	0.596
	1.097	0.471
WV-8312	1.164	1.210
	1.034	1.003
	1.006	0.969
WV-8313	1.201	1.550
	1.082	1.277
	1.024	1.268
WV-8314	1.105	1.044
	1.176	1.052
	1.351	1.044
WV-8316	0.926	0.930
	0.789	0.873
	0.846	0.898
WV-8317	1.013	0.996
	0.882	0.886
	0.876	0.861
WV-8318	1.078	1.136
	0.919	0.969
	0.972	1.010
WV-2549	0.885	0.903
	0.897	0.915
	0.989	0.922
WV-6028	0.840	0.855
	0.876	0.879
	1.006	0.976
WV-6936	0.958	0.969
	0.999	0.892
	1.140	1.046
WV-7027	0.752	0.873

Table 5B. Activity of C9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

	A (1 μM)	B (10 μM)
WV-8114	0.880	0.372
	0.904	0.608
	0.826	0.704

WV-8122	0.936	0.708
	1.003	0.689
	0.936	0.596
WV-8311	0.917	0.377
	0.898	0.364
	0.930	0.377
WV-8315	1.018	0.552
	1.039	0.508
	0.997	0.313
WV-8312	0.803	0.655
	0.803	0.683
	0.855	0.651
WV-8313	0.793	0.501
	0.862	0.544
	0.832	0.511
WV-8314	0.593	0.335
	0.564	0.364
	0.576	0.313
WV-8316	0.891	0.801
	0.843	0.707
	0.787	0.818
WV-8317	0.648	0.497
	0.671	0.467
	0.699	0.518
WV-8318	0.360	0.235
	0.372	0.283
	0.388	0.276
WV-2549	1.076	1.052
	1.076	1.002
	1.053	1.044
WV-6028	0.955	1.065
	0.975	1.133
	0.996	1.133
WV-6936	0.891	0.722
	0.873	0.665
	0.982	0.717
WV-7027	0.680	0.655
	0.719	0.624
	0.676	0.587

Table 5C. Activity of C9orf72 oligonucleotides (residual level of Intron/AS C9orf72 transcripts)

	A (1 μM)	**B (10 μM)**
WV-8114	1.960	0.449
	1.906	1.090
	1.742	1.399
WV-8122	1.284	0.734
	1.517	0.416
	1.008	0.317
WV-8311	1.987	1.193

	1.485	1.306
	1.766	1.500
WV-8315	1.396	0.370
	0.934	0.298
	1.126	0.294
WV-8312	2.898	2.346
	3.305	1.602
	1.965	0.940
WV-8313	2.072	5.115
	1.302	3.282
	1.506	3.305
WV-8314	2.464	1.664
	2.696	1.585
	2.380	1.333
WV-8316	1.965	2.028
	1.630	0.835
	1.279	1.879
WV-8317	1.687	
	2.337	1.028
	1.872	1.117
WV-8318	2.354	
	1.898	1.569
	1.500	2.000
WV-2549	1.718	1.185
	1.455	1.046
	1.581	1.244
WV-6028	2.063	1.214
	1.821	1.248
	2.437	2.099
WV-6936	2.593	1.454
	2.471	1.050
	3.398	2.144
WV-7027	1.270	1.705
	1.075	0.742
	1.024	0.521

Table 5D. Activity of C9orf72 oligonucleotides (residual level of Exon 1a C9orf72 transcripts)

	A (1 μM)	**B (10 μM)**
WV-8114	1.422	0.339
	1.462	0.713
	1.402	0.974
WV-8122	1.212	0.665
	1.163	0.480
	1.063	0.401
WV-8311	1.392	0.222
	1.123	0.194
	1.229	0.157
WV-8315	1.070	0.377
	0.919	0.347

	0.365	0.119
WV-8312	1.407	1.605
	1.304	1.081
	1.030	0.713
WV-8313	1.667	1.103
	1.255	0.819
	1.308	0.796
WV-8314	1.373	1.043
	1.392	0.980
	1.611	0.994
WV-8316	0.948	1.200
	0.797	0.744
	0.797	1.096
WV-8317	0.941	
	0.941	0.837
	0.808	0.872
WV-8318	0.903	
	0.866	0.948
	0.825	1.002
WV-2549	1.255	0.954
	0.971	0.859
	1.432	0.974
WV-6028	0.872	0.961
	0.819	0.954
	0.941	1.388
WV-6936	1.059	0.749
	1.216	0.878
	1.216	0.890
WV-7027	0.713	1.089
	0.770	0.770
	0.791	0.872

EXAMPLE 7.

Activities of various C9orf72 oligonucleotides in various assays

Tables 6A and B show activity of various C9orf72 oligonucleotides in knocking down C9orf72 transcripts (Table 6A, all transcripts; and Table 6B, only V3 transcripts). Relative-fold change in C9orf72 / HPRT1 is shown. Three replicate experiments are shown for the various C9orf72 oligonucleotides, at a concentration of 10 μM. As with Tables 3A to D, numbers represent residual transcript level relative to HPRT1. Delivery of oligonucleotides was gymnotic and cells were tested after 1 week. As a control, C9orf72 oligonucleotides were tested and found not to be efficacious in knocking down Malat1 (data not shown). C9orf72 oligonucleotides were also found not to be efficacious against another target, PFN1 (data not shown).

Table 6A. Activity of C9orf72 oligonucleotides (residual level of all C9orf72 transcripts)

	Replicate experiments (10 μM)		
WV-8008	0.592	0.564	0.608
WV-8548	0.625	0.634	0.630
WV-8010	0.639	0.497	0.579
WV-8549	0.680	0.643	0.621
WV-8012	0.579	0.445	0.617
WV-8550	0.634	0.580	0.608
WV-8454	0.527	0.405	0.489
WV-8455	0.440	0.381	0.437
WV-8551	0.640	0.649	0.691
WV-6408	0.687	0.687	0.762
WV-3662	0.148	0.153	0.157
WV-6936	0.951	0.875	1.255
WV-5302	0.979	0.945	
WV-2376	0.926	0.972	
Water (negative control)	1.013	0.932	1.056

Table 6B. Activity of C9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

	Replicate experiments (10 μM)		
WV-8008	0.104	0.100	0.121
WV-8548	0.313	0.318	0.294
WV-8010	0.222	0.229	0.229
WV-8549	0.347	0.367	0.280
WV-8012	0.135	0.107	0.117
WV-8550	0.313	0.302	0.290
WV-8454	0.161	0.131	0.137
WV-8455	0.087	0.082	0.109
WV-8551	0.316	0.308	0.293
WV-6408	0.546	0.499	0.562
WV-3662	0.121	0.121	0.132
WV-6936	0.845	0.554	
WV-5302	0.926	0.907	
WV-2376	0.876	0.907	
Water (negative control)	1.055	0.945	

Table 6C, below, shows the IC50 of various C9orf72 oligonucleotides tested in a full dose-response assay in ALS MN (motor neurons), delivered gymnotically and evaluated after 1 week. 10, 2.5, 0.625, 0.16, 0.04 and 0.001 μM concentrations were tested.

Table 6C. IC50 of some C9orf72 oligonucleotides

	IC50 (μM)
WV-8011	0.9119
WV-8012	0.5319
WV-8454	0.5982
WV-8455	0.5803
WV-8551	1.47
WV-8550	0.7681

EXAMPLE 8.

In vitro screening protocol

This example describes an in vitro screening protocol for C9orf72 oligonucleotides.

oligonucleotides were delivered gymnotically to ALS neurons for 48 hours in 24-well plates.

RNA extraction

RNA extraction with RNeasy Plus 96 kit (Qiagen, Waltham, Mass.) following protocol: Purification of Total RNA from Cells Using Vacuum/Spin Technology. (gDNA removal is critical.)

For each well, total RNA was eluted in 60ul of RNase-free water.

Reverse transcription

Reverse transcription with High-Capacity RNA-to-cDNA™ Kit (Applied Biosystems; available from ThermoFisher, Waltham, Mass.)

2X RT Buffer Mix	9ul
RNA sample	13.5ul

Heat denaturation at 72 °C for 5mins, Cool down the plate on ice for at least 2 mins.

To each well of heat denatured RNA, add:

2X RT Buffer Mix	6
20X RT Enzyme Mix	1.5ul

The final volume of the cDNA is 30ul.

Real-time PCR

Taqman Probes:

C9orf72 all variants: Hs00376619_m1 (FAM), Catalog # 4351368 (ThermoFisher, Waltham, Mass.)

C9orf72 V3: Hs00948764_m1(FAM), Catalog # 4351368 (ThermoFisher, Waltham, Mass.)

C9orf72 Exon 1a:

Forward primer	AGATGACGCTTGGTGTGTC
Reverse primer	TAAACCCACACCTGCTCTTG
probe	CTGCTGCCCGGTTGCTTCTCTTT

C9orf72 antisense RNA/intron:

Forward primer	GGTCAGAGAAATGAGAGGGAAAG
Reverse primer	CGAGTGGGTGAGTGAGGA
probe	AAATGCGTCGAGCTCTGAGGAGAG

Internal control: Human HPRT1 (VIC)

Hs02800695_m1, Catalog # 4448486 (ThermoFisher, Waltham, Mass.)

PCR reaction:

Lightcycler 480 master mix	10ul
C9 probe (FAM)	0.5ul
HPRT 1 (VIC)	0.5ul
cDNA *	up to 9ul
Nuclease-free H2O	to 20ul

*2ul of cDNA for all variants probe. 9ul of cDNA for other C9 probes.

Real-time PCR using Bio-rad CFX96 Touch

Run information:

1 95.0 C for 3:00

2 95.0 C for 0:10

3 60.0 C for 0:30

+ Plate Read

4 GOTO 2, 39 more times

END

EXAMPLE 9.

Activities of various C9orf72 oligonucleotides in various assays

[001128] Tables 7A to 7C, below, present the activities of various C9orf72 oligonucleotides tested in various assays.

[001129] **Brief description of various assays performed:**

[001130] **Reporter:**

[001131] Luciferase assay, as described herein. For some oligonucleotides, two numbers are given (e.g., 1.32 / 2.63 for WV-6408); these indicate replicate experiments.

[001132] **ALS neurons:**

[001133] Neuronal differentiation of iPSCs: iPSCs derived from fibroblasts from a C9orf72-associated ALS patient (female, 64 years old) were obtained from RUCDR Infinite Biologics. iPSCs were maintained as colonies on Corning Matrigel matrix (Sigma-Aldrich, St. Louis, MO) in mTeSR1 medium (STEMCELL Technologies, Vancouver, BC). Neural progenitors were produced using the STEMdiff Neural System (STEMCELL Technologies, Vancouver, BC). iPSCs were suspended in an AggreWell800 plate and grown as embryoid bodies in STEMdiff Neural Induction Medium for 5 days, with daily 75% medium changes. Embryoid bodies were harvested with a 37 μm cell strainer and plated onto Matrigel-coated plates in STEMdiff Neural Induction Medium. Medium was changed daily for 7 days, with 85-95% of embryoid bodies exhibiting neural rosettes 2 days post-plating. Rosettes were picked manually and transferred to plates coated with poly-L-ornithine and laminin in STEMdiff Neural Induction Medium (STEMCELL Technologies, Vancouver, BC). Medium was changed daily for 7 days,

until cells reached 90% confluence and were considered neural progenitor cells (NPCs). NPCs were dissociated with TrypLE (Gibco, available through ThermoFisher, Waltham, Massachusetts) and passaged at a ratio of 1:2 or 1:3 on poly-L-ornithine/laminin plates in a neural maintenance medium (NMM, 70% DMEM, 30% Ham's F12, 1X B27 supplement) supplemented with growth factors (20 ng/ml FGF2, 20 ng/ml EGF, 5 μg/ml heparin). For maturation into neurons, NPCs were maintained and expanded for fewer than five passages, and at >90% confluence were passaged 1:4 onto poly-L-orinithine/laminin-coated plates in NMM supplemented with growth factors. The next day, Day 0 of differentiation, medium was changed to fresh NMM without growth factors. Differentiating neurons were maintained in NMM for 4 or more weeks, with twice weekly 50% medium changes. Cells were re-plated with TrypLE at a density of 125,000 cells/cm^2 as needed.

[001134] **V3/intron:** Knockdown (KD) of V3 RNA transcript and intron RNA transcript were measured in ALS neurons. V3 transcripts knocked down are both wild-type and repeat-containing (indicated as "Healthy allele" V3 and "Pathological allele" V3 in Figure 1). Note, however, that, while the present disclosure is not bound by any particular theory, the repeat-containing transcript may have a longer retention time in the nucleus and thus may be preferentially knocked down. Intron transcript is indicated by the backwards AS arrow in Figure 1. Two numbers indicate the V3 and intron knockdown; for example, for WV-6408, V3 was knocked down by 59% and intron by 65%.

[001135] **Stability:**

[001136] Stability was assayed in vitro using Mouse (Ms) brain homogenates.

[001137] **TLR9:**

[001138] TLR9 Reporter Assay Protocol: Induction of NF-κB (NF-κB inducible SEAP) activity was analyzed using a human TLR9 or mouse TLR9 reporter assay (HEK-Blue™ TLR9 cells, InvivoGen, San Diego, California). Oligonucleotides at a concentration of 50 μM (330 μg/mL) and 2-fold serial dilution were plated into 96-well-plates in the final volume of 20 μL in water. HEK-Blue™ TLR9 cells were added to each well at a density of 7.2x10^4 cells in a volume of 180 μL of HEK Blue™ detection medium. Final working concentration of oligonucleotides in the wells was 5, 2.5, 1.25, 0.625, 0.312, 0.156, 0.078, and 0.0375 μM. HEK-Blue™ TLR9 cells were incubated with oligonucleotides for 16 hours at 37°C and 5% CO_2. At the end of the incubation, absorbance at 655 nM was measured by Spectramax. Water was a negative control. Positive controls were WV-2021 and ODN 2359, a CpG oligonucleotide. The results are expressed as fold change in NF-κB activation over vehicle control-treated cells. Reference: Human TLR9 Agonist Kit (InvivoGen, San Diego, California). In this assay, an oligonucleotide is considered "Clean" if no or essential no activity was detected. In some experiments, WV-8005, WV-8006, WV-8007, WV-8008, WV-8009, WV-8010, WV-8011, WV-8012 and WV-8321 showed no appreciable hTLR9 activity, though some showed small activity in mTRL9.

[001139] Complement

[001140] In some embodiments, complement is assessed in a cynomolgus monkey serum complement activation ex vivo assay. The effects of oligonucleotides on complement activation were measured in cynomolgus monkey serum ex vivo. Serum samples from 3 individual male cynomolgus monkeys were pooled and the pool was used for the studies.

[001141] The time course of C3a production was measured by incubating oligonucleotides at a final concentration of 330 μg/mL or the water control at 37 °C in freshly thawed cynomolgus monkey serum (1:30 ratio, v/v). Specifically, 9.24 μL of 10 mg/mL stock of oligonucleotide in vehicle or vehicle alone was added to 270.76 μL of pooled serum, and the resulting mixtures were incubated at 37 °C. At 0, 5, 10, and 30 minutes, 20-μL aliquots were collected and the reaction was terminated immediately by addition of 2.2 μL of 18 mg/mL EDTA.

[001142] C3a concentrations were measured using MicroVue C3a Plus Enzyme Immunoassays at a 1:3000 dilution. The results were presented as the complement split product concentration increase upon the treatment of pooled serum with oligonucleotides compared with the treatment with the vehicle control.

[001143] PD (Pharmacodynamics) (C9-BAC, icv or Intracerebroventricular injection):

[001144] PD and Efficacy were tested in: C9orf72-BAC (C9-BAC) mouse model:

[001145] The transgenic mice used for in vivo pharmacological studies have been described in O'Rourke et al. 2015 Neuron. 88(5): 892–901. Briefly, the transgenic construct was designed using a bacterial artificial chromosome (BAC) clone derived from fibroblasts of a patient with amyotrophic lateral sclerosis (ALS), carrying the human chromosome 9 open reading frame 72 gene (C9orf72) with a hexanucleotide repeat expansion (GGGGCC) in the intron between the alternatively-spliced non-coding first exons 1a and 1b (variant 3). The BAC isolated a ~166 kbp sequence (~36 kbp human C9orf72 genomic sequence, with ~110 kbp upstream and ~20 kbp downstream sequences). Upon amplification of different BAC subclones, one subclone with a limited contraction to 100-1000 GGGGCC repeats was used. The Tg(C9orf72_3) line 112 mice (JAX Stock No. 023099, Jackson Laboratories, Bar Harbor, Maine) have several tandem copies of the C9orf72_3 transgene, with each copy having between 100-1000 repeats ([GGGGCC]100-1000). However, only mice expressing 500 or more repeats were selected for in vivo studies used herein.

[001146] In vivo procedures:

[001147] For injections of oligonucleotides into the lateral ventricle, mice were anesthetized and placed on a rodent stereotaxic apparatus; they were then implanted with a stainless-steel guide cannula in one of their lateral ventricles (coordinates: -0.3mm posterior, +1.0mm lateral and -2.2mm vertically from bregma), which was secured in place using dental cement. Mice were allowed a one-week recovery

period prior to the injection of compounds. Typical pharmacological studies involved the injection of up to 50μg oligonucleotide in a volume of 2.5μl on day 1, which was followed by another injection of the same amount and volume on day 8. Euthanasia was performed on day 15; the mice were deeply anesthetized with avertin and transcardiacally perfused with saline. Brains were rapidly removed from the skull, one hemisphere was processed for histological analyses, the other hemisphere dissected and frozen on dry ice for biochemical analyses. Similarly, spinal cord was dissected and frozen on dry ice (lumbar) or processed for histological analyses (cervical/thoracic).

[001148] **Efficacy (C9-BAC): foci:**

[001149] Tissue Preparation and Histological Analyses

[001150] Hemibrains and spinal cord were drop-fixed in 4% paraformaldehyde for 24 hours, then transferred to 30% sucrose for 24-48 hours and frozen in liquid nitrogen. Serial sagittal 20-μm thick sections were cut at −18° C. in a cryostat and placed on Superfrost slides.

[001151] **Efficacy (C9-BAC) : PolyGP (DPR assay):**

[001152] Tissue preparation for protein and PolyGP quantification:

[001153] Brain and spinal cord samples were processed using a 2-step extraction procedure; each step was followed by centrifugation at 10,000 rpm for 10 minutes at 4° C. The first step consisted of homogenizing samples in RIPA (50 mM Tris, 150 mM NaCl, 0.5% DOC, 1% NP40, 0.1% SDS and Complete™, pH 8.0). The second step consisted of re-suspension of the pellet in 5M guanidine-HCl.

[001154] PolyGP's were quantified in each pool using a Mesoscale-based assay. Briefly, the polyclonal antibody AB1358 (Millipore, available from Millipore Sigma, Billerica, Ma.) was used as both capture and detection antibody. MULTI-ARRAY 96 Sm Spot Plate Pack, SECTOR Plate was coated with 1 μl of 10 ug/ml purified anti-polyGP antibody (Millipore, AB1358, available from Millipore Sigma, Billerica, Ma.) in PBS directly on small spot overnight at 4 C. After washing 3 times with PBST (0.05% Tween-20 in PBS), the plates were blocked with MSD Blocker A Kit (R93AA-2) or 10% FBS/PBS, at room temperature for 1 hour. Poly-GP purified from HEK-293 cells (by anti-FLAG affinity purification after plasmids transfection, Genescript custom made) were serial diluted with 10% FBS/PBS and used as standard. 25 μl of standard poly-GP and samples (diluted or non-diluted) were added to each well, incubated at room temperature for 1-2 hours. After 3 washes with PBST, sulfo-tagged anti-GP (AB1358) were added 25 μl per well, and incubated at room temperature for another hour. The plates were then washed 3 times, 150 μl/well of MSD Read Buffer T (1x) (R92TC-2, MSD) was added to each well and read by MSD (MESO QUICKPLEX SQ 120) according to manufacturer's default setting.

[001155] Expression of C9orf72 protein was determined by western blotting. Briefly, proteins from RIPA extracts were size fractionated by 4-12% SDS-PAGE (Criterion gel, Bio-Rad) and transferred onto

PVDF membrane. To detect C9orf72, the membrane was immunoblotted using the mouse monoclonal anti-C9orf72 antibody GT779 (1:2000; GeneTex, Irvine, California), followed by secondary DyLight conjugated antibody. Visualization was conducted using the Odyssey/Li-Cor imaging system.

Some additional abbreviations:
Cx: Cortex
HP: Hippocampus
KD: knockdown
SC: Spinal Cord
Str: Striatum

Table 7A.1. Activity of various C9orf72 oligonucleotides.

