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(54) Title: COMPOUNDS AND METHODS FOR REDUCING PCDH19 EXPRESSION

(57) Abstract: Provided are oligomeric agents, oligomeric compounds, methods, and pharmaceutical compositions for reducing the amount or activity of Protocadherin 19 (PCDH19) RNA in a cell or subject, and in certain instances reducing the amount of PCDH19 protein in a cell or subject. Such oligomeric agents, oligomeric compounds, methods, and pharmaceutical compositions are useful to ameliorate at least one symptom or hallmark of a neurodevelopmental disease or disorder. Such neurodevelopmental diseases or disorders include PCDH19 Epilepsy. Such symptoms or hallmarks include seizures, cognitive impairment, intellectual disabilities, autism spectrum disorder, behavioral problems, aggression, anxiety, obsessive-compulsive disorder, hyperactivity, attention deficit disorder (ADD), and attention deficit hyperactivity disorder (ADHD).

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COMPOUNDS AND METHODS FOR REDUCING PCDH19 EXPRESSION

Sequence Listing

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0443SEQ.xml, created on December 16, 2022, which is 1.37 MB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field

Provided are oligomeric agents, oligomeric compounds, methods, and pharmaceutical compositions for reducing the amount or activity of Protocadherin 19 (PCDH19) RNA in a cell or subject, and in certain instances reducing the amount of PCDH19 protein in a cell or subject. Such oligomeric agents, oligomeric compounds, methods, and pharmaceutical compositions are useful to ameliorate at least one symptom or hallmark of a neurodevelopmental disease or disorder. Such neurodevelopmental diseases or disorders include PCDH19-Epilepsy. Such symptoms or hallmarks include seizures, cognitive impairment, intellectual disabilities, autism spectrum disorder, behavioral problems, aggression, anxiety, obsessive-compulsive disorder, hyperactivity, attention deficit disorder (ADD), and attention deficit hyperactivity disorder (ADHD).

Background

The X-linked gene encoding Protocadherin 19 (PCDH19) is predominantly expressed in the central nervous system and has been implicated in cell-cell adhesion and synaptic function. PCDH19 mutations lead to PCDH19-associated neurodevelopmental diseases and disorders, including PCDH19-Epilepsy (also known as PCDH19-Girl Clusterng Epilepsy (GCE) Epilepsy, PCDH19 Disorder, and Mental Retardation Limited to Females (EFMR)) (Hoshima, N., et al., 2021, Science, Apr 16;372(6539):eaaz3893. doi: 10.1126/science.aaz3893). PCDH19-Epilepsy is the second most common cause of epilepsy; about one in ten girls who have seizures before the age of five have PCDH19-Epilepsy. PCDH19-Epilepsy has a unique pattern of inheritance, due to random X chromosome inactivation, PCDH19-Epilepsy is associated with mosaic expression of mutant PCDH19. The mutation leads to aberrant neural development and is found in females who are heterozygous for PCDH19 mutations, and males who are mosaic carriers of somatic PCDH19 mutaions. Hemizygous males generally do not experience symptoms or have more subtle phenotypes (Thomas, P., et al., 2018, Neuron, 97, 59-66). PCDH19 mutations are associated with seizures (including clusters of seizures, generalized tonic-clonic and/or focal seizures, which may evolve to bilateral, tonic-clonic seizures), cognitive impairment, intellectual disabilities, autism spectrum disorder, behavioral problems, aggression, anxiety, obsessive-compulsive disorder, hyperactivity, attention deficit disorder (ADD), and attention deficit hyperactivity disorder (ADHD). Upon reaching adolescence, there may be a reduction or remission of seizures, however, one or more of cognitive impairment, intellectual disabilities, autism spectrum disorder, behavioral problems, aggression, anxiety, obsessive-compulsive disorder, hyperactivity, attention deficit disorder (ADD), and attention deficit hyperactivity disorder (ADHD) remain (Kolc., K.L., et al., 2019, Mol. Psych. 24, 241-251; Kolc, K.L., et al., 2020, Transl. Psych. 10, 127).

Currently there is a lack of acceptable options for treating diseases and disorders associated with PCDH19 mutations. It is therefore an objective herein to provide compounds and pharmaceutical compositions for the treatment of such diseases and disorders.

Summary

Oligomeric agents, oligomeric compounds, and pharmaceutical compositions of certain embodiments described herein are useful for reducing or inhibiting PCDH19 expression in a cell or subject. In certain embodiments, PCDH19 RNA or protein levels can be reduced in a cell or subject. Also provided are methods of treating PCDH19 Epilepsy.

Detailed Description

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of "or" means "and/or" unless stated otherwise. Furthermore, the use of the term "including" as well as other forms, such as "includes" and "included" is not limiting. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit, unless specifically stated otherwise.

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including, but not limited to, patents, patent applications, articles, books, treatises, and GenBank, ENSEMBL, and NCBI reference sequence records, are hereby expressly incorporated-by-reference for the portions of the document discussed herein, as well as in their entirety.

DEFINITIONS

Unless specific definitions are provided, the nomenclature used in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Where permitted, all patents, applications, published applications and other publications and other data referred to throughout the disclosure are incorporated by reference herein in their entirety.

Unless otherwise indicated, the following terms have the following meanings:

As used herein, "2'-deoxynucleoside" means a nucleoside comprising a 2'-H(H) deoxyribosyl sugar moiety. In certain embodiments, a 2'-deoxynucleoside is a 2'-β-D-deoxynucleoside and comprises a 2'-β-D-deoxyribosyl sugar moiety, which has the β-D configuration as found in naturally occurring deoxyribonucleic acids (DNA). In certain embodiments, a 2'-deoxynucleoside or a nucleoside comprising an unmodified 2'-deoxyribosyl sugar moiety may comprise a modified nucleobase or may comprise an RNA nucleobase (uracil).

As used herein, "2'-MOE" means a 2'-$OCH_2CH_2OCH_3$ group in place of the 2'-OH group of a furanosyl sugar moiety. A "2'-MOE sugar moiety" or a "2'-O-methoxyethyl sugar moiety" means a sugar moiety with a 2'-$OCH_2CH_2OCH_3$ group in place of the 2'-OH group of a furanosyl sugar moiety. Unless otherwise indicated, a 2'-MOE sugar moiety is in the β-D-ribosyl configuration. "MOE" means O-methoxyethyl.

As used herein, "2'-MOE nucleoside" means a nucleoside comprising a 2'-MOE sugar moiety.

As used herein, "2'-OMe" means a 2'-OCH_3 group in place of the 2'-OH group of a furanosyl sugar moiety. A"2'-O-methyl sugar moiety" or "2'-OMe sugar moiety" means a sugar moiety with a 2'-OCH_3 group in place of the 2'-OH group of a furanosyl sugar moiety. Unless otherwise indicated, a 2'-OMe sugar moiety is in the β-D-ribosyl configuration.

As used herein, "2'-OMe nucleoside" means a nucleoside comprising a 2'-OMe sugar moiety.

As used herein, "2'-F" means a 2'-F group in place of the 2'-OH group of a furanosyl sugar moiety. A"2'-O-fluoro sugar moiety" or "2'-F sugar moiety" means a sugar moiety with a 2'-OF group in place of the 2'-OH group of a furanosyl sugar moiety. Unless otherwise indicated, a 2'-F sugar moiety is in the β-D-ribosyl configuration.

As used herein, "xylo 2'-F" means a