Assay	**End-points**	**Selec-tion Cri-teria**	**WV-6408**	**WV-3688**	**WV-7121**	**WV-7122**	**WV-7123**	**WV-7124**	**WV-7125**	**WV-7126**
Reporter	IC_{50} (nM)	< 5 nM	1.32 / 2.63	5.56 / 8.65	3.11	2.08	3.16	6.95	4.39	3.481
ALS neurons	V3/ intron	50% KD	66 / 0	50 / 23	38% / 44%	63% / 88%	47% / 42%	55% / 75%	31% / 60%	35% / 64% (Foci KD)
Stability	Ms brain	80% at Day 5	100	63.2	1.81	0.95	2.23	2.63	90.3	92.5
TLR9	Human	Clean	clean	clean	clean	clean	clean	1.3 fold	clean	1.3 fold
Comple-ment	panel	Clean								
PD (C9-BAC, icv)	V3/ intron	50% KD in relevant brain regions	KD in HP, Str and SC	Trends in HP, Str. and SC	N/A	N/A	N/A	KD in SC, not cortex	N/A	

Table 7A.2. Activity of various C9orf72 oligonucleotides.

Assay	End-points	Selec-tion Criteria	WV-6408	WV-3688	WV-7127	WV-7128	WV-7129	WV-7130	WV-7131	WV-7132
Reporter	IC_{50} (nM)	< 5 nM	1.32 / 2.63	5.56 / 8.65	2.45	2.71	2.27	2.8	2.04	1.91
ALS neurons	V3/ intron	50% KD	59% / 65%	55% / 79%	0% / 22%	13% / 45%	28% / 66%	11% / 55%	0% / 24%	30% / 70%
Stability	Ms brain	80% at Day 5	100	63.2	100	100	100	90.7	100	100
TLR9	Human	Clean	clean	clean	clean	clean	clean	clean	clean	1.3 fold

Comple-ment	panel	Clean								
PD (C9-BAC, icv)	V3/ intron	50% KD in relevant brain regions	KD in HP, Str and SC	Trends in HP, Str. and SC	N/A	N/A		KD in SC, not cortex	N/A	N/A
Efficacy (C9-BAC)	• foci • Poly GP	50% KD 50% KD	•YES •	YES						

Table 7B. Activity of various C9orf72 oligonucleotides.

Assay	**End-points**	**WV-7603**	**WV-7604**	**WV-7605**	**WV-7606**	**WV-7601**	**WV-7657**	**WV-7658**	**WV-7659**	**WV-7774**	**WV-7775**
Report-er	IC_{50} (nM)	1.8	1.6	1.3	1.2	2.4	1.3	0.28	0.20	1.1	1.6
ALS neurons	V3/ intron	55 / 33	60 / 67	64 / 41	72 / 48	73 / 72	60 / 48	68 / 67	69 / 57		
Stabi-lity	Ms brain	100	100	100	100	88	72	82	100	100	100
TLR9	Human	clean	clean	clean	clean	clean	clean	clean	clean	5-fold	clean
PD (C9-BAC, icv)	V3/intro n	N/A		N/A	N/A	Trend for KD in Cx, KD in Spinal Cord	Trend for KD in Cx, KD in Spinal Cord	Trend for KD in Cx, KD in Spinal Cord	Trend for KD in Cx, KD in Spinal Cord	N/A	

Table 7C. Activity of various C9orf72 oligonucleotides.

Assay	Endpoints	WV-6408	WV-3688	WV-8005	WV-8006	WV-8007	WV-8008	WV-8009	WV-8010	WV-8011	WV-8012
Reporter	IC_{50} (nM)	1.32 / 2.63	5.56 / 8.65	0.5	0.5	0.4	0.3	0.5	0.4	0.4	0.2
ALS neurons	V3/intron	66 / 0	50 / 23	87 / 53	84 / 52	94 / 52	95 / 46	87 / 41	87 / 61	94 / 35	95 / 22
Stability	Ms brain	100	63.2	72	88	77	77	93	92	22?	77
TLR9	Human	clean	clean	clean	clean	clean	clean	clean	clean	clean	clean
PD (C9-BAC, icv)	V3/ intron	20 / 30	Trends in HP, Str. and SC					38 / 39	28 / 43	61 / 77	59 / 73
Efficacy (C9-BAC)	foci DPR	TBD 25 %						TBD 37 %	TBD 11 %	TBD 56 %	TBD 69 %

Table 7D. Activity of various C9orf72 oligonucleotides.

Assay	Endpoints	WV-6408	WV-3688	WV-8321	WV-8322	WV-8329	WV-8454	WV-8455
Reporter	**IC_{50} (nM)**	1.32 / 2.63	5.56 / 8.65					
ALS neurons	**V3/intron**	66 / 0	50 / 23					
Stability	**Ms brain**	100	63.2	100	100			
TLR9	**Human**	clean	clean					
PD (C9-BAC, icv)	**V3/intron**	KD in HP, Str and SC	Trends in HP, Str. and SC					

TBD, to be determined.

Table 8. Activity of various c9orf72 oligonucleotides.

In Table 8A to 8X, various c9orf72 oligonucleotides were tested at 10 μM in ALS motor neurons (MN). The oligonucleotides differ, inter alia, in base sequence, chemistry pattern (e.g., pattern of 2' sugar modifications), backbone internucleotidic linkage pattern and/or pattern of stereochemistry. In Tables 8A to 8X, shown are residual levels of various c9orf72 transcripts (e.g., all transcripts, or only V3, V1, intron 1, etc.) relative to HPRT1, after treatment with c9orf72 oligonucleotides, wherein 1.000 would represent 100% relative transcript level (no knockdown) and 0.000 would represent 0% relative transcript level (e.g., 100% knockdown). In Tables 8A to 8X, results from replicate experiments are shown.

Table 8A. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

WV-3688	0.619	0.817	0.806
WV-7124	0.800	0.641	0.711
WV-6408	0.646	0.574	0.582
WV-7130	0.344	0.321	1.070
WV-8550	0.310	0.253	0.316
WV-8011	0.113	0.144	0.111
WV-8012	0.157	0.185	0.153
WV-2376	1.188	1.108	1.180
WV-9491	1.034	1.027	1.108
WV-5302	1.140	1.101	1.078
WV-6493	1.056	1.049	1.063
WV-8552	1.300	1.140	0.932
water	0.834	1.041	0.985

Table 8B. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts)

WV-3688	0.845	0.881	0.862
WV-7124	0.799	0.845	0.893
WV-6408	0.810	0.751	0.767
WV-7130	0.788	0.542	
WV-8550	0.686	0.538	0.667
WV-8011	0.440	0.446	0.495
WV-8012	0.597	0.509	0.565
WV-2376	1.092	1.012	0.944
WV-9491	1.245	1.146	1.069
WV-5302	1.170	0.839	1.077
WV-6493	1.115	0.868	0.991
WV-8552	1.092	0.875	1.122

water	1.122	0.950	1.122

Table 8C. Activity of various c9orf72 oligonucleotides (residual level of V1 C9orf72 transcripts)

WV-3688	0.901	0.829	0.655
WV-7124	0.594	0.829	0.702
WV-6408	0.784	0.732	0.888
WV-7130	0.476	0.539	0.972
WV-8550	0.379	0.341	0.466
WV-8011	0.207	0.279	0.216
WV-8012	0.250	0.241	0.291
WV-2376	0.993	0.864	0.920
WV-9491	1.156	0.946	1.049
WV-5302	0.920	1.101	0.933
WV-6493	1.056	0.858	1.071
WV-8552	0.901	1.148	1.140
Water	1.197	0.846	0.999

Table 8D. Activity of various c9orf72 oligonucleotides (residual level of intron 1 C9orf72 transcripts)

WV-3688		0.538	0.685
WV-7124		0.681	0.538
WV-6408	0.516	0.408	0.509
WV-7130	0.399	0.523	
WV-8550	0.443	0.350	0.298
WV-8011	0.336	0.378	0.434
WV-8012	0.446	0.446	0.475
WV-2376	0.685	0.681	0.714
WV-9491	0.880	0.923	1.261
WV-5302	0.745	1.510	1.091
WV-6493	0.826	0.997	1.017
WV-8552	1.210	0.963	1.010
Water	1.315	1.193	0.990

Table 8E. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

WV-3688	0.619	0.817	0.806
WV-6408	0.646	0.574	0.582
WV-8550	0.310	0.253	0.316
WV-3662	0.105	0.121	0.119

WV-7188	0.065	0.074	0.062
WV-9494	0.009	0.006	0.009
WV-6936	0.795	0.972	0.800
WV-7027	0.741	0.882	0.900
WV-8595	0.926	0.741	0.919
WV-2376	1.188	1.108	1.180
WV-9491	1.034	1.027	1.108
WV-5302	1.140	1.101	1.078
Water	0.834	1.041	0.985

Table 8F. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts)

WV-3688	0.845	0.881	0.862
WV-6408	0.810	0.751	0.767
WV-8550	0.686	0.538	0.667
WV-3662	0.160	0.155	0.145
WV-7188	0.116	0.116	0.108
WV-9494	0.013	0.010	0.012
WV-6936	1.099	1.084	0.957
WV-7027	1.040	0.991	0.931
WV-8595	1.280	1.005	1.186
WV-2376	1.092	1.012	0.944
WV-9491	1.245	1.146	1.069
WV-5302	1.170	0.839	1.077
water	1.122	0.950	1.122

Table 8G. Activity of various c9orf72 oligonucleotides (residual level of V1 C9orf72 transcripts)

WV-3688	0.901	0.829	0.655
WV-6408	0.784	0.732	0.888
WV-8550	0.379	0.341	0.466
WV-3662	0.185	0.099	0.182
WV-7188	0.114	0.128	0.106
WV-9494	0.023	0.018	0.026
WV-6936	0.913	0.939	0.907
WV-7027	0.702	0.757	0.926
WV-8595	0.952	0.959	0.959
WV-2376	0.993	0.864	0.920
WV-9491	1.156	0.946	1.049
WV-5302	0.920	1.101	0.933
Water	1.197	0.846	0.999

Table 8H. Activity of various c9orf72 oligonucleotides (residual level of intron 1 C9orf72 transcripts)

WV-3688		0.538	0.685
WV-6408	0.516	0.408	0.509
WV-8550	0.443	0.350	0.298
WV-3662		0.700	0.576
WV-7188	0.787	0.455	0.527
WV-9494	0.534	0.302	0.512
WV-6936	0.676	0.815	0.930
WV-7027	1.500	0.936	0.976
WV-8595	0.983	1.361	0.930
WV-2376	0.685	0.681	0.714
WV-9491	0.880	0.923	1.261
WV-5302	0.745	1.510	1.091
Water	1.315	1.193	0.990

Table 8I. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

WV-8550	0.310	0.253	0.316
WV-8011	0.113	0.144	0.111
WV-8012	0.157	0.185	0.153
WV-9493	1.013	0.978	1.034
WV-9492	0.784	0.811	0.741
WV-3536	0.789	0.510	0.678
WV-2376	1.188	1.108	1.180
Water	0.834	1.041	0.985

Table 8J. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts)

WV-8550	0.686	0.538	0.667
WV-8011	0.440	0.446	0.495
WV-8012	0.597	0.509	0.565
WV-9493	1.122	1.084	1.069
WV-9492	1.107	0.816	0.924
WV-3536	0.991	0.783	0.977
WV-2376	1.092	1.012	0.944
water	1.122	0.950	1.122

Table 8K. Activity of various c9orf72 oligonucleotides (residual level of V1 C9orf72 transcripts)

WV-8550	0.379	0.341	0.466

WV-8011	0.207	0.279	0.216
WV-8012	0.250	0.241	0.291
WV-9493	0.933	0.979	0.952
WV-9492	0.712	0.737	0.858
WV-3536	0.687	0.493	0.598
WV-2376	0.993	0.864	0.920
Water	1.197	0.846	0.999

Table 8L. Activity of various c9orf72 oligonucleotides (residual level of intron 1 C9orf72 transcripts)

WV-8550	0.443	0.350	0.298
WV-8011	0.336	0.378	0.434
WV-8012	0.446	0.446	0.475
WV-9493	0.917	0.838	0.917
WV-9492	1.075	0.714	
WV-3536	0.710	0.969	1.061
WV-2376	0.685	0.681	0.714
Water	1.315	1.193	0.990

Table 8M. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

WV-3688	0.751	0.677	0.573
WV-7124	0.546	0.482	0.799
WV-6408	0.649	0.593	0.573
WV-7130	0.365	0.343	0.389
WV-8550	0.297	0.286	0.260
WV-8011	0.135	0.123	0.097
WV-8012	0.111	0.162	0.106
WV-2376	0.833	1.033	1.092
WV-3542	0.977	1.069	0.970
WV-9491	1.047	0.899	1.011
WV-5302	1.011	0.944	1.162
WV-6493	0.984	1.099	1.502
WV-8552	1.146	1.077	0.991
water	0.899	1.122	1.122

Table 8N. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts)

WV-3688	0.940	0.847	0.813
WV-7124	0.737	0.764	1.022

WV-6408	0.774	0.717	0.646
WV-7130	0.591	0.559	0.525
WV-8550	0.567	0.536	0.555
WV-8011	0.451	0.421	0.421
WV-8012	0.451	0.429	0.470
WV-2376	1.182	1.029	1.058
WV-3542	0.966	0.902	0.871
WV-9491	1.087	0.973	0.933
WV-5302	0.902	0.966	0.980
WV-6493	1.043	0.966	0.947
WV-8552	1.149	1.087	0.947
water	0.895	1.029	0.987

Table 8O. Activity of various c9orf72 oligonucleotides (residual level of V1 C9orf72 transcripts)

WV-3688	0.846	0.920	0.858
WV-7124	0.829	0.779	1.064
WV-6408	0.946	0.801	0.790
WV-7130	0.758	0.664	0.582
WV-8550	0.562	0.426	0.384
WV-8011	0.213	0.235	0.272
WV-8012	0.368	0.283	0.351
WV-2376	1.086	0.835	0.858
WV-3542	0.846	1.101	0.972
WV-9491	0.939	1.140	0.779
WV-5302	0.979	1.035	1.274
WV-6493	1.181	1.035	0.993
WV-8552	1.214	0.966	0.926
water	1.079	0.870	0.889

Table 8P. Activity of various c9orf72 oligonucleotides (residual level of intron 1 C9orf72 transcripts)

WV-3688	0.324	0.481	0.626
WV-7124	0.734	0.354	0.181
WV-6408	0.261	0.340	0.548
WV-7130	0.452	0.288	0.449
WV-8550	0.484	0.382	0.424
WV-8011	0.391	0.296	
WV-8012	0.461	0.508	0.375

WV-2376		1.038	1.269
WV-3542	1.184	0.879	0.600
WV-9491	1.060	1.023	1.674
WV-5302	1.217	1.295	1.097
WV-6493	1.136	1.418	
WV-8552	1.128	1.332	0.776
water	0.968	0.903	0.685

Table 8Q. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

WV-3688	0.751	0.677	0.573
WV-6408	0.649	0.593	0.573
WV-8550	0.297	0.286	0.260
WV-3662	0.267	0.216	0.248
WV-7118	0.311	0.219	0.249
WV-9494	0.031	0.043	0.042
WV-6936	0.827	0.874	0.667
WV-7027	0.868	0.788	0.874
WV-8595	0.725	0.681	0.822
WV-2376	0.833	1.033	1.092
WV-3542	0.977	1.069	0.970
WV-9491	1.047	0.899	1.011
water	0.899	1.122	1.122

Table 8R. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts)

WV-3688	0.940	0.847	0.813
WV-6408	0.774	0.717	0.646
WV-8550	0.567	0.536	0.555
WV-3662	0.261	0.235	0.238
WV-7118	0.276	0.263	0.291
WV-9494	0.046	0.043	0.047
WV-6936	1.014	1.007	1.007
WV-7027	1.065	0.966	0.947
WV-8595	0.994	0.818	0.830
WV-2376	1.182	1.029	1.058
WV-3542	0.966	0.902	0.871
WV-9491	1.087	0.973	0.933
water	0.895	1.029	0.987

Table 8S. Activity of various c9orf72 oligonucleotides (residual level of V1 C9orf72 transcripts)

WV-3688	0.846	0.920	0.858
WV-6408	0.946	0.801	0.790
WV-8550	0.562	0.426	0.384
WV-3662	0.299	0.272	0.381
WV-7118	0.387	0.358	0.325
WV-9494	0.065	0.050	0.063
WV-6936	0.712	0.966	1.035
WV-7027	0.959	0.952	1.049
WV-8595	0.742	0.790	0.841
WV-2376	1.086	0.835	0.858
WV-3542	0.846	1.101	0.972
WV-9491	0.939	1.140	0.779
water	1.079	0.870	0.889

Table 8T. Activity of various c9orf72 oligonucleotides (residual level of intron 1 C9orf72 transcripts)

WV-3688	0.324	0.481	0.626
WV-6408	0.261	0.340	0.548
WV-8550	0.484	0.382	0.424
WV-3662	0.995	0.831	0.891
WV-7118	0.596	0.724	0.584
WV-9494	0.699	0.455	0.556
WV-6936		1.144	0.948
WV-7027	0.729	1.176	1.260
WV-8595	1.045	0.837	1.209
WV-2376		1.038	1.269
WV-3542	1.184	0.879	0.600
WV-9491	1.060	1.023	
water	0.968	0.903	0.685

Table 8U. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

WV-8550	0.297	0.286	0.260
WV-8011	0.135	0.123	0.097
WV-8012	0.111	0.162	0.106
WV-9493	0.761	0.705	0.649
WV-9492	0.506	0.520	0.478
WV-3536	0.663	0.606	0.805
WV-2376	0.833	1.033	1.092

water	0.899	1.122	1.122

Table 8V. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts)

WV-8550	0.567	0.536	0.555
WV-8011	0.451	0.421	0.421
WV-8012	0.451	0.429	0.470
WV-9493	1.014	0.824	0.807
WV-9492	0.859	0.818	0.801
WV-3536	0.830	0.790	1.126
WV-2376	1.182	1.029	1.058
water	0.895	1.029	0.987

Table 8W. Activity of various c9orf72 oligonucleotides (residual level of V1 C9orf72 transcripts)

WV-8550	0.562	0.426	0.384
WV-8011	0.213	0.235	0.272
WV-8012	0.368	0.283	0.351
WV-9493	1.049	0.870	0.586
WV-9492	0.993	0.795	0.758
WV-3536	0.683	0.697	1.021
WV-2376	1.086	0.835	0.858
water	1.079	0.870	0.889

Table 8X. Activity of various c9orf72 oligonucleotides (residual level of intron 1 C9orf72 transcripts)

WV-8550	0.484	0.382	0.424
WV-8011	0.391	0.296	0.781
WV-8012	0.461	0.508	0.375
WV-9493	0.391	0.942	0.724
WV-9492	0.481	0.989	0.942
WV-3536	0.729	0.948	0.580
WV-2376		1.038	1.269
water	0.968	0.903	0.685

Table 9. Activity of various c9orf72 oligonucleotides.

In Tables 9A to 9D, various c9orf72 oligonucleotides were tested at 1 μM in ALS motor neurons (MN). The oligonucleotides differ, inter alia, in base sequence, chemistry pattern (e.g., pattern of 2' sugar modifications), backbone internucleotidic linkage pattern and/or pattern of stereochemistry. In Tables 9A

to 9D, shown are residual levels of various c9orf72 transcripts (e.g., all transcripts, or only V3, V1, intron 1, etc.) relative to HPRT1, after treatment with c9orf72 oligonucleotides, wherein 1.000 would represent 100% relative transcript level (no knockdown) and 0.000 would represent 0% relative transcript level (e.g., 100% knockdown). In Tables 9A to 9D, results from replicate experiments are shown.

Table 9A. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

WV-8550	0.557	0.672
WV-8011	0.389	0.417
WV-9505	0.370	0.378
WV-9506	0.465	0.446
WV-9507	0.799	0.822
WV-9508	0.502	0.478
WV-9509	0.428	0.397
WV-9510	0.589	0.478
WV-2376	1.047	1.018
water	0.899	1.122

Table 9B. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts)

WV-8550	0.683	0.790
WV-8011	0.571	0.567
WV-9505	0.651	0.651
WV-9506	0.824	0.743
WV-9507	0.835	0.847
WV-9508	0.717	0.679
WV-9509	0.703	0.688
WV-9510	0.801	0.830
WV-2376	1.198	1.149
water	0.895	1.029

Table 9C. Activity of various c9orf72 oligonucleotides (residual level of V1 C9orf72 transcripts)

WV-8550	0.758	0.979
WV-8011	1.000	0.818
WV-9505	0.702	0.603
WV-9506	0.476	0.972
WV-9507	0.993	1.265
WV-9508	0.870	0.926
WV-9509	0.907	0.806
WV-9510	1.109	1.049

WV-2376	1.301	1.310
water	1.079	0.870

Table 9D. Activity of various c9orf72 oligonucleotides (residual level of intron 1 C9orf72 transcripts)

WV-8550	0.781	0.533
WV-8011	1.002	0.600
WV-9505	1.009	0.916
WV-9506	0.910	0.765
WV-9507	0.634	0.843
WV-9508	0.724	0.657
WV-9509	0.512	0.873
WV-9510	0.245	1.045
WV-2376	1.128	1.226
water	0.968	0.903

Table 10. Activity of various c9orf72 oligonucleotides.

In Tables 10A to 10B, various c9orf72 oligonucleotides were tested at various concentrations from 0.01 to 10 μM in ALS motor neurons (MN). The oligonucleotides differ, inter alia, in backbone internucleotidic linkage pattern and/or pattern of stereochemistry. In the DNA core, various oligonucleotides comprise one or two SSO [5'-PS (Phosphorothioate) in the Sp configuration, PS in the Sp configuration, PO (Phophodiester)-3'] or one or two SSR [5'-PS (Phosphorothioate) in the Sp configuration, PS in the Sp configuration, PS in the Rp configuration-3']. In Tables 10A to 10B, shown are residual levels of various c9orf72 transcripts (e.g., all transcripts, or only V3), relative to HPRT1, after treatment with c9orf72 oligonucleotides, wherein 1.000 would represent 100% relative transcript level (no knockdown) and 0.000 would represent 0% relative transcript level (e.g., 100% knockdown). In Tables 10A to 10B, results from replicate experiments are shown.

Table 10A. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts)

	WV-8011	WV-9394	WV-8012	WV-9395
	0.617	0.621	0.639	0.680
10uM	0.613	0.643	0.617	0.760
	0.724	0.724	0.739	0.754
2.5uM	0.699	0.704	0.680	0.849
	0.843	0.855	0.814	0.897
0.625uM	0.792	0.855	0.831	0.897

	0.891	0.897	0.849	0.948
0.16uM	0.982	0.968	0.922	0.879
	1.038	1.097	1.009	0.962
0.04uM	1.082	0.975	0.942	1.082
	1.002	1.024	1.009	1.002
0.01uM	0.935	0.948	0.922	0.955

Table 10B. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

	WV-8011	WV-9394	WV-8012	WV-9395
	0.023	0.042	0.026	0.026
10uM	0.033	0.032	0.023	0.025
	0.061	0.072	0.049	0.061
2.5uM	0.050	0.055	0.060	
	0.125	0.147	0.133	0.130
0.625uM	0.152	0.146	0.139	0.169
	0.266	0.318	0.227	0.291
0.16uM	0.236	0.310	0.277	0.332
	0.726	0.668	0.578	0.687
0.04uM	0.711	0.628	0.444	0.906
	0.992	0.932	0.817	0.992
0.01uM	0.888	0.978	0.932	0.900

Table 11. Activity of various c9orf72 oligonucleotides.

In Tables 11A and 11B, various c9orf72 oligonucleotides were tested at 10 μM in ALS motor neurons (MN). The oligonucleotides differ, inter alia, in base sequence, pattern of internucleotidic linkages, and pattern of chemistry (e.g., pattern of 2'-modifications of sugars), wherein some oligonucleotides have a symmetric (e.g., Table 11B) and some have an asymmetric format (e.g., Table 11A). In Tables 11A and 11B, shown are residual levels of V3 c9orf72 transcript relative to HPRT1, after treatment with c9orf72 oligonucleotides, wherein 1.000 would represent 100% relative transcript level (no knockdown) and 0.000 would represent 0% relative transcript level (e.g., 100% knockdown). In Tables 11A and 11B, results from replicate experiments are shown. In this and other tables, all positive and negative controls performed in various experiments are not necessarily shown.

Table 11A. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

WV-10406	0.250	0.267	0.264
WV-10407	0.301	0.314	0.297
WV-10408	0.201	0.211	0.228

WV-10409	0.301	0.314	0.279
WV-10410	0.301	0.363	0.287
WV-10411	0.381	0.332	0.325
WV-10412	0.368	0.414	0.400
WV-10413	0.492	0.428	0.459
WV-10414	0.341	0.358	0.437
WV-10415	0.160	0.239	0.231
WV-10416	0.239	0.239	0.214
WV-8550	0.173	0.184	0.200
WV-10417	0.309	0.479	0.411
WV-10418	0.198	0.279	0.244
WV-10419	0.314	0.420	0.332
WV-10420	0.453	0.517	0.546
WV-10421	0.447	0.658	0.539
WV-10422	0.485	0.444	0.577
WV-10423	0.573	0.602	0.479
WV-10424	0.711	0.741	0.811
WV-10425	0.558	0.341	0.403
WV-9491	0.984	1.107	1.317
WV-3662	0.047	0.051	0.058
WV-10426	0.531		1.005

Table 11B. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

WV-6936	0.517	0.420	0.502
WV-6989	0.746	0.828	0.767
WV-7002	0.691	0.726	0.598
WV-6474	0.649	0.778	0.716
WV-3688	0.581	0.606	0.593
WV-6969		0.677	0.558
WV-6951	0.672	0.636	0.731
WV-3690	0.767	0.736	0.677
WV-6952	0.857	0.799	0.731
WV-6976	0.658	0.558	0.645
WV-6981	0.686	0.731	0.663
WV-6982	0.863	0.751	0.658
WV-9694	0.610	0.663	0.645
WV-9695	0.663	0.636	0.585
WV-3662	0.043	0.038	0.029
WV-2376	0.899	1.040	0.822

Table 12. Activity of various c9orf72 oligonucleotides.

In Tables 12A and 12B, various c9orf72 oligonucleotides were tested at 2.5 or 10 μM in ALS motor neurons (MN). The oligonucleotides differ, inter alia, in base sequence, pattern of internucleotidic linkages, and pattern of chemistry (e.g., pattern of 2'-modifications of sugars), wherein some oligonucleotides have a symmetric and some have an asymmetric format. In Tables 12A and 12B, shown are residual levels of V3 or all V c9orf72 transcript relative to HPRT1, after treatment with c9orf72 oligonucleotides, wherein 1.000 would represent 100% relative transcript level (no knockdown) and 0.000 would represent 0% relative transcript level (e.g., 100% knockdown). In Tables 12A and 12B, results from replicate experiments are shown. In this and other tables, all positive and negative controls performed in various experiments are not necessarily shown.

Table 12A. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

WV-6408 (10uM)	0.564	0.740	0.714
WV-6408 (2.5uM)	0.700	0.745	0.657
WV-12480 (10uM)	0.936	1.024	0.880
WV-12480 (2.5uM)	0.956	0.873	0.798
WV-12481 (10uM)	0.541	0.667	0.657
WV-12481 (2.5uM)	0.676	0.626	0.676
WV-12482 (10uM)	0.378	0.407	0.357
WV-12482 (2.5uM)	0.431	0.462	0.475
WV-12483 (10uM)	0.446	0.458	0.458
WV-12483 (2.5uM)	0.530	0.478	0.505
WV-12484 (10uM)	0.580	0.667	0.705
WV-12484 (2.5uM)	0.530	0.662	0.714
WV-12486 (10uM)	0.527	0.597	0.657
WV-12486 (2.5uM)	0.538	0.719	0.667
WV-8548 (10uM)	0.372	0.383	0.367
WV-8548 (2.5uM)	0.523	0.509	0.516
WV-12439 (10uM)	0.419	0.549	0.446
WV-12439 (2.5uM)	0.755	0.609	0.478
WV-12440 (10uM)	0.352	0.485	0.462
WV-12440 (2.5uM)	0.635	0.485	0.588
WV-12441 (10uM)		0.246	0.261
WV-12441 (2.5uM)	0.434	0.360	0.357
WV-12442 (10uM)	0.861		0.505
WV-12442 (2.5uM)	0.671	0.553	

WV-12443 (10uM)			
WV-12443 (2.5uM)	0.481	0.613	0.315
WV-12444 (10uM)	0.251	0.391	0.367
WV-12444 (2.5uM)		0.471	0.561
WV-12446 (10uM)	0.481	0.495	0.564
WV-12446 (2.5uM)		0.644	0.850
WV-12445 (10uM)	0.657	0.605	0.588
WV-12445 (2.5uM)		0.662	0.880
WV-12447 (10uM)	0.286	0.491	0.329
WV-12447 (2.5uM)		0.618	0.564
WV-12448 (10uM)	0.191	0.320	0.214
WV-12448 (2.5uM)		0.468	0.440
WV-12449 (10uM)	0.505	0.465	
WV-12449 (2.5uM)		0.597	0.478
WV-12450 (10uM)			
WV-12450 (2.5uM)	0.491	0.534	0.553
WV-12451 (10uM)	0.443	0.458	0.462
WV-12451 (2.5uM)	0.545	0.452	0.502
WV-8550 (10uM)	0.273	0.298	0.278
WV-8550 (2.5uM)	0.478	0.488	0.440
WV-9491 (10uM)	0.635	1.053	1.010
WV-9491 (2.5uM)	1.106	0.815	0.850
WV-3542 (10uM)	0.962	1.053	1.061
WV-3542 (2.5uM)	1.113	0.983	1.039

Table 12B. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts)

WV-6408 (10uM)	0.861	0.843	0.861
WV-6408 (2.5uM)	0.861	0.949	0.861
WV-12480 (10uM)	0.982	0.982	0.969
WV-12480 (2.5uM)	0.923	0.910	0.956
WV-12481 (10uM)	0.838	0.832	0.809
WV-12481 (2.5uM)	0.838	0.820	0.867
WV-12482 (10uM)	0.714	0.714	0.653
WV-12482 (2.5uM)	0.699	0.744	0.734
WV-12483 (10uM)	0.976	0.936	0.936
WV-12483 (2.5uM)	0.820	0.861	0.917
WV-12484 (10uM)	0.996	0.969	0.976
WV-12484 (2.5uM)	0.929	0.923	0.982
WV-12486 (10uM)	0.760	0.820	0.724

WV-12486 (2.5uM)	0.782	0.843	0.832
WV-8548 (10uM)	0.729	0.760	0.771
WV-8548 (2.5uM)	0.771	0.826	0.798
WV-12439 (10uM)	0.898	0.873	0.855
WV-12439 (2.5uM)	0.949	0.873	0.820
WV-12440 (10uM)	0.803	0.809	0.771
WV-12440 (2.5uM)	0.849	0.792	0.771
WV-12441 (10uM)	0.431	0.657	0.685
WV-12441 (2.5uM)	0.657	0.719	0.695
WV-12442 (10uM)	0.976	0.861	0.996
WV-12442 (2.5uM)	0.929	0.461	0.495
WV-12443 (10uM)	0.923	0.798	0.996
WV-12443 (2.5uM)	0.484	0.879	0.601
WV-12444 (10uM)	0.653	0.680	0.666
WV-12444 (2.5uM)		0.734	0.792
WV-12446 (10uM)	0.820	0.849	0.849
WV-12446 (2.5uM)		0.838	0.898
WV-12445 (10uM)	0.861	0.849	0.855
WV-12445 (2.5uM)		0.898	0.898
WV-12447 (10uM)	0.744	0.755	0.739
WV-12447 (2.5uM)		0.782	0.798
WV-12448 (10uM)	0.704	0.699	0.662
WV-12448 (2.5uM)		0.792	0.776
WV-12449 (10uM)	1.098	0.676	0.443
WV-12449 (2.5uM)		0.873	0.861
WV-12450 (10uM)	0.580	0.695	0.704
WV-12450 (2.5uM)	0.917	0.923	0.996
WV-12451 (10uM)	0.832	0.885	0.820
WV-12451 (2.5uM)	0.861	0.792	0.867
WV-8550 (10uM)	0.724	0.739	0.771
WV-8550 (2.5uM)	0.803	0.815	0.873
WV-9491 (10uM)	0.982	0.969	1.060
WV-9491 (2.5uM)	0.962	0.996	1.053
WV-3542 (10uM)	1.017	1.038	1.024
WV-3542 (2.5uM)	1.031	0.879	0.949

Table 13. Activity of various c9orf72 oligonucleotides.

In Tables 13A to 13F, various c9orf72 oligonucleotides were tested in c9 BAC mice; mice were administered c9orf72 oligonucleotides ICV in two doses, each 50 μg, one week apart, and tissue was

collected a week after the second dose. The oligonucleotides differ, inter alia, in base sequence, pattern of internucleotidic linkages, and pattern of chemistry (e.g., pattern of 2'-modifications of sugars), wherein some oligonucleotides have a symmetric and some have an asymmetric format. In Tables 13A to 13F, shown are residual levels of c9orf72 transcriptions [e.g., all transcripts (all V) or only V3] relative to HPRT1, after treatment with c9orf72 oligonucleotides, wherein 1.000 would represent 100% relative transcript level (no knockdown) and 0.000 would represent 0% relative transcript level (e.g., 100% knockdown). Results from replicate experiments are shown. Tissues evaluated: SC, spinal cord; and CX, cerebral cortex.

Table 13A. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts in CX)

PBS	WV-8548	WV-12482	WV-12483	WV-12444	WV-12448
1.011	0.798	0.676	0.735	0.705	0.523
0.862	1.011	0.553	0.787	0.963	0.530
1.032	0.969	0.745	0.725	0.950	0.549
1.091	0.976	0.720	0.777	0.997	0.827
1.039	0.950	0.750	0.844	0.844	0.715
0.997	0.838	0.868	0.740	0.917	0.976
0.856	0.771	0.333	0.761	0.844	0.662
1.114	0.850	0.750	0.671	0.705	0.690

Table 13B. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts in CX)

PBS	WV-8548	WV-12482	WV-12483	WV-12444	WV-12448
0.935	0.754	0.708	0.684	0.739	0.439
0.897	1.089	0.537	0.643	0.968	0.556
1.002	0.891	0.666	0.670	1.059	0.413
1.009	0.928	0.704	0.781	1.009	0.775
0.968	0.981	0.792	0.497	0.837	0.643
1.167	0.749	0.928	0.568	0.848	1.030
0.872	0.533	0.229	0.814	0.803	0.759
1.151	0.968	0.968	0.694	0.575	0.808

Table 13C. Activity of various c9orf72 oligonucleotides (residual level of intron 1/AS C9orf72 transcripts in CX)

PBS	WV-8548	WV-12482	WV-12483	WV-12444	WV-12448

0.426	1.124	1.248	0.619	2.712	1.256
0.441	0.840	1.944	2.113	2.344	2.280
0.852	0.846		3.072	0.993	2.377
1.213	0.646		3.137	0.888	
1.433	0.325		3.704	1.109	2.693
1.230		1.453	3.247		1.568
	1.180	0.673			1.740
1.404	1.827	0.301	1.931	2.218	0.864

Table 13D. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts in SC)

PBS	WV-8548	WV-12482	WV-12483	WV-12444	WV-12448
1.635	0.747	0.692	0.603	0.528	0.747
0.999	1.042	0.747	1.504	0.673	0.507
1.525	0.768	0.692	0.536	0.779	0.659
0.742	0.835	0.721	0.598	0.806	0.727
0.779	0.717	0.603	0.632	0.551	0.712
0.678	1.172	0.615	1.515	0.574	0.517
0.697	0.727	0.795	0.558	0.574	0.586
0.945	0.939	0.578	0.582	0.795	0.558

Table 13E. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts in SC)

PBS	WV-8548	WV-12482	WV-12483	WV-12444	WV-12448
1.325	0.681	0.686	0.465	0.513	0.805
1.122	1.307	0.735	0.816	0.746	0.355
1.382	0.725	0.827	0.408	0.905	0.725
0.788	0.772	0.799	0.389	0.856	0.475
0.874	0.499	0.672	0.416	0.557	0.833
0.761	0.887	0.527	0.931	0.550	0.309
0.777	0.715	1.069	0.443	0.557	0.301
0.970	0.950	0.431	0.482	0.816	0.499

Table 13F. Activity of various c9orf72 oligonucleotides (residual level of intron 1/AS C9orf72 transcripts in SC)

PBS	WV-8548	WV-12482	WV-12483	WV-12444	WV-12448
1.812	0.054	1.070	0.065	0.070	0.869
1.942	1.545	0.998		0.241	0.074

	0.055	1.163	0.258	0.131	0.438
0.528	0.075	1.503	0.281	0.072	0.721
0.789	0.149	0.124	0.381	0.099	0.091
0.701	2.293	0.015		0.057	0.058
0.757	0.450	0.206	0.129	0.358	0.016
0.472		0.027	0.287		0.021

Table 14. Activity of various c9orf72 oligonucleotides.

In Tables 14A to 14B, various c9orf72 oligonucleotides were tested in motor neurons, with oligonucleotides delivered gymnotically at concentrations from 0.003 to 10 μM (Concentrations are provided as exp10). Tested c9orf72 oligonucleotide WV-11532 comprises three neutral internucleotidic linkages. In Tables 14A and 14B, shown are residual levels of c9orf72 transcriptions [e.g., all transcripts (all V) or only V3] relative to HPRT1, after treatment with c9orf72 oligonucleotides, wherein 1.000 would represent 100% relative transcript level (no knockdown) and 0.000 would represent 0% relative transcript level (e.g., 100% knockdown). Results from replicate experiments are shown.

Table 14A. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts)

Conc.	WV-8008			WV-11532		
-2.495	0.999	0.958	0.913	1.006	0.894	0.900
-1.796	0.965	0.864	0.882	0.972	0.829	0.858
-1.097	1.006	0.900	0.932	0.907	0.888	0.858
-0.398	0.800	0.742	0.806	0.795	0.747	0.742
0.301	0.624	0.611	0.687	0.562	0.554	0.554
1	0.524	0.500	0.521	0.409	0.411	0.387

Table 14B. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts)

Conc.	WV-8008			WV-11532		
-2.495	0.947	0.871	1.014	0.927	0.853	0.908
-1.796	0.877	0.841	0.908	0.836	0.769	0.841
-1.097	0.665	0.743	0.871	0.620	0.633	0.717
-0.398	0.555	0.427	0.707	0.421	0.415	0.427
0.301	0.210	0.178	0.304	0.096	0.105	0.094
1	0.056	0.071	0.083	0.012	0.015	0.015

Table 15. Activity of various c9orf72 oligonucleotides.

In Tables 15A to 15H, various c9orf72 oligonucleotides which target the AS (antisense strand) were tested in c9 BAC mice; mice were administered c9orf72 oligonucleotides ICV in two doses, each 50 μg, one week apart, and tissue was collected a week after the second dose. In Tables 15A to 15H, shown are

residual levels of AS (antisense strand) c9orf72 transcripts relative to HPRT1, after treatment with c9orf72 oligonucleotides, wherein 1.000 would represent 100% relative transcript level (no knockdown) and 0.000 would represent 0% relative transcript level (e.g., 100% knockdown). Results from replicate experiments are shown. Tissues evaluated: SC, spinal cord; and CX, cerebral cortex.

Table 15A. Activity of various c9orf72 oligonucleotides (residual level of AS C9orf72 transcripts in CX)

PBS	1.385	0.973	0.642		
WV-3542	0.727	0.901	0.927	1.065	1.729
WV-7117	0.637	0.895	1.000	0.559	0.953
WV-5969	1.973	1.102	1.141	1.506	0.895
WV-5979	1.214	1.094	1.079	1.249	1.506
WV-5980	0.669	1.591	1.206	0.993	1.636
WV-5981	1.320	0.859	0.454	0.769	1.157
WV-5982	1.157	1.189	0.540	0.940	1.206
WV-5985	0.927	1.275	1.537	1.223	0.933
WV-5987	0.616	1.311	1.249	1.117	0.591

Table 15B. Activity of various c9orf72 oligonucleotides (residual level of AS C9orf72 transcripts in SC)

PBS	0.932	1.048	1.020		
WV-3542	1.238	1.131	0.965	1.155	0.882
WV-7117	0.645	0.472	0.687	0.389	0.363
WV-5969	1.108	0.971	1.213	1.247	1.213
WV-5979	1.264	0.965	1.085	0.846	0.913
WV-5980	0.397	1.070	1.027	0.823	1.355
WV-5981	0.876	0.992	1.085	0.823	1.155
WV-5982	1.238	1.171	0.806	0.811	0.664
WV-5985	0.741	0.817	0.925	0.773	0.789
WV-5987	0.659	0.517	0.602	0.757	0.566

Table 15C. Activity of various c9orf72 oligonucleotides (residual level of AS C9orf72 transcripts in CX)

PBS	0.928	0.596	1.388		1.089
WV-3542	0.455	0.744	0.872	1.251	0.537
WV-7117	0.744	0.436	0.814	0.544	1.052
WV-5967	0.604	0.526	0.915	1.175	0.749

WV-5970	0.723	0.961	1.467	1.200	1.104
WV-5971	0.592	1.167	1.167	1.074	1.183
WV-5972	1.331	0.974	1.009	0.890	1.436
WV-5973	0.744	0.638	1.359	0.708	1.009
WV-5974	1.104	0.837	0.802	0.837	1.127
WV-5978	0.703	0.703	0.842	0.575	1.066

Table 15D. Activity of various c9orf72 oligonucleotides (residual level of AS C9orf72 transcripts in SC)

PBS	0.843	0.860	1.037		1.260
WV-3542	1.313	1.217	1.304	1.260	1.037
WV-7117	0.781	0.362	0.357	0.458	1.151
WV-5967	1.437	1.097	0.909	1.151	1.175
WV-5970	1.313	1.030	0.808	1.175	1.097
WV-5971	1.628	3.102	1.313	1.417	1.794
WV-5972	1.572	2.757	1.819	1.794	2.060
WV-5973	1.143	0.922	1.192	1.313	1.304
WV-5974	1.467	1.674	1.175	1.037	1.407
WV-5978	0.975	1.104	1.081	0.848	1.030

Table 15E. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts in CX)

PBS	1.061	0.943	0.997		
WV-3542	1.068	1.025	1.061	1.137	1.235
WV-7117	0.443	0.388	0.787	0.509	0.561
WV-5969	1.270	1.083	1.137	1.113	1.046
WV-5979	1.161	1.083	1.010	1.137	1.010
WV-5980	1.046	1.253	1.129	1.053	1.297
WV-5981	0.917	0.983	0.815	0.892	1.053
WV-5982	1.017	1.039	0.886	1.068	1.075
WV-5985	1.075	1.169	1.177	1.161	0.868
WV-5987	0.990	1.032	1.153	1.010	0.868

Table 15F. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts in SC)

PBS	0.960	0.953	1.087		
WV-3542	1.029	1.087	0.933	0.953	0.973
WV-7117	0.268	0.203	0.722	0.190	0.196

WV-5969	0.987	0.921	0.960	1.014	1.014
WV-5979	0.933	0.980	0.987	0.980	0.973
WV-5980	0.774	0.987	0.940	0.980	1.095
WV-5981	0.921	0.940	0.994	0.933	1.036
WV-5982	1.072	1.014	0.927	0.940	0.871
WV-5985	1.036	1.000	0.960	0.927	0.927
WV-5987	0.946	0.824	0.883	0.841	0.883

Table 15G. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts in CX)

PBS	1.073	0.859	1.095	0.818	0.973
WV-3542	0.813	0.824	0.947	1.149	0.830
WV-7117	0.470	0.274	0.703	0.563	1.001
WV-5967	0.404	0.818	0.973	1.065	0.896
WV-5970	0.987	1.095	0.960	0.973	1.118
WV-5971	0.830	0.953	1.087	0.947	1.134
WV-5972	1.182	0.960	0.987	1.065	1.103
WV-5973	0.973	0.896	0.987	0.902	1.103
WV-5974	1.142	1.058	0.967	0.967	1.043
WV-5978	0.980	0.836	1.001	0.953	0.973

Table 15H. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts in SC)

PBS	1.062	0.950	0.912	1.018	1.077
WV-3542	0.997	0.924	0.918	0.937	0.887
WV-7117	0.700	0.207	0.256	0.241	0.761
WV-5967	1.099	1.004	1.077	0.977	0.977
WV-5970	1.026	0.931	0.899	0.970	1.004
WV-5971	1.004	1.162	0.931	0.997	1.146
WV-5972	0.977	1.114	0.977	1.033	1.178
WV-5973	0.931	0.964	0.997	1.018	1.033
WV-5974	1.062	1.077	0.905	0.912	0.997
WV-5978	0.991	0.997	1.054	0.984	0.964

In Table 15I.1 to Table 15I.6 and Table 15J.1 to Table 15J.6, various c9orf72 oligonucleotides were tested in C9 BAC mice. Tested c9orf72 oligonucleotides have different base sequences and varying numbers and positions of non-negatively charged internucleotidic linkages. Shown are residual levels of c9orf72 transcriptions [e.g., all transcripts (all V) or only V3] relative to HPRT1, after treatment with

c9orf72 oligonucleotides, wherein 1.000 would represent 100% relative transcript level (no knockdown) and 0.000 would represent 0% relative transcript level (e.g., 100% knockdown).

In Tables 15I.1 to 15M.3, and various other tables herein, C9orf72 transcript levels are shown relative to HPRT1, and data from replicates are shown.

Table 15I.1. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts in CX)

PBS	WV-12441	WV-13803	WV-13804	WV-13805
0.94	0.89	0.70	0.91	0.90
1.02	0.71	0.76	0.71	0.77
0.94	0.77	0.54	0.70	0.72
0.98	0.81	0.60	0.66	0.75
1.09	0.62	0.76	0.66	0.73
1.08	0.75	0.63	0.78	0.68
0.94	0.73	0.39	0.81	0.81
	0.58	0.63	0.57	0.80

Table 15I.2. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts in CX)

PBS	WV-12441	WV-13803	WV-13804	WV-13805
1.12	0.75	0.71	1.11	0.86
1.09	0.66	0.78	0.76	0.76
0.99	0.89	0.48	0.85	0.58
0.94	0.77	0.63	0.65	0.76
0.97	0.61	0.77	0.70	0.78
0.94	0.93	0.75	0.80	0.76
0.95	0.83	0.24	0.91	0.87
	0.57	0.56	0.56	0.81

Table 15I.3. Activity of various c9orf72 oligonucleotides (residual level of intron 1 transcripts in CX)

PBS	WV-12441	WV-13803	WV-13804	WV-13805
0.45	0.62	0.86	0.29	0.87
1.54	0.61	0.99	0.40	0.84
0.83	0.35	0.31	0.54	0.70
0.90	0.44	0.55	0.68	0.55
0.82	0.18	0.86	0.73	0.31

1.76	0.64	0.67	0.70	0.75
0.70	0.60	0.32		1.15
	0.55	0.47	0.36	1.20

Table 15I.4. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts in SC)

PBS	WV-12441	WV-13803	WV-13804	WV-13805
	0.67	0.49	0.63	0.71
0.88	0.99	0.44	0.62	0.60
0.94	0.52	0.53	0.51	0.78
1.03	0.91	0.47	0.85	0.64
1.16	0.78	0.59	0.43	0.99
1.03	0.59	0.47	0.74	0.63
0.96	0.72	0.50	0.79	0.64
	0.43	0.49	0.51	0.82

Table 15I.5. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts in SC)

PBS	WV-12441	WV-13803	WV-13804	WV-13805
	0.46	0.19	0.40	0.54
0.91	0.58	0.16	0.41	0.45
1.03	0.26	0.18	0.25	0.76
0.96	0.73	0.16	0.24	0.58
1.19	0.54	0.31	0.16	1.21
1.02	0.39	0.21	0.55	0.54
0.89	0.62	0.23	0.39	0.41
	0.19	0.17	0.22	0.61

Table 15I.6. Activity of various c9orf72 oligonucleotides (residual level of intron 1 C9orf72 transcripts in SC)

PBS	WV-12441	WV-13803	WV-13804	WV-13805
	0.16	0.11	0.13	0.20
0.67	1.40	0.07	0.22	0.16
1.72	0.22	0.04	0.09	0.64
1.10	0.99	0.06	0.22	0.11
1.58	0.09	0.25	0.17	1.33
0.45	0.27	0.08	0.44	0.15
0.48	0.52	0.12	0.60	0.19

	0.12	0.25	0.12	0.41

Table 15J.1. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts in CX)

PBS	WV-12483	WV-13806	WV-13807	WV-13808
0.86	0.84	0.80	0.76	0.90
1.03	0.91	0.92	0.60	0.89
0.93	0.79	0.83	0.77	0.98
1.00	0.74	0.96	0.83	0.76
1.05	0.73	0.68	0.71	0.85
1.15	0.76	0.90	0.85	0.78
	0.75	0.96	0.98	0.82
	0.79	0.79	0.86	0.81

Table 15J.2. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts in CX)

PBS	WV-12483	WV-13806	WV-13807	WV-13808
0.98	0.71	0.79	0.88	0.94
1.18	0.95	1.08	0.58	0.77
0.91	0.83	0.78	0.92	0.94
1.03	0.82	1.08	0.82	0.73
1.03	0.80	0.64	0.61	1.08
0.87	1.06	1.08	0.74	1.00
	0.83	1.19	0.94	1.11
	0.89	0.94	0.72	0.78

Table 15J.3. Activity of various c9orf72 oligonucleotides (residual level of intron 1 transcripts in CX)

PBS	WV-12483	WV-13806	WV-13807	WV-13808
0.46	0.67	1.31	1.04	1.45
1.50	2.15	1.39	0.42	1.40
0.95	1.13	0.75	0.63	1.98
1.24	1.66	1.51	1.33	1.29
0.78	0.88	0.87	0.89	1.58
1.08	0.45	1.16	0.88	0.96
	0.80	0.83	1.56	1.54
	1.37	1.37	0.53	1.49

Table 15J.4. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts in SC)

PBS	WV-12483	WV-13806	WV-13807	WV-13808
0.90	1.00	0.83	0.87	0.79
0.99	0.64	0.71	0.70	0.74
1.08	0.68	0.80	0.77	0.73
0.98	0.64	1.13	0.75	0.77
0.99	0.70	0.68	0.67	0.79
1.05	0.72	0.67	0.95	0.68
	0.75	0.68	0.87	0.85
	0.76	0.76	0.79	0.77

Table 15J.5. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts in SC)

PBS	WV-12483	WV-13806	WV-13807	WV-13808
0.95	0.77	0.47	0.87	0.51
1.06	0.49	0.49	0.60	0.54
1.10	0.42	0.51	0.75	0.48
0.91	0.37	0.95	0.80	0.54
0.95	0.48	0.40	0.48	0.76
1.04	0.54	0.40	0.54	0.79
	0.49	0.52	0.53	1.02
	0.56	0.49	0.37	0.79

Table 15J.6. Activity of various c9orf72 oligonucleotides (residual level of intron 1 C9orf72 transcripts in SC)

PBS	WV-12483	WV-13806	WV-13807	WV-13808
0.97	0.42	0.67	0.50	0.75
1.81	0.32	0.60	0.15	0.75
1.10	0.35	0.74	0.24	0.59
0.94	0.60	1.10	1.14	0.76
0.77	0.57	0.56	0.68	0.59
0.41	0.12	0.72	0.58	0.39
	0.27	0.45	0.58	0.14
	2.11	0.37	0.69	0.67

Tables 15K.1 to 15L.2 show the activity of various C9orf72 oligonucleotides in ALS motor neurons in vitro.

Table 15K.1. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts/HPRT1)

WV-13312 (1uM)	0.61	0.69	0.66
WV-13312 (0.2uM)	0.90	0.97	0.92
WV-8007 (1uM)	0.69	0.80	0.71
WV-8007 (0.2uM)	1.05	0.83	0.92
WV-13313 (1uM)	0.68	0.67	0.64
WV-13313 (0.2uM)	0.93	0.89	0.90
WV-8008 (1uM)	0.63	0.76	0.66
WV-8008 (0.2uM)	0.90	0.99	0.98
WV-13305 (1uM)	0.63	0.68	0.71
WV-13305 (0.2uM)	0.72	0.96	0.88
WV-13308 (1uM)	0.60	0.75	0.62
WV-13308 (0.2uM)	0.77	0.79	0.90
WV-13309 (1uM)	0.67	0.63	0.66
WV-13309 (0.2uM)	0.84	0.77	0.79
WV-14552 (1uM)	0.70	0.71	0.65
WV-14552 (0.2uM)	0.79	0.73	0.81
WV-14553 (1uM)	0.79	0.58	0.62
WV-14553 (0.2uM)	0.81	0.83	0.75
WV-14554 (1uM)	0.63	0.64	0.69
WV-14554 (0.2uM)	0.81	0.64	0.63
WV-14555 (1uM)	0.70	0.66	0.62
WV-14555 (0.2uM)	0.65	0.78	0.88
WV-8550 (1uM)	0.81	0.67	0.76
WV-8550 (0.2uM)	0.86	0.75	0.80
Water	1.17	1.13	1.02

Table 15K.2. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts/HPRT1)

WV-13312 (1uM)	0.17	0.20	0.21
WV-13312 (0.2uM)	0.56	0.63	0.59
WV-8007 (1uM)	0.42	0.42	0.39
WV-8007 (0.2uM)	0.79	0.76	0.76
WV-13313 (1uM)	0.24	0.25	0.22
WV-13313 (0.2uM)	0.67	0.60	0.64
WV-8008 (1uM)	0.29	0.34	0.30

WV-8008 (0.2uM)	0.64	0.83	0.68
WV-13305 (1uM)	0.23	0.22	0.21
WV-13305 (0.2uM)	0.48	0.65	0.60
WV-13308 (1uM)	0.27	0.31	0.27
WV-13308 (0.2uM)	0.51	0.63	0.68
WV-13309 (1uM)	0.17	0.15	0.12
WV-13309 (0.2uM)	0.52	0.60	0.55
WV-14552 (1uM)	0.28	0.29	0.24
WV-14552 (0.2uM)	0.77	0.73	0.79
WV-14553 (1uM)	0.27	0.20	0.21
WV-14553 (0.2uM)	0.75	0.74	0.58
WV-14554 (1uM)	0.24	0.24	0.31
WV-14554 (0.2uM)	0.64	0.53	0.55
WV-14555 (1uM)	0.19	0.25	0.20
WV-14555 (0.2uM)	0.55	0.55	0.65
WV-8550 (1uM)	0.42	0.38	0.38
WV-8550 (0.2uM)	0.87	0.73	0.76
Water	1.19	1.21	1.09

Tables 15L.1 to 15M.3 show activity of various C9orf72 oligonucleotides.

Shown are residual levels of c9orf72 transcriptions [e.g., all transcripts (all V) or only V3] relative to HPRT1, after treatment with c9orf72 oligonucleotides, wherein 1.000 would represent 100% relative transcript level (no knockdown) and 0.000 would represent 0% relative transcript level (e.g., 100% knockdown). In these and other tables, not all controls are shown.

In these and various other tables, tested C9orf72 oligonucleotides vary in base sequence, format (e.g., some have an asymmetrical format), pattern of internucleotidic linkages and/or in pattern of stereochemistry of internucleotidic linkages.

Table 15L.1. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts/HPRT1)

WV-12441 (10uM)	WV-13803 (10uM)	WV-12483 (10uM)	WV-13806 (10uM)	Water
0.47	0.10	0.68	0.79	1.17
0.48	0.14	0.89	0.68	1.13

Table 15L.2. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts/HPRT1)

WV-12441 (10uM)	WV-13803 (10uM)	WV-12483 (10uM)	WV-13806 (10uM)	Water
0.14	0.02	0.17	0.11	1.19
0.13	0.02	0.18	0.07	1.21

Table 15M.1. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts/HPRT1)

WV-10406	0.25	0.27	0.26
WV-10407	0.30	0.31	0.30
WV-10408	0.20	0.21	0.23
WV-10409	0.30	0.31	0.28
WV-10410	0.30	0.36	0.29
WV-10411	0.38	0.33	0.32
WV-10412	0.37	0.41	0.40
WV-10413	0.49	0.43	0.46
WV-10414	0.34	0.36	0.44
WV-10415	0.16	0.24	0.23
WV-10416	0.24	0.24	0.21
WV-8550	0.17	0.18	0.20
WV-10417	0.31	0.48	0.41
WV-10418	0.20	0.28	0.24
WV-10419	0.31	0.42	0.33
WV-10420	0.45	0.52	0.55
WV-10421	0.45	0.66	0.54
WV-10422	0.49	0.44	0.58
WV-10423	0.57	0.60	0.48
WV-10424	0.71	0.74	0.81
WV-10425	0.56	0.34	0.40
WV-9491	0.98	1.11	1.32
WV-3662	0.05	0.05	0.06
WV-10426	0.53		1.00

Table 15M.2. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts/HPRT1)

WV-10406	0.62	0.60	0.62
WV-10407	0.60	0.60	0.67
WV-10408	0.57	0.54	0.60
WV-10409	0.57	0.63	0.52
WV-10410	0.59	0.58	0.52

WV-10411	0.68	0.58	0.56
WV-10412	0.67	0.75	0.67
WV-10413	0.73	0.68	0.67
WV-10414	0.68	0.60	0.66
WV-10415	0.57	0.56	0.58
WV-10416	0.64	0.67	0.61
WV-8550	0.56	0.60	0.62
WV-10417	0.62	0.62	0.60
WV-10418	0.49	0.54	0.58
WV-10419	0.48	0.47	0.44
WV-10420	0.56	0.50	0.53
WV-10421	0.57	0.56	0.60
WV-10422	0.56	0.61	0.59
WV-10423	0.63	0.58	0.59
WV-10424	0.81	0.79	0.76
WV-10425	0.77	0.73	0.76
WV-9491	1.04	1.08	1.05
WV-3662	0.08	0.07	0.08
WV-10426	0.87	0.72	0.97

Table 15M.3. Activity of various c9orf72 oligonucleotides (residual level of intron/AS C9orf72 transcripts/HPRT1)

WV-10406	0.39	0.56	0.67
WV-10407	0.57	0.54	0.66
WV-10408	0.65	0.57	0.74
WV-10409	0.39	0.77	0.72
WV-10410	0.55	0.64	0.63
WV-10411	0.77	0.74	0.66
WV-10412	0.50	0.71	0.64
WV-10413	0.71	0.64	0.74
WV-10414	0.72	0.75	0.73
WV-10415	0.40	0.49	0.66
WV-10416	0.60	0.54	0.53
WV-8550	0.45	0.44	0.49
WV-10417	0.26	0.62	0.67
WV-10418	0.44	0.63	0.59
WV-10419	0.59	0.65	0.60
WV-10420	0.65	0.66	0.73
WV-10421	0.48	0.59	0.62

WV-10422	0.52	0.22	0.74
WV-10423	0.73	0.50	0.52
WV-10424	0.40	0.47	0.65
WV-10425	0.52	0.28	0.40
WV-9491	0.64	0.81	1.03
WV-3662	0.53	0.48	0.73
WV-10426	1.85		1.47

Table 16. Activity of various c9orf72 oligonucleotides.

In Tables 16A to 16H, combination of various S and AS (sense and antisense) c9orf72 oligonucleotides were tested in c9 BAC mice; mice were administered c9orf72 oligonucleotides ICV in two doses one week apart, and tissue was collected a week after the second dose. WV-7117 was administered in two doses of 50 μg each; WV-5987 was administered in two doses of 50 μg each; WV-5987 was administered in two doses of 100 μg each; and the combination of WV-7117 (50 μg) and WV-5987 (50 μg) was administered in two doses. In Tables 16A to 16H, shown are residual levels of c9orf72 transcripts relative to HPRT1, after treatment with c9orf72 oligonucleotides, wherein 1.000 would represent 100% relative transcript level (no knockdown) and 0.000 would represent 0% relative transcript level (e.g., 100% knockdown). Results from replicate experiments are shown. Tissues evaluated: SC, spinal cord; and CX, cerebral cortex.

Table 16A. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts in CX)

PBS	WV-7117(50ug)	WV-5987(50ug)	WV-5987(100ug)	WV-7117+WV-5987(50ug)
1.111	0.490	1.233	1.001	0.433
1.134	0.451	1.058	1.358	0.608
1.158	0.642	1.312	1.921	0.427
1.103	0.548		2.716	0.439
1.001	0.395	1.073	1.466	0.769
0.836	0.326	1.036	1.436	0.689
0.866	0.290	1.377	1.103	0.390
0.791	0.497	1.780		0.445

Table 16B. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts in CX)

PBS	WV-7117(50ug)	WV-5987(50ug)	WV-5987(100ug)	WV-7117+WV-5987(50ug)

1.155	0.510	0.978	0.971	0.546
1.131	0.417	1.055	1.027	0.650
0.999	0.711	1.070	1.308	0.450
1.147	0.450		1.600	0.506
0.881	0.363	0.840	0.985	0.636
1.027	0.327	0.800	1.108	0.985
0.888	0.318	1.273	1.131	0.339
0.773	0.489	1.318		0.506

Table 16C. Activity of various c9orf72 oligonucleotides (residual level of intron/AS C9orf72 transcripts in CX)

PBS	WV-7117(50ug)	WV-5987(50ug)	WV-5987(100ug)	WV-7117+WV-5987(50ug)
0.178	0.799	1.203	2.080	0.649
1.019	0.307	1.849	3.964	0.828
0.696	0.350	1.523	5.303	0.203
0.517	0.042		4.104	0.550
2.214	0.189	1.667	3.242	1.019
0.887	0.108	1.092	3.829	0.408
1.471	0.293	0.428	1.811	2.184
1.019	0.706	1.115		1.187

Table 16D. Activity of various c9orf72 oligonucleotides (residual level of all V C9orf72 transcripts in SC)

PBS	WV-7117(50ug)	WV-5987(50ug)	WV-5987(100ug)	WV-7117+WV-5987(50ug)
0.955	0.256	0.916	1.082	0.324
1.017	0.226	0.989	0.929	0.251
1.128	0.201	0.989	1.144	0.244
0.962	0.340		0.942	0.260
1.038	0.370	0.929	1.168	0.355
0.975	0.234	0.982	1.168	0.237
0.982	0.214	0.955	1.053	0.237
0.942	0.221	0.975		0.236

Table 16E. Activity of various c9orf72 oligonucleotides (residual level of V3 C9orf72 transcripts in SC)

PBS	WV-7117(50ug)	WV-5987(50ug)	WV-5987(100ug)	WV-7117+WV-5987(50ug)

0.924	0.213	1.047	0.998	0.262
1.040	0.155	1.069	0.950	0.248
0.984	0.121	1.004	1.335	0.196
0.905	0.234		0.931	0.175
1.033	0.244	0.924	1.325	0.248
1.069	0.136	0.931	1.211	0.180
1.047	0.154	0.937	1.092	0.146
0.998	0.130	1.047		0.163

Table 16F. Activity of various c9orf72 oligonucleotides (residual level of AS C9orf72 transcripts in SC)

PBS	WV-7117(50ug)	WV-5987(50ug)	WV-5987(100ug)	WV-7117+WV-5987(50ug)
0.484	0.209	1.023	1.159	0.286
0.604	0.223	0.968	0.878	0.168
1.059	0.125	0.734	0.981	0.399
0.734	0.078		1.104	0.209
1.662	0.229	0.728	0.935	0.078
1.192	0.254	0.885	1.508	0.106
1.242	0.377	0.854	1.870	0.232
1.023	0.224	0.670		0.315

EXAMPLE 10.

Activity of various oligonucleotides

[001156] The efficacy of various additional chemical moieties, which can be used in construction of C9orf72 oligonucleotides, were tested in oligonucleotides which target a different gene target, Malat1. Data is provided in Figures 7A to 7D and described here.

[001157] Single-stranded Malat1 oligonucleotide WV-3174 was conjugated to any of various conjugates (Mod027, Mod028 or Mod007), to produce WV-7558, WV-7559, and WV-7560, detailed below in Table 17, and diagrammed in Example 1. WV-3174 is a cross-species oligonucleotide, as its base sequence has no mismatches with the corresponding sequence in human, dog (*Canis lupis familiaris* (mm10)), mouse (*Mus musculus* (mm10)), rat (*Rattus norvegicus* (m6)), and monkeys *Macaca mulatta* (rheMac8) and *Macaca fascicularis* (macFas5).

[001158] Table 17, below, provides information for some Malat1 oligonucleotides. Included in Table 17 is WV-8448, which is described elsewhere herein.

Table 17. Malat1 oligonucleotides

Name	Modified Sequence	Base Sequence	Stereochemistry
WV-3174	mU * mG * mC * mC * mA *G *G *C *T *G *G *T *T *A *T * mG * mA * mC * mU * mC	UGCCAGGCTGGTTATGACUC	XXXXXXXXXXXXXXXXXXX
WV-7558	Mod027L001 mU * mG * mC * mC * mA *G *G *C *T *G *G *T *T *A *T * mG * mA * mC * mU * mC	UGCCAGGCTGGTTATGACUC	OXXXXXXXXXXXXXXXXXXX
WV-7559	Mod028L001 mU * mG * mC * mC * mA *G *G *C *T *G *G *T *T *A *T * mG * mA * mC * mU * mC	UGCCAGGCTGGTTATGACUC	OXXXXXXXXXXXXXXXXXXX
WV-7560	Mod007L001 mU * mG * mC * mC * mA *G *G *C *T *G *G *T *T *A *T * mG * mA * mC * mU * mC	UGCCAGGCTGGTTATGACUC	OXXXXXXXXXXXXXXXXXXX
WV-8448	Mod059L001mU * mG * mC * mC * mA * G * G * C * T * G * G * T * T * A * T * mG * mA * mC * mU * mC	UGCCAGGCTGGTTATGACUC	OXXXXXXXXXXXXXXXXXXX

For definitions of various components in Modified Sequence and Stereochemistry, see descriptions and texts following and related to Table 1A.

[001159] These experiments demonstrate greater biodistribution and greater knockdown with sulfonamide- or anisamide-conjugated WV-3174. Animals tested: Male C57BL/6 mice, 10-12 week-old, 5 groups, 50 mice. ICV cannulation was performed. Phase 1: N=10; ICV injections of PBS, 50, 100, 150 or 250mg ICV (2 mice per group), Clin Obs for 2 days. Phase 2: N=40; ICV injection of PBS or oligonucleotide on Day 1 in awake animals. Necropsy 7 days after injection. Necropsy: whole body perfusion with PBS. Procedure: Dissect lumbar spinal cord (PD) and place thoracic/cervical spinal cord in formalin (histology); dissect one hemibrain (cortex, hippocampus, striatum, cerebellum), flash freeze (exposures / transcripts). Second hemibrain post fixed in formalin, cryoprotected and flash frozen (Malat1 KD / oligonucleotide visualization).

[001160] The parameters for Phase 2 were as follows:

Table 18. Parameters for Phase 2 Malat1 animal testing

Group	Test Article	Dose	Dosing Regimen	Dose Volume	# mice
1	PBS	NA	ICV	2.5 ml	8
2	WV-3174	50 mg	ICV	2.5 ml	8
3	WV-7558	50 mg	ICV	2.5 ml	8
4	WV-7559	50 mg	ICV	2.5 ml	8
5	WV-7560	50 mg	ICV	ml	8

[001161] Figures 7B to 7D show MALAT1 knockdown in spinal cord. Triantennary anisamide conjugated Malat1 oligonucleotide (WV-3174) shows significant knockdown of Malat1 (~70%). Triantennary anisamide conjugated Malat1 oligonucleotide (WV-3174) also shows significant accumulation in spinal cord.

[001162] Figures 7E, 7F and 7G show MALAT1 knockdown in cortex. Triantennary anisamide conjugated Malat1 oligonucleotide (WV-3174) shows knockdown of Malat1 (~34%). Triantennary anisamide conjugated Malat1 oligonucleotide (WV-3174) also shows higher accumulation in Cortex.

EXAMPLE 11.

Effects of C9orf72 oligonucleotides in vivo on C9orf72 transcripts in C9-BAC mice

[001163] A pharmacodynamics study was performed to compare the effects of C9orf72 oligonucleotides on knockdown of C9orf72 transcripts in C9-BAC mice.

[001164] C9orf72 oligonucleotides tested were: WV-6408, WV-8009, WV-8010, WV-8011, and WV-8012. Negative controls were PBS (phosphate-buffered saline) and WV-2376, which does not target C9orf72.

[001165] Animals used: Male and Female C9-BAC mice, 12 week-old, 7 groups, 50 mice.

[001166] ICV cannulation was performed. ICV injection of PBS or 50 μg of oligonucleotide on Day 1 in awake animals. 2nd dose of PBS or 50 μg of oligonucleotide on Day 8. Dose volume, 2.5 μl. Necropsy 2 weeks after first injection.

[001167] Necropsy: whole body perfusion with PBS. Dissect lumbar spinal cord (PD) and place thoracic/cervical spinal cord in formalin (histology); dissect one hemibrain (cortex, hippocampus, striatum, cerebellum), flash freeze (exposures / transcripts). Second hemibrain post fixed in formalin, cryoprotected and flash frozen (RNA foci / oligonucleotide visualization).

[001168] Results are shown in Figures 8A to H.

[001169] Transcripts were analyzed from the cerebral cortex (Figures 8A to D) and spinal cord (Figures 8E to H). Transcripts analyzed were: All transcripts (Figures 8A and E); V3 (Figures 8B and F); V3 (exon 1a) (Figures 8C and G); and Intron1/AS (Figures 8D and H).

[001170] Several C9orf72 oligonucleotides were shown to be capable of knocking down C9orf72 transcripts, including V3, in the cortex and spinal cord of C9-BAC mice.

EXAMPLE 12.

Distribution of C9orf72 oligonucleotides in vivo in spinal cord and cerebral cortex of C9-BAC mice

[001171] A pharmacokinetics study was performed to examine the distribution of C9orf72 oligonucleotides in vivo in spinal cord and cerebral cortex of C9-BAC mice.

[001172] C9orf72 oligonucleotides tested were: WV-6408, WV-8009, WV-8010, WV-8011, and WV-8012. Negative controls were PBS (phosphate-buffered saline) and WV-2376, which does not target C9orf72.

[001173] Results are shown in Figures 9A (spinal cord) and 9B (cerebral cortex). The color red indicates points outside the standard curve range.

[001174] Several C9orf72 oligonucleotides showed significant accumulation in spinal cord and cortex.

EXAMPLE 13.

Effect of C9orf72 oligonucleotides in vivo on polyGP levels in hippocampus of C9-BAC mice

[001175] A study was performed to evaluate the effect of C9orf72 oligonucleotides in vivo on polyGP (a dipeptide repeat protein) levels in hippocampus of C9-BAC mice.

[001176] C9orf72 oligonucleotides tested were: WV-6408, WV-8009, WV-8010, WV-8011, and WV-8012. Negative controls were PBS (phosphate-buffered saline) and WV-2376, which does not target

C9orf72. WT is a control.

[001177] Method:

[001178] Tissues were homogenized in RIPA buffer and clarified by centrifugation. Lysate concentration was determined by Pierce Protein 660nm assay (reagent available as Catalog number: 22660 from ThermoFisher, Waltham, Ma.) and normalized in RIPA lysis and extraction buffer (reagent available as Catalog number: 89900 from ThermoFisher, Waltham, Ma.). MSD 96-well Small Spot Standard plates were coated with anti-polyGP (Millipore ABN1358, available from Millipore Sigma, Billerica, Ma.) overnight at 4C, washed in PBST, and blocked with PBS containing 10% fetal bovine serum. Lysate samples were diluted 1:4 in PBS/10% FBS and loaded at 75ug per well, and incubated at room temperature. A standard curve was composed of affinity purified Flag-polyGP (GenScript, Piscataway, New Jersey) diluted into wild-type mouse brain RIPA lysate. Detection was performed with Sulfo-tag-conjugated anti-polyGP, and read with MSD Read Buffer T with Surfactant in a MSD QuickPlex SQ 120 (Meso Scale Diagnostics, Rockville, Maryland) instrument.

[001179] The data, shown in Figure 10, was quantified from a standard curve of GenScript Flag-polyGP diluted in wild-type mouse brain lysate.

[001180] The data show that the C9orf72 oligonucleotides were capable of decreasing the level of polyGP (a dipeptide repeat protein) in hippocampus in C9-BAC mice.

EXAMPLE 14.

Additional Protocols

Additional protocols for experiments are presented below.

A non-limiting example of a hybridization assay for detecting a target nucleic acid is described herein. Such an assay can be used for detecting and/or quantifying a C9orf72 oligonucleotide, or any other nucleic acid or oligonucleotide to any target, including targets which are not C9orf72.

Pharmacokinetics studies:

Tissue preparation for oligonucleotide quantification and transcript quantification:

Tissues were dissected and fresh-frozen in the pre-weighted Eppendorf tubes. Tissue weight were calculated by re-weight the tubes. 4 volume of Trizol or lysis buffer (4 M Guanidine; 0.33% N-Lauryl Sarcosine; 25 mM Sodium Citrate; 10 mM DTT) were added to one unit weight (4 µl of buffer for 1 mg tissue). Tissue lysis were done by Precellys Evolution tissue homogenizer (Bertin Technologies, Montigny-le-Bretonneux, France) until all the tissue pieces were dissolved at 4 C. 30-50 µl of tissue lysates were saved in 96 well plate for PK measurement, and rest of lysates were stored at -80 C (if it is in lysis buffer) or continue with RNA extraction (if it is in Trizol buffer).

Transcript quantification:

Hybridization probes (IDT-DNA)

Capture probe: "C9-Intron-Cap" /5AmMC12/TGGCGAGTGG

Detection probe: "C9-Intron-Det": GTGAGTGAGG/3BioTEG/

5AmC12 is a 5'-amine with C_{12} linker.

3BioTEG is a Biotinylated probe.

Maleic anhydride activated 96 well plate (Pierce 15110) was coated with 50 µl of capture probe at 500 nM in 2.5% NaHCO3 (Gibco, 25080-094) for 2 hours at 37 C. The plate then washed 3 times with PBST (PBS + 0.1% Tween-20), blocked with 5% fat free milk-PBST at 37 C for 1 hour. Payload oligonucleotide was serial diluted into matrix. This standard together with original samples were diluted with lysis buffer (4 M Guanidine; 0.33% N-Lauryl Sarcosine; 25 mM Sodium Citrate; 10 mM DTT) so that oligonucleotide amount in all samples is less than 50 ng/ml. 20 µl of diluted samples were mixed with 180 µl of 333 nM detection probe diluted in PBST, then denatured in PCR machine (65 C, 10 min, 95 C, 15 min, 4 C ∞). 50 µl of denatured samples were distributed in blocked ELISA plate in triplicates, and incubated overnight at 4 C. After 3 washes of PBST, 1:2000 streptavidin-AP (SouthernBiotech, 7100-04) in PBST was added, 50 µl per well and incubated at room temperature for 1 hour. After extensive wash with PBST, 100 µl of AttoPhos (Promega S1000) was added, incubated at room temperature in dark for 10 min and read on plate reader (Molecular Device, M5) fluorescence channel: Ex435nm, Em555nm. The oligonucleotide in samples were calculated according to standard curve by 4-parameter regression.

[001181] **FISH protocol for GGGGCC and GGCCCC RNA foci**

[001182] Fixation:

[001183] The slides were dried at room temperature for 30mins then fixed in 4%PFA for 20mins. After fixation, the slides were washed for 3 times in PBS then stored at 4 °C in 70% prechilled ethanol for at least 30min.

[001184] Pre-hybridization:

[001185] The slides were rehydrated in FISH washing buffer (40% formamide, 2XSSC in DEPC water) for 10min. Hybridization buffer (40% Formamide, 2X SSC, 0.1mg/ml BSA, 0.1g/ml dextran sulfate, 1% Vanadyl sulfate complex, 0.25mg/ml tRNA in DEPC water) was added on slides and incubated at 55°C for 30min.

[001186] Preparation of the probe:

[001187] Cy3-(GGCCCC)3 (detecting sense repeat expansion) and Cy3-(GGGGCC)3 (detecting antisense repeat expansion) probes were denatured at 95°C for 10mins. After cooling down on ice, the probes were diluted to 200ng/ml with cold hybridization buffer.

[001188] Hybridization:

[001189] The slides were briefly washed with FISH washing buffer and diluted probes were added on the slides. The slides were incubated at 55°C for 3 hours in a hybridization oven. After hybridization, slides were washed 3 times at 55°C with FISH washing buffer, 15min per wash. Then slides were briefly washed once with 1XPBS.

[001190] Neuronal nuclei immunofluorescence staining:

[001191] The slides were blocked with blocking solution (2% normal goat serum in PBS) for 1 hour. Anti-NeuN antibody (MAB377, Millipore) was diluted 1:500 in blocking solution and applied to the slides at 4°C over night. The slides were then washed 3 times with PBS and incubate with 1:500 diluted goat anti-mouse secondary antibody with Alexa Fluor 488(Life technology) at room temperature for 1 hour. Then the slides were washed 3 times with PBS. Finally, the sides were mounted with DAPI for imaging.

[001192] Imaging and foci quantification:

[001193] The images were taken with RPI spinning disk confocal microscope (Zeiss) at 40X magnification. 488, CY3 and DAPI channels were collected. RNA foci were quantified with ImageJ software(NIH).

[001194] While various embodiments have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described in the present disclosure, and each of such variations and/or modifications is deemed to be included. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be example and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present disclosure is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the disclosure described in the present disclosure. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, claimed technologies may be practiced otherwise than as specifically described and claimed. In addition, any combination of two or more features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the scope of the present disclosure.

CLAIMS

1. A composition comprising an oligonucleotide, wherein the oligonucleotide comprises at least one modification of a sugar, base or internucleotidic linkage, and the base sequence of the oligonucleotide comprises at least 15 contiguous bases of a base sequence that is identical with or complementary to a base sequence of a C9orf72 gene or a transcript thereof.

2. The composition of claim 1, wherein the oligonucleotide reduces level of a repeat expansion-containing C9orf72 transcript when administered to a system comprising the C9orf72 transcript.

3. The composition of claim 2, wherein the repeat expansion-containing C9orf72 transcript comprises at least 30, 50, 100, 150, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 GGGGCC repeats.

4. The composition of claim 4, wherein the reduction of level of the repeat-expansion-containing C9orf72 transcript as measured by percentage is at least 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, or 10 fold of the reduction of level of the non-repeat-expansion-containing C9orf72 transcript as measured by percentage.

5. The composition of claim 1, wherein the oligonucleotide hybridizes a site in C9orf72 exon 1a, intron 1, exon 1b, or exon 2.

6. The composition of any of the preceding claims, wherein the oligonucleotide comprises at least one internucleotidic linkage wherein the linkage phosphorus is in the Sp configuration.

7. The composition of claim 6, wherein the oligonucleotide comprises a core and at least two wings.

8. The composition of claim 7, wherein the pattern of sugar modifications of the first wing differs from the pattern of sugar modifications of the second wing.

9. The composition of claim 8, wherein the first wing comprises a 2'-OMe and the second wing does not.

10. The composition of claim 8, wherein the second wing comprises a 2'-MOE and the first wing does not.

11. The composition of claim 8, wherein the first wing comprises a 2'-OMe and the second wing does not and wherein the second wing comprises a 2'-MOE and the first wing does not.

12. A 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;

which composition is chirally controlled in that it 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 the oligonucleotide targets C9orf72.

13. An oligonucleotide of or comprising a wing-core-wing structure, or a wing-core structure, or a core-wing structure, wherein the core comprises a pattern of backbone chiral centers (linkage phosphorus) of:

(*N*p)t[(*O*p/*R*p)n(*S*p)m]y,

wherein:

t is 1-50;

n is 1-10;

m is 1-50;

y is 1-10;

*N*p is either *R*p or *S*p;

*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

*R*p indicates the *S* configuration of a chiral linkage phosphorus of a chiral modified internucleotidic linkage;

y is 1-10;

each wing independently comprises one or more nucleobases; and

wherein the base sequence of the oligonucleotide comprises at least 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous bases of a base sequence that is identical with or complementary to a base sequence of a C9orf72 gene or a transcript thereof.

14. The oligonucleotide of claim 13, wherein the oligonucleotide is of a wing-core-wing structure.

15. The oligonucleotide of any one of claims 13-14, wherein *N*p is *S*p.

16. The oligonucleotide of any one of claims 13-14, wherein the pattern comprises at least one *R*p.

17. The oligonucleotide of any one of 13-16, wherein the pattern comprises at least one *O*p.

18. The oligonucleotide of any one of claims 13-14, wherein the pattern is (*N*p)t[(*O*p)n(*S*p)m]y.

19. The oligonucleotide of any one of claims 13-14, wherein the pattern is (*N*p)t[(*R*p)n(*S*p)m]y.

20. The oligonucleotide of any one of claims 13-19, wherein at least one n is 1.

21. The oligonucleotide of any one of claims 13-19, wherein each n is 1.

22. The oligonucleotide of any one of claims 13-21, wherein y is 1.

23. The oligonucleotide of any one of claims 13-21, wherein y is 2.

24. The oligonucleotide of any one of claims 13-23, wherein t is 2-20.

25. The oligonucleotide of any one of claims 13-24, wherein at least one m is 2-20.

26. The oligonucleotide of any one of claims 13-24, wherein at least one m is 3, 4, 5, 6, 7, 8, 9, or 10.

27. The oligonucleotide of any one of claims 13-26, wherein each m is independently 2-20.

28. The oligonucleotide of any one of claims 13-27, wherein the two rings comprise different sugar modifications.

29. The oligonucleotide of any one of claims 13-27, wherein one wing comprises a sugar modification that is not in the other wing.

30. The oligonucleotide of any one of claims 13-29, wherein nucleoside units of the core comprise no 2'-substitutions (two –H at 2' position).

31. The oligonucleotide of any one of claims 13-30, wherein nucleoside units of the core comprise no sugar modifications.

32. The oligonucleotide of any one of claims 13-31, wherein each wing nucleoside unit independently comprises a sugar modification.

33. The oligonucleotide of any one of claims 13-32, wherein the base sequence of the oligonucleotide comprises a sequence that is not identical or complementary to any repeats.

34. The oligonucleotide of any one of claims 13-32, wherein the base sequence of the oligonucleotide comprises a sequence that is not identical or complementary to the GGGGCC repeats.

35. The oligonucleotide of any one of claims 13-32, wherein the base sequence of the oligonucleotide is not identical or complementary to the GGGGCC repeats.

36. The oligonucleotide of any one of claims 13-35, wherein the base sequence of the oligonucleotide comprises a sequence targeting a C9orf72 intro sequence.

37. The oligonucleotide of claim 36, wherein the oligonucleotide preferentially reduces level of a disease-associated C9orf72 product.

38. The oligonucleotide of claim 37, wherein the product is a transcript comprising expanded GGGGCC repeats.

39. The oligonucleotide of claim 37, wherein the product is a transcript comprising at least 30, 50, 100, 200, 300, 400, or 500 GGGGCC repeats.

40. The oligonucleotide of claim 37, wherein the product is an antisense transcript comprising expanded GGGGCC repeats.

41. The oligonucleotide of claim 37, wherein the product is a dipeptide repeat protein.

42. The oligonucleotide of claim 13, wherein the oligonucleotide is WV-5987, WV-6408, WV-7117, WV-8009, WV-8010, WV-8011, WV-8012, WV-8548, WV-8550, WV-9510, WV-11532, WV-12444, WV-12446, WV-12481, WV-12482, WV-12483, or WV-12484.

43. The oligonucleotide of claim 13, wherein the oligonucleotide is WV-12481, WV-12482, WV-12483, or WV-12484.

44. The oligonucleotide of claim 13, wherein the oligonucleotide is WV-5987 or WV-7117.

45. The oligonucleotide of claim 13, wherein the oligonucleotide is WV-8011.

46. The oligonucleotide of claim 13, wherein the oligonucleotide is WV-8012.

47. The oligonucleotide of claim 13, wherein the oligonucleotide is WV-11532.

48. The oligonucleotide of claim 13, wherein the oligonucleotide is WV-6408.

49. The oligonucleotide of claim 13, wherein the oligonucleotide is WV-12446.

50. The oligonucleotide of any one of claims 13-49, having a diastereomeric purity of at least 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%.

51. The composition of any one of claims 1-12, wherein the oligonucleotide is an oligonucleotide of any one of claims 13-50.

52. A pharmaceutical composition comprising an oligonucleotide of any one of the preceding claims or a pharmaceutically acceptable salt thereof.

53. An 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;

which composition is chirally controlled in that 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 of claims 13-50 or a salt thereof.

54. 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;

which composition is chirally controlled in that it 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 of claims 13-50 or a salt thereof.

55. A method, comprising administering to a subject suffering from or susceptible to a condition, disorder, and/or disease related to C9orf72 expanded repeats an oligonucleotide or composition of any one of the preceding claims.

56. The method of claim 55, wherein the condition, disorder, and/or disease is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), corticobasal degeneration syndrome (CBD), atypical Parkinsonian syndrome, olivopontocerebellar degeneration (OPCD), or Alzheimer's disease.

57. The method of claim 55, wherein the condition, disorder, and/or disease is amyotrophic lateral sclerosis (ALS).

58. The method of claim 55, wherein the condition, disorder, and/or disease is frontotemporal dementia (FTD).

59. A method of decreasing the activity, expression and/or level of a C9orf72 target gene or its gene product in a cell, comprising introducing into the cell an oligonucleotide or composition of any of preceding claims.

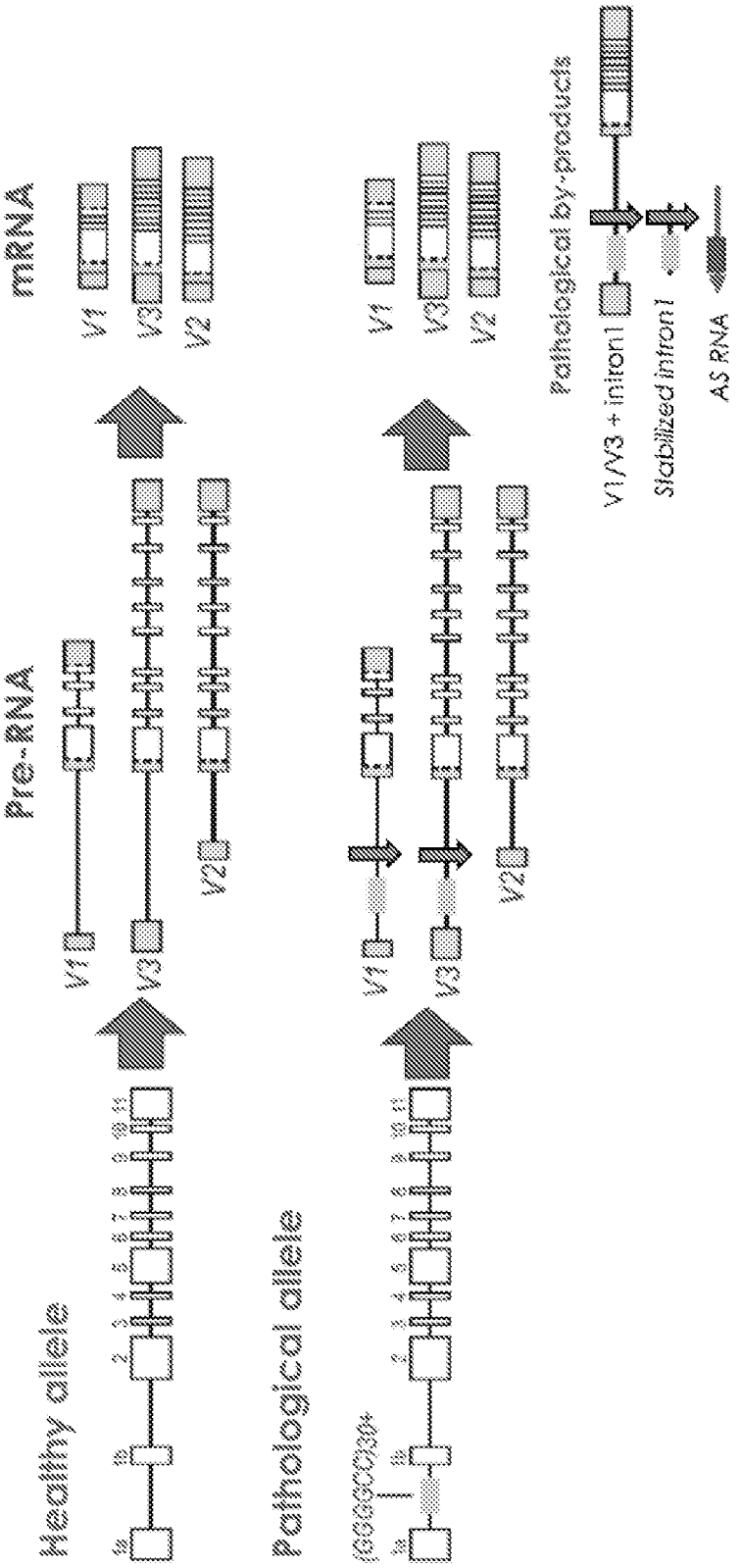
60. A method for preferential knockdown of a repeat expansion-containing C9orf72 RNA transcript relative to a non-repeat expansion-containing C9orf72 RNA transcript in a cell, comprising contacting a cell comprising the repeat expansion-containing C9orf72 RNA transcript and the non-repeat expansion-containing C9orf72 RNA transcript with an oligonucleotide or composition of any one of the preceding claims,

wherein the oligonucleotide comprises a sequence present in or complementary to a sequence in the repeat expansion-containing C9orf72 RNA transcript,

wherein the oligonucleotide directs preferential knockdown of a repeat expansion-containing C9orf72 RNA transcript relative to a non-repeat expansion-containing C9orf72 RNA transcript in a cell.

61. A compound, oligonucleotide, composition, or method described in the specification.

FIG. 1


Healthy allele
Pre-RNA
mRNA
V1
V3
V2
Pathological allele
GGGCCC
Pathological by-products
V1/V3 + intron1
Stabilized intron1
AS RNA

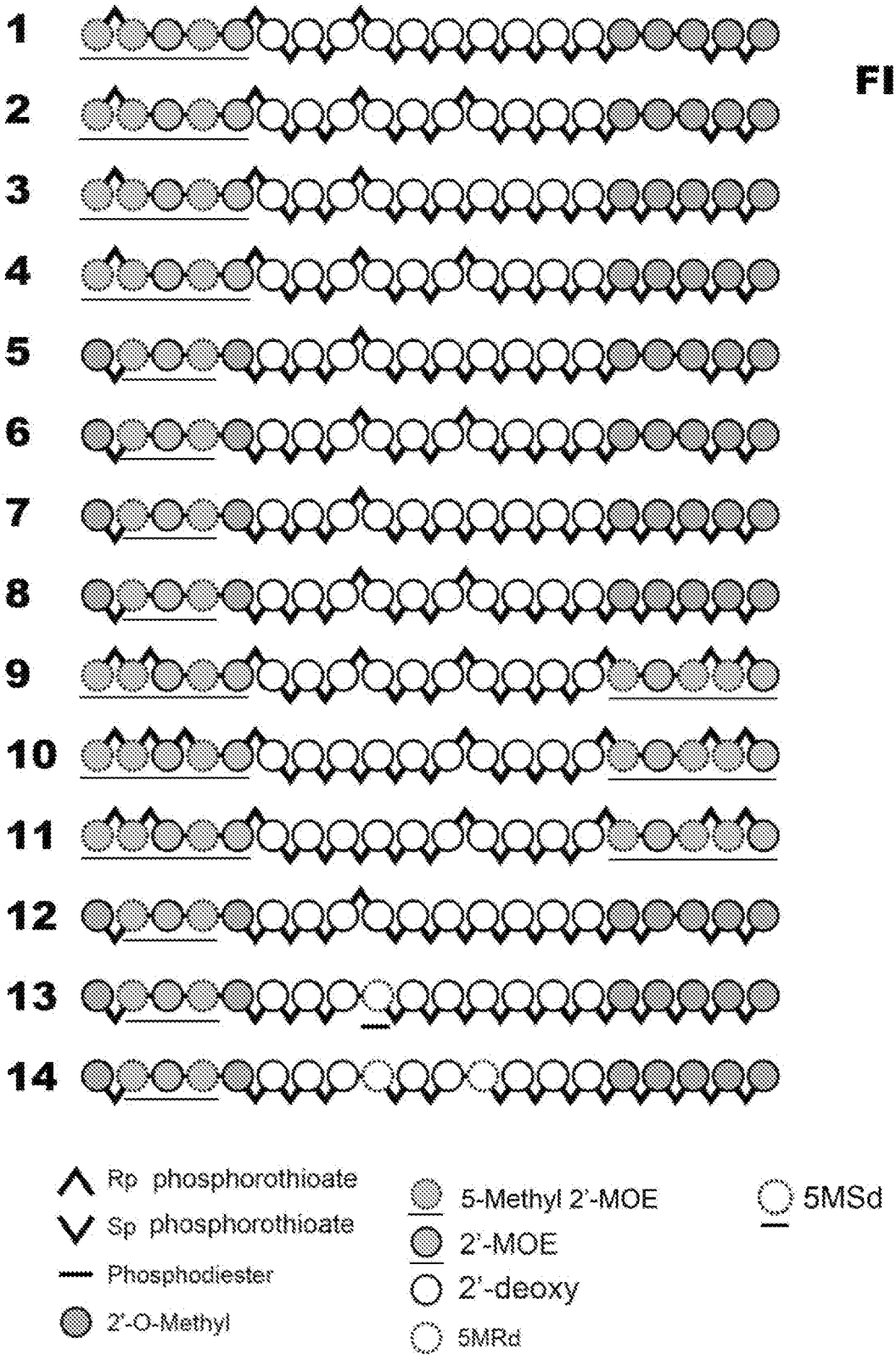
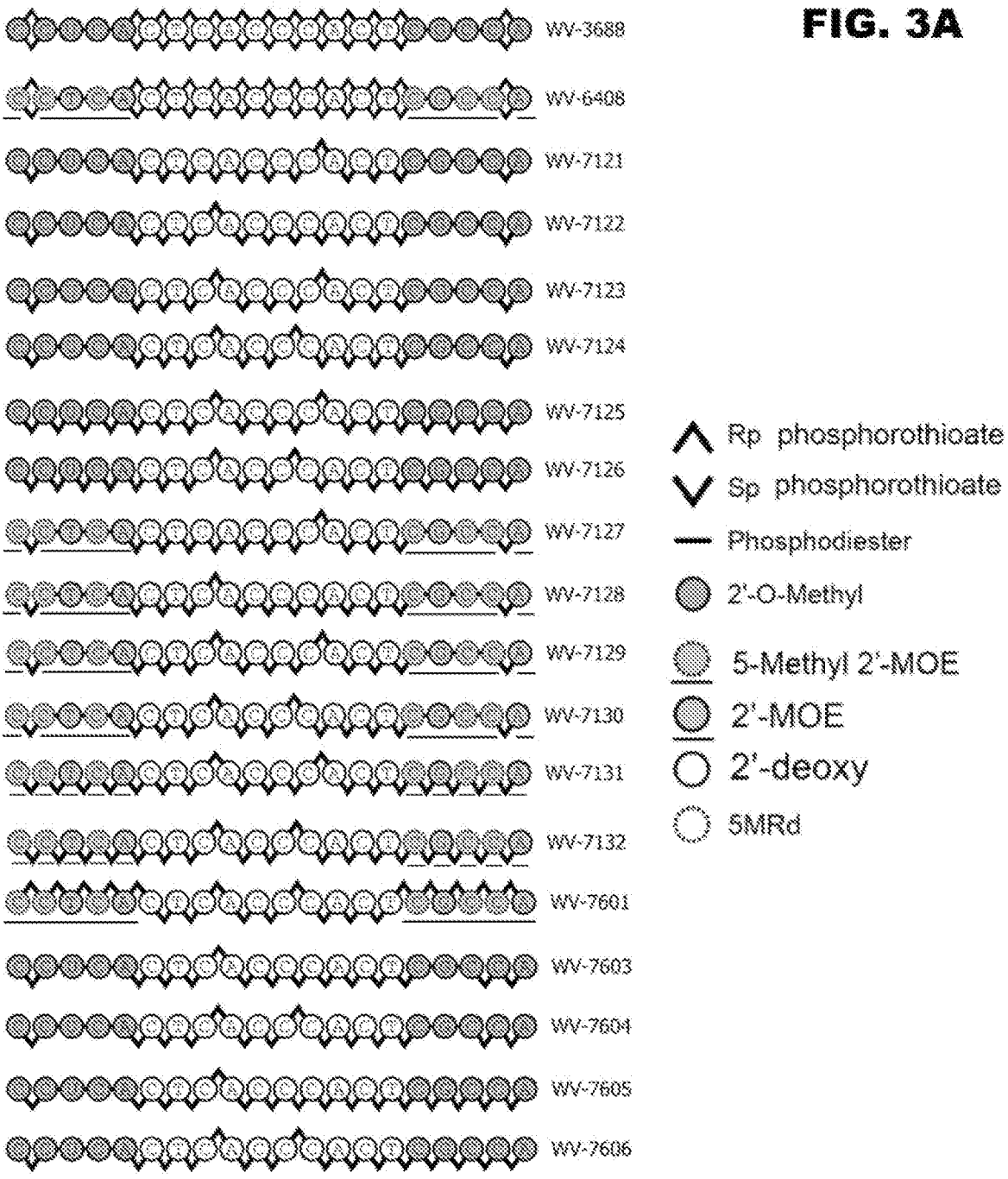

1
2
3
4
5
6
7
8
9
10
11
12
13
14
Rp phosphorothioate
Sp phosphorothioate
Phosphodiester
2'-O-Methyl
5-Methyl 2'-MOE
2'-MOE
2'-deoxy
5MRd
5MSd

FIG. 2

FIG. 3A


WV-3688
WV-6408
WV-7121
WV-7122
WV-7123
WV-7124
WV-7125
WV-7126
WV-7127
WV-7128
WV-7129
WV-7130
WV-7131
WV-7132
WV-7601
WV-7603
WV-7604
WV-7605
WV-7606
Rp phosphorothioate
Sp phosphorothioate
Phosphodiester
2'-O-Methyl
5-Methyl 2'-MOE
2'-MOE
2'-deoxy
5MRd

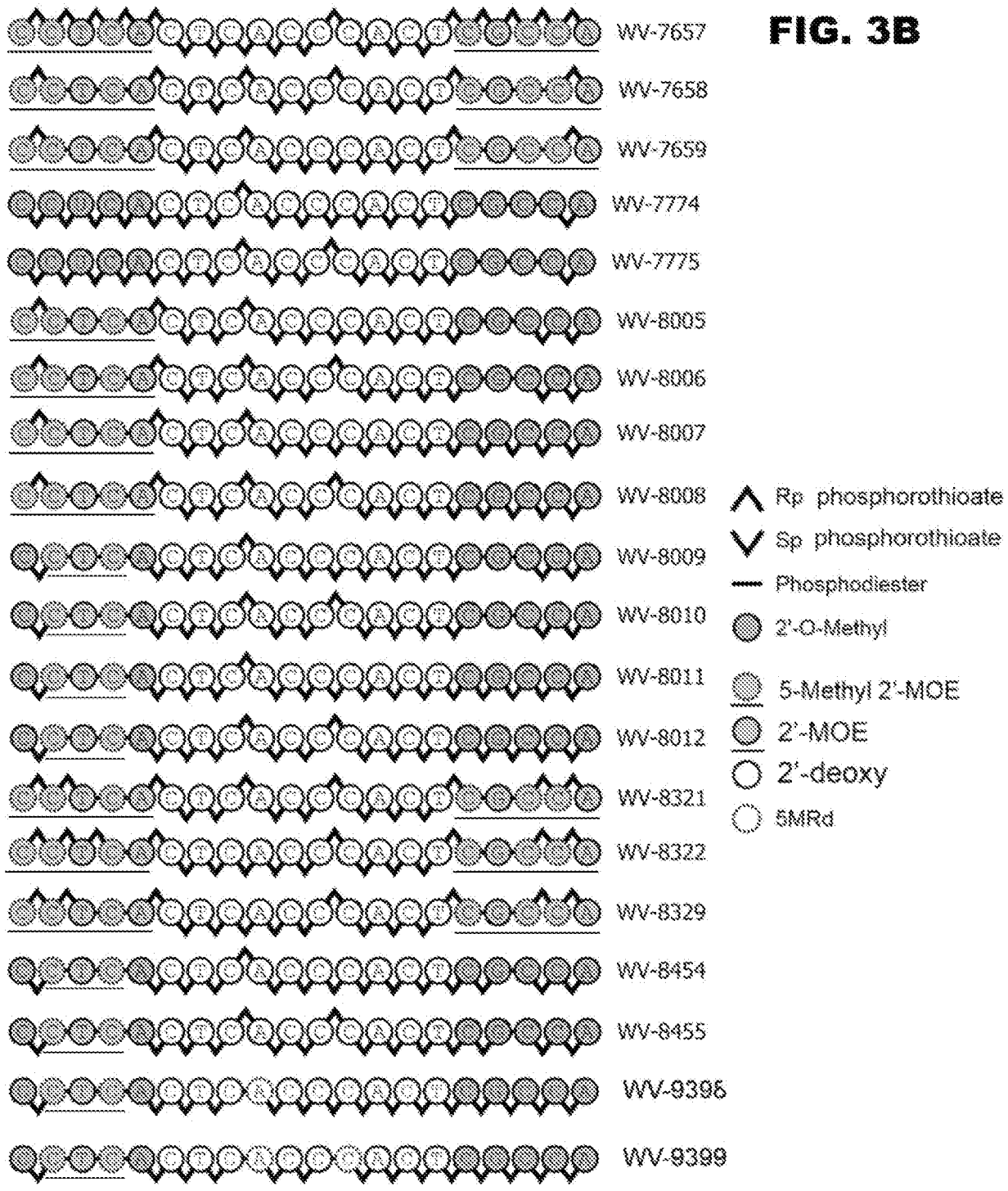

WV-7657
WV-7658
WV-7659
WV-7774
WV-7775
WV-8005
WV-8006
WV-8007
WV-8008
WV-8009
WV-8010
WV-8011
WV-8012
WV-8321
WV-8322
WV-8329
WV-8454
WV-8455
WV-9398
WV-9399
Rp phosphorothioate
Sp phosphorothioate
Phosphodiester
2'-O-Methyl
5-Methyl 2'-MOE
2'-MOE
2'-deoxy
5MRd

FIG. 3B

FIG. 4

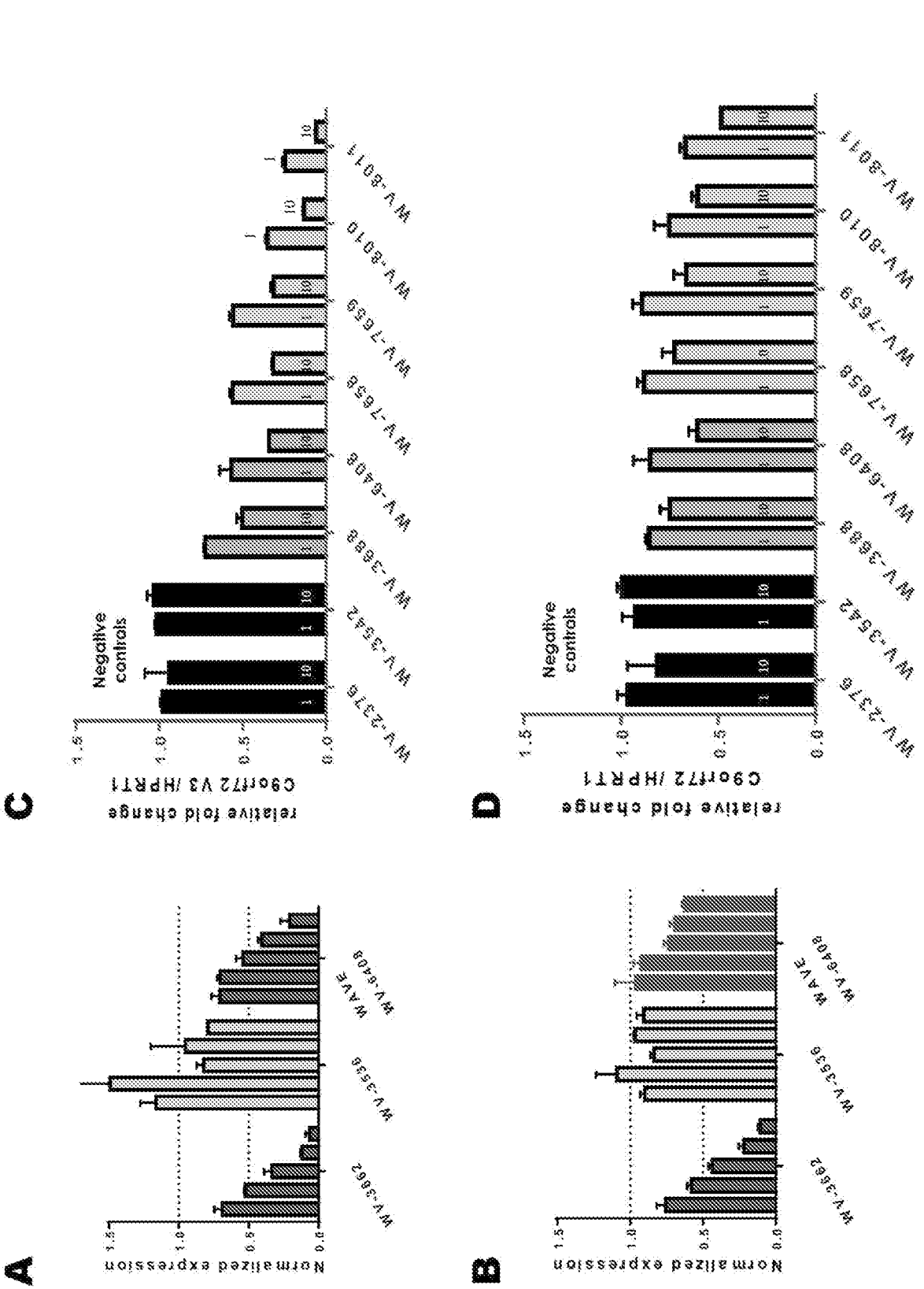

A
Normalized expression
1.5
1.0
0.5
0.0
WV-3062
WV-3536
WAVE
WV-6408
B
Normalized expression
1.5
1.0
0.5
0.0
WV-3662
WV-3536
WAVE
WV-6408
C
relative fold change
C9orf72 V3 /HPRT1
1.5
1.0
0.5
0.0
Negative controls
1
10
1
10
WV-2376
WV-3542
WV-3688
WV-6408
WV-7658
WV-7659
WV-8010
WV-8011
D
relative fold change
C9orf72 /HPRT1
1.5
1.0
0.5
0.0
Negative controls
1
10
1
10
WV-2376
WV-3542
WV-3688
WV-6408
WV-7658
WV-7659
WV-8010
WV-8011

FIG. 5

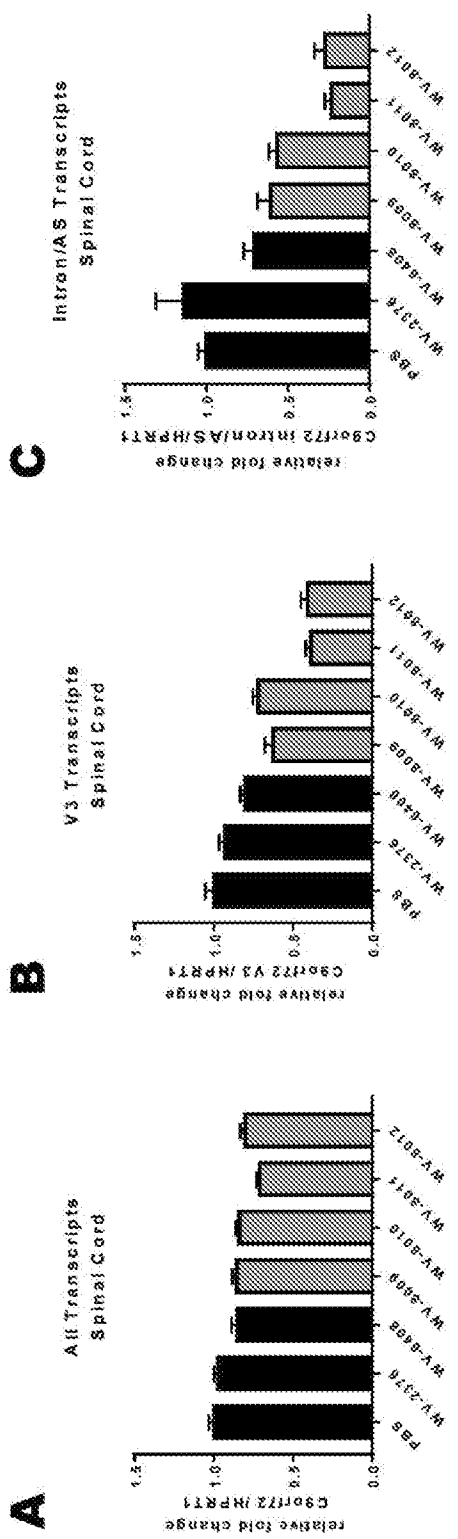

A
All Transcripts
Spinal Cord
relative fold change
C9orf72 /HPRT1
1.5
1.0
0.5
0.0
PBS
AAV-2376
AAV-6462
AAV-8569
AAV-8010
AAV-8011
AAV-8012
B
V3 Transcripts
Spinal Cord
relative fold change
C9orf72 V3 /HPRT1
1.5
1.0
0.5
0.0
PBS
AAV-2376
AAV-6462
AAV-8569
AAV-8010
AAV-8011
AAV-8012
C
Intron/AS Transcripts
Spinal Cord
relative fold change
C9orf72 intron/AS/HPRT1
1.5
1.0
0.5
0.0
PBS
AAV-2376
AAV-6462
AAV-8569
AAV-8010
AAV-8011
AAV-8012

FIG. 6

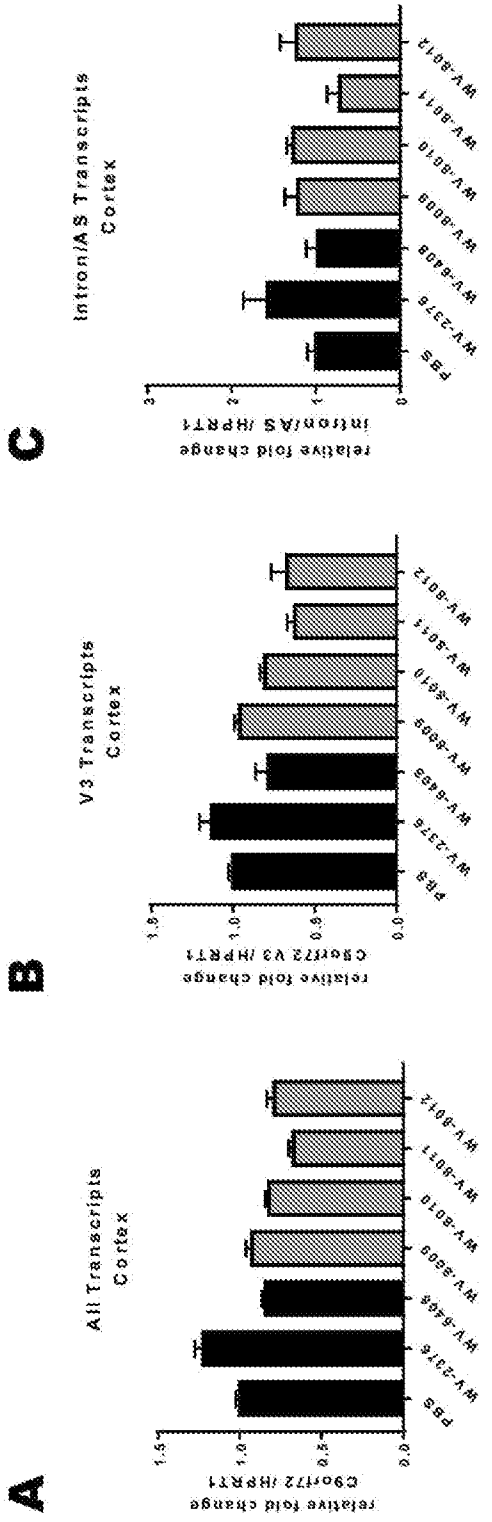

A
All Transcripts
Cortex
relative fold change
C9orf72 /HPRT1
1.5
1.0
0.5
0.0
PBS
WV-2376
WV-6456
WV-8509
WV-8610
WV-8011
WV-8012
B
V3 Transcripts
Cortex
relative fold change
C9orf72 V3 /HPRT1
1.5
1.0
0.5
0.0
PBS
WV-2376
WV-6455
WV-8509
WV-8610
WV-8011
WV-8012
C
Intron/AS Transcripts
Cortex
relative fold change
Intron/AS /HPRT1
3
2
1
0
PBS
WV-2376
WV-6456
WV-8509
WV-8610
WV-8011
WV-8012

FIG. 7

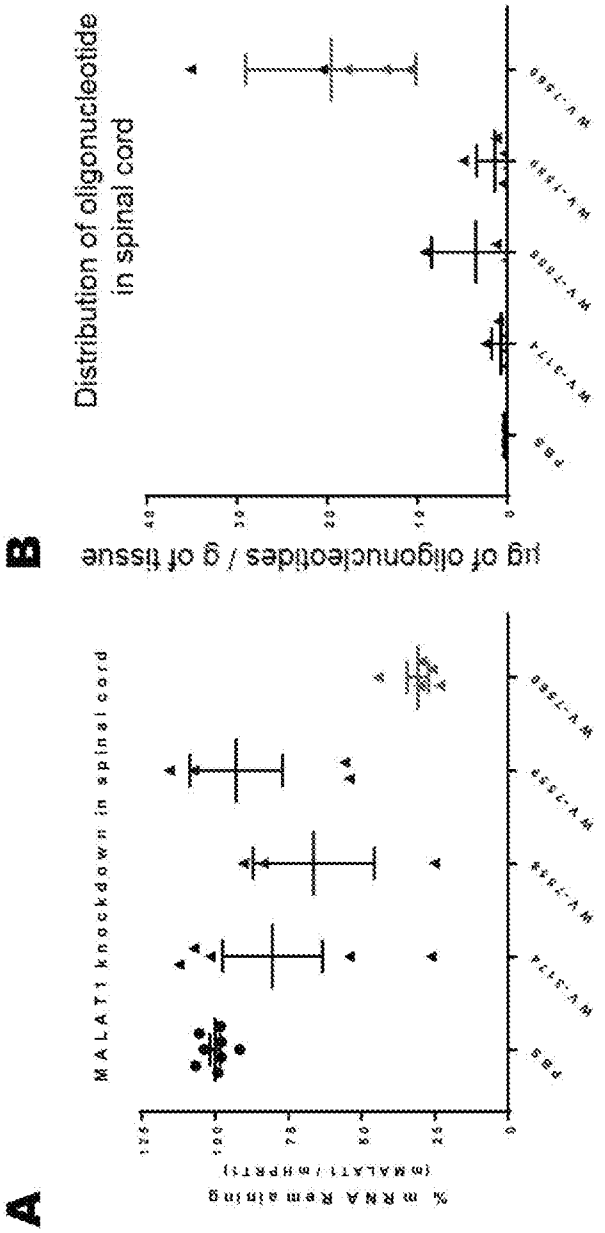

A
MALAT1 knockdown in spinal cord
% mRNA Remaining
(mMALAT1 / mHPRT1)
125
100
75
50
25
0
PBS
MV-3174
MV-7588
MV-7589
MV-7590
B
Distribution of oligonucleotide
in spinal cord
µg of oligonucleotides / g of tissue
40
30
20
10
0
PBS
MV-3174
MV-7588
MV-7589
MV-7590

FIG. 7

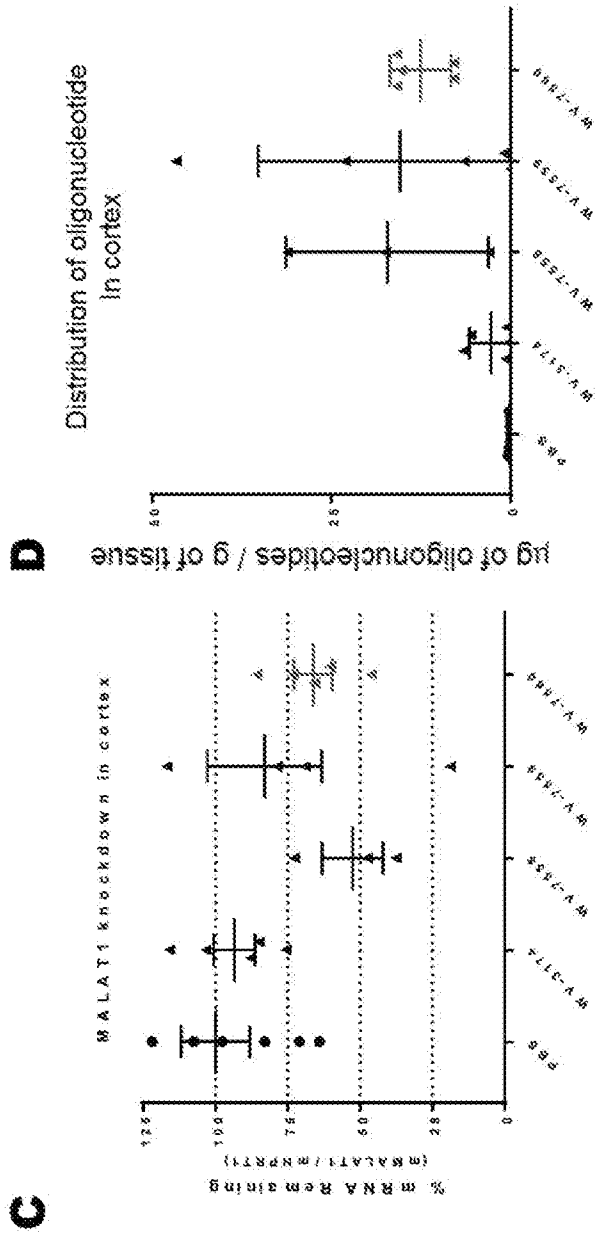

D
Distribution of oligonucleotide
In cortex
µg of oligonucleotides / g of tissue
PBS
ISIS-317174
ISIS-725558
ISIS-725559
ISIS-725560
C
MALAT1 knockdown in cortex
% mRNA Remaining
(mMALAT1 / mNPRT1)
PBS
ISIS-317174
ISIS-725558
ISIS-725559
ISIS-725560

FIG. 8

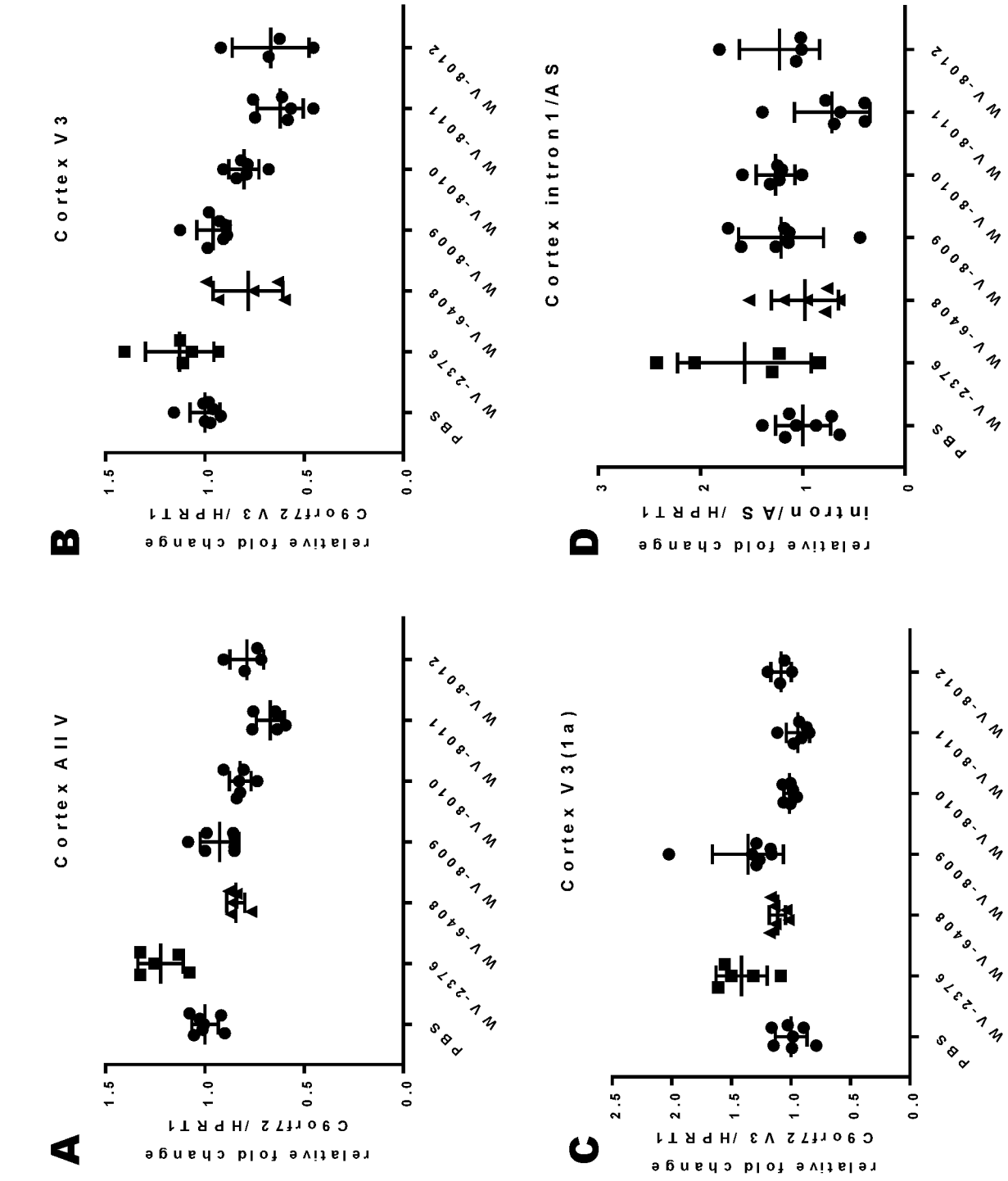

A
Cortex All V
relative fold change
C9orf72 /HPRT1
1.5
1.0
0.5
0.0
PBS
WV-2376
WV-6408
WV-8009
WV-8010
WV-8011
WV-8012
B
Cortex V3
relative fold change
C9orf72 V3 /HPRT1
1.5
1.0
0.5
0.0
PBS
WV-2376
WV-6408
WV-8009
WV-8010
WV-8011
WV-8012
C
Cortex V3(1a)
relative fold change
C9orf72 V3 /HPRT1
2.5
2.0
1.5
1.0
0.5
0.0
PBS
WV-2376
WV-6408
WV-8009
WV-8010
WV-8011
WV-8012
D
Cortex intron1/AS
relative fold change
intron/AS /HPRT1
3
2
1
0
PBS
WV-2376
WV-6408
WV-8009
WV-8010
WV-8011
WV-8012

FIG. 8

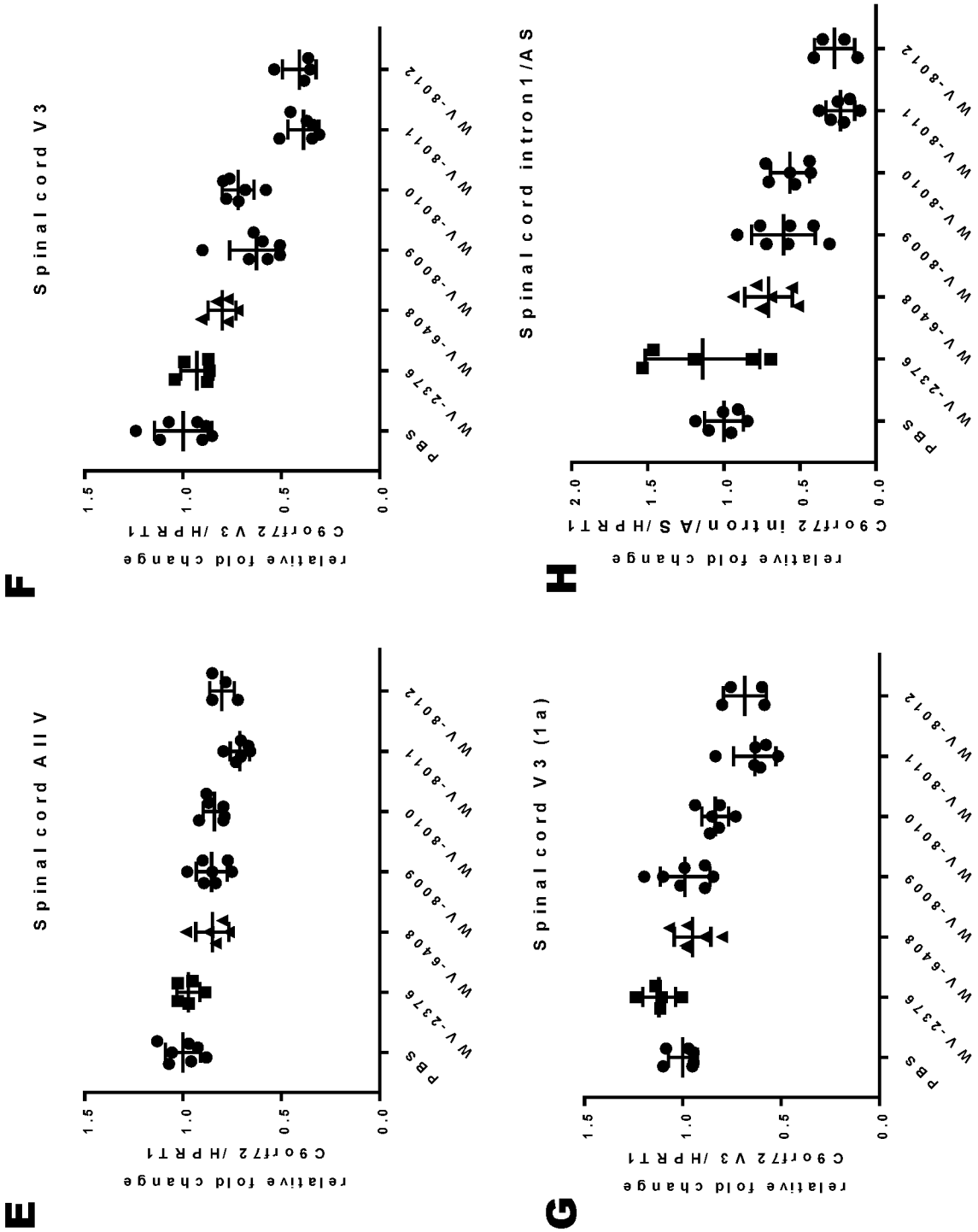

E
Spinal cord All V
relative fold change
C9orf72 /HPRT1
1.5
1.0
0.5
0.0
PBS
WV-2376
WV-6408
WV-8009
WV-8010
WV-8011
WV-8012
F
Spinal cord V3
relative fold change
C9orf72 V3 /HPRT1
1.5
1.0
0.5
0.0
PBS
WV-2376
WV-6408
WV-8009
WV-8010
WV-8011
WV-8012
G
Spinal cord V3 (1a)
relative fold change
C9orf72 V3 /HPRT1
1.5
1.0
0.5
0.0
PBS
WV-2376
WV-6408
WV-8009
WV-8010
WV-8011
WV-8012
H
Spinal cord intron1/AS
relative fold change
C9orf72 intron/AS /HPRT1
2.0
1.5
1.0
0.5
0.0
PBS
WV-2376
WV-6408
WV-8009
WV-8010
WV-8011
WV-8012

FIG. 9

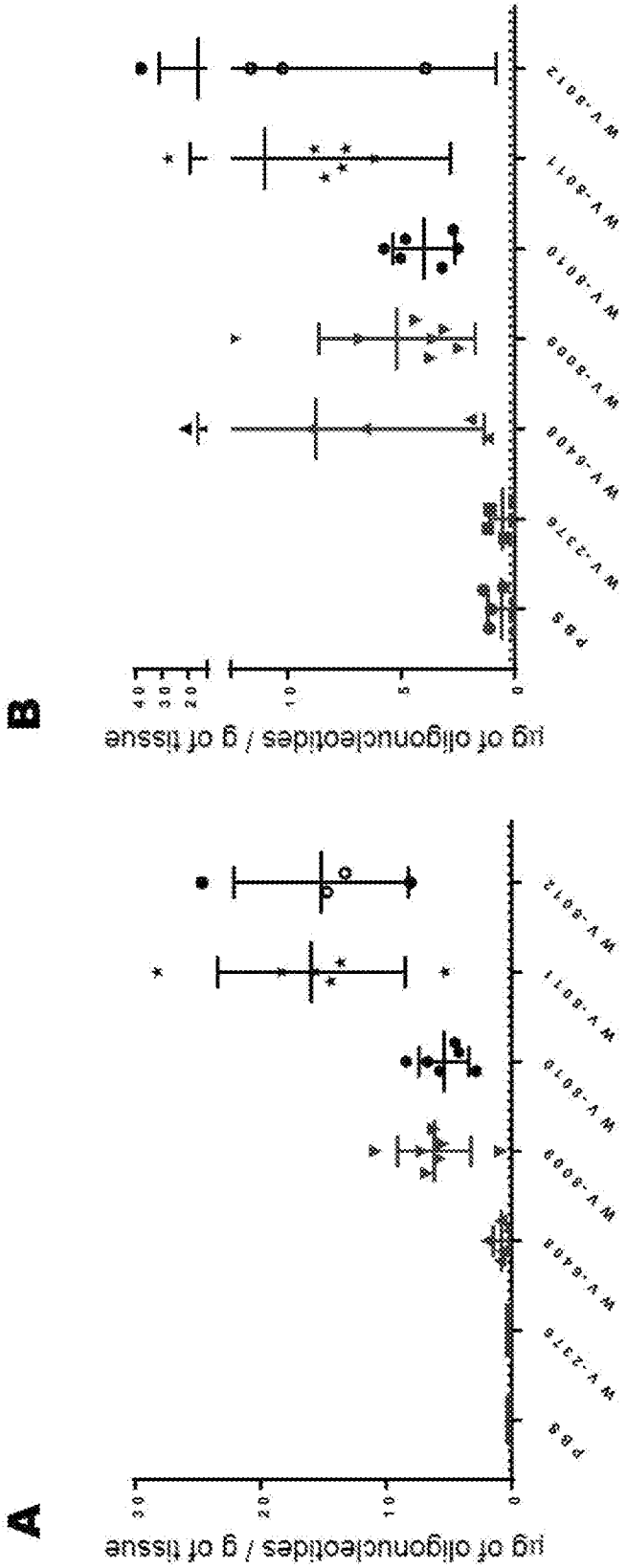

A
B
μg of oligonucleotides / g of tissue
μg of oligonucleotides / g of tissue
PBS
WV-2375
WV-6408
WV-8009
WV-8010
WV-8011
WV-8012
0
10
20
30
40
5

FIG. 10

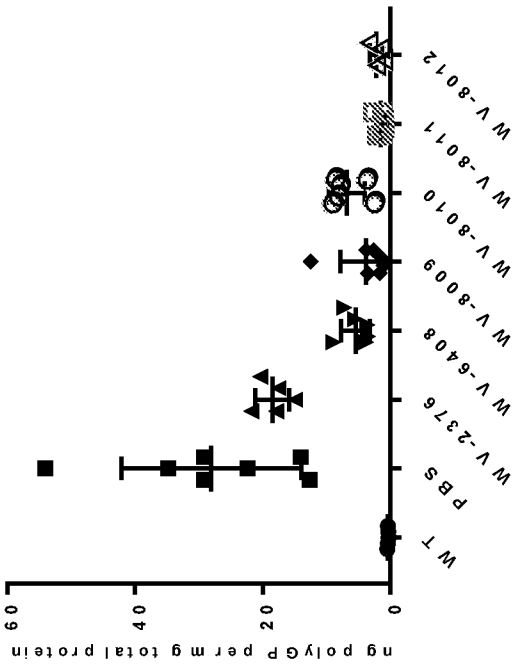
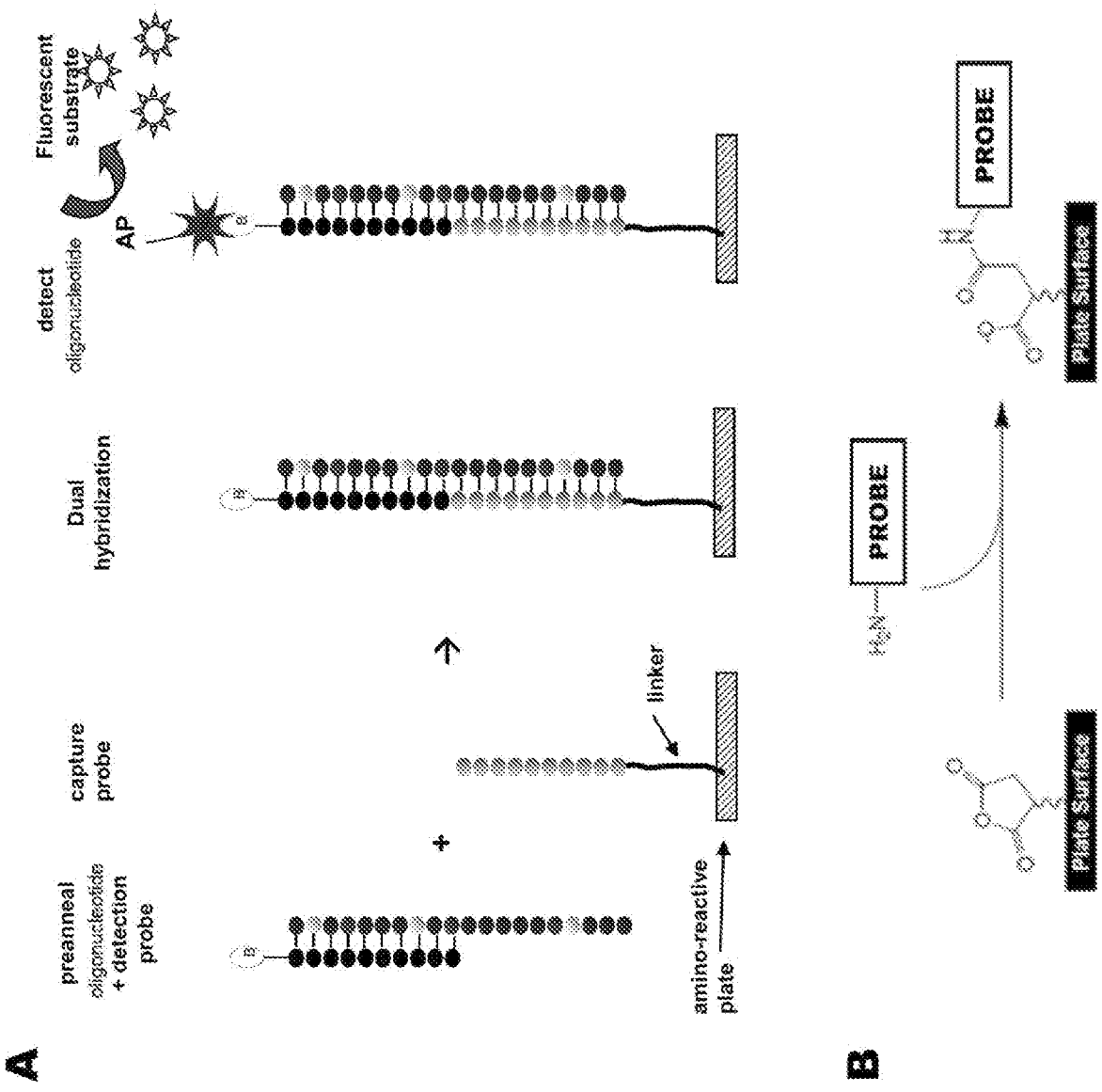

ng polyGP per mg total protein
0
20
40
60
WT
PBS
WV-2376
WV-6408
WV-8009
WV-8010
WV-8011
WV-8012

FIG. 11


A
preanneal oligonucleotide + detection probe
capture probe
linker
amino-reactive plate
Dual hybridization
detect oligonucleotide
AP
Fluorescent substrate
B
PROBE
Plate Surface
PROBE
Plate Surface

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/45653

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/7115, 31/712, 31/7125, 48/00; C07H 21/02, 21/04; C12N 15/11, 15/113 (2018.01)

CPC - A61K 31/7115, 31/712, 31/7125, 48/005; C07H 21/02, 21/04; C12N 15/11, 15/113

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 2017/079291 A1 (IONIS PHARMACEUTICALS, INC., et al.) 11 May 2017; page 2, lines 32-38; page 3, lines1-8, lines 34-36; page 8, lines 12-13; page 9, lines 20-21; page 14, lines 1-8; page 16, lines 16-31; page 17, lines 5-11; page 50, lines 33-34; Figure 1A; page 2, lines 35-38; page 17, lines 4-7	1-2, 4-5 ---------- 3, 6/1-5, 12-14, 15/13-14, 16/13-14, 19/13-14
Y	(DEJESUS-HERNANDES, M et al.) Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS. Neuron, 20 October 2011, Epub 21 September 2011, Vol. 72, No. 2; pages 245-256; abstract; page 247, 1st column, 1st paragraph; DOI: 10.1016/j.nouron.2011.09.011	3, 6/3
Y	WO 2017/062862 A2 (WAVE LIFE SCIENCES LTD.) 13 April 2017; abstract; paragraphs [0003], [0009], [0014], [0030], [0047], [0048], [0054], [0064], [0067], [00308], [00313], [00315], [00490], [00563], [00572], [00626]	6/1-5, 12-14, 15/13-14, 16/13-14, 19/13-14
A	US 2015/0267197 A1 (ISIS PHARMACEUTICALS, INC., et al.) 24 September 2015; paragraph [0320]	42

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 2018 (31.10.2018)	17 DEC 2018
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/45653

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 17, 20-41, 43, 44, 48-61
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-***-Please See Supplemental Page-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-16, 18, 19, 42, 45-47; WV-8009 (oligonucleotide)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/45653

-***-Continued from Box No. III: Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-16, 18, 19, 42, 45-47, and WV-8009 (oligonucleotide) are directed toward compositions comprising an oligonucleotide.

The compositions will be searched to the extent they encompass WV-8009 (first exemplary oligonucleotide). Applicant is invited to elect additional oligonucleotide(s), with specified ID for each, to be searched. Additional oligonucleotide ID(s), will be searched upon the payment of additional fees. It is believed that claims 1-4, 5 (in-part), 6 (in-part), 12-16, 19, and 42 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass WV-8009 (oligonucleotide). Applicants must specify the claims that encompass any additionally elected oligonucleotide ID(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be WV-8010 (oligonucleotide).

No technical features are shared between the oligonucleotides of Groups I+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features including: a 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; which composition is chirally controlled in that it 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 the oligonucleotide targets C9orf72; and an oligonucleotide comprising a wing-core-wing structure, or a wing-core structure, or a core-wing structure, wherein the core comprises a pattern of backbone chiral centers (linkage phosphorus) of: (Np)t[(Op/Rp)n(Sp)m]y; wherein: t is 1-50; n is 1-10; m is 1-50; y is 1-10; Np is either Rp or Sp; Sp indicates the S configuration of a chiral linkage phosphorus of a chiral modified internucleotidic linkage; Op indicates an achiral linkage phosphorus of a natural phosphate linkage; and Rp indicates the S configuration of a chiral linkage phosphorus of a chiral modified internucleotidic linkage; y is 1-10; each wing independently comprises one or more nucleobases; and wherein the base sequence of the oligonucleotide comprises at least 15-25 contiguous bases of a base sequence that is identical with or complementary to a base sequence of a C9orf72 gene or a transcript thereof; these shared technical features are previously disclosed by WO 2017/062862 A2 to Wave Life Sciences Ltd. (hereinafter 'Wave') in view of WO 2017/079291 A1 to Ionis Pharmaceuticals, Inc. et al. (hereinafter 'Ionis').

Wave discloses a composition comprising oligonucleotides (a composition comprising oligonucleotides; paragraphs [0009], [0048]) of a particular oligonucleotide type (of a particular oligonucleotide type; paragraph [0048]) characterized by: a) a common base sequence (characterized by a common base sequence; paragraphs [0009], [0048]); b) a common pattern of backbone linkages (a common pattern of backbone linkages; paragraph [0048]); c) a common pattern of backbone chiral centers (common stereochemistry (a common pattern of backbone chiral centers); paragraphs [0009], [0048]); which composition is chirally controlled in that it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same common base sequence (which composition is chirally controlled in that it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same common base sequence; paragraph [0048]), for oligonucleotides of the particular oligonucleotide type (for oligonucleotides of the particular oligonucleotide type; paragraph [0048]); and wherein the oligonucleotide targets C9orf72 (wherein the oligonucleotide targets, among a list of targets, C9orf72; paragraph [00308]); and an oligonucleotide comprising a wing-core-wing structure (an oligonucleotide comprising a wing-core-wing structure; paragraphs [0009], [0037]), wherein the core comprises a pattern of backbone chiral centers (linkage phosphorus) of: (Np)t[(Op/Rp)n(Sp)m]y (wherein the core comprises a pattern of backbone chiral centers (linkage phosphorus) of: (Np)t (Rp)n(Sp)m {(Np)t[(Op/Rp)n(Sp)m]y)}; paragraphs [0026], [0067]) wherein: t is 1-50 (wherein t is 1-50; paragraphs [00315], [00562]); n is 1-10 (n is 1-10; paragraphs [00315], [00561]); m is 1-50 (m is 1-50; paragraph [00315]); Np is either Rp or Sp (Np is either Rp or Sp; paragraph [00563]); Sp indicates the S configuration of a chiral linkage phosphorus of a chiral modified internucleotidic linkage (Sp indicates the S configuration of a chiral linkage phosphorus of a chiral modified internucleotidic linkage; paragraph [00626]); and Rp indicates the R configuration of a chiral linkage phosphorus of a chiral modified internucleotidic linkage (Rp indicates the R configuration of a chiral linkage phosphorus of a chiral modified internucleotidic linkage; paragraph [00626]); each wing independently comprises one or more nucleobases (each wing independently comprises one or more nucleobases; paragraphs [0009], [0038]); and wherein the base sequence of the oligonucleotide comprises at least 15-25 contiguous bases of a base sequence that is identical with or complementary to a base sequence (and wherein the base sequence of the oligonucleotide comprises at least 15-25 contiguous bases of a base sequence that is identical with or complementary to a base sequence; paragraphs [0054], [0234]) of a C9orf72 gene or a transcript thereof (including, amongst other targets, a C9orf72 gene or a transcript thereof; paragraph [00308]).

Wave does not disclose wherein y is 1-10; and a specific embodiment targeting a C9orf72 gene or a transcript thereof.

Ionis discloses compounds comprising modified oligonucleotides complementary to a C9orf72 transcript (compounds comprising modified oligonucleotides complementary to a C9orf72 transcript; page 1, lines 32-33), for treatment of a neurodegenerative disease (for treatment of a neurodegenerative disease; page 14, lines 4-5).

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Wave to have determined an appropriate value for the number of repeats, y, given the length of the repeats, the length of the wings disclosed by Wave, and the overall length of the oligonucleotide, as disclosed by Wave. It further would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Wave to have provided modified oligonucleotides complementary to a C9orf72 transcript, as disclosed by Ionis, with controlled and enriched chirality, as disclosed by Wave, in order to provide more effective treatment for a neurodegenerative disease, as disclosed by Ionis.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Wave and Ionis references, unity of invention is lacking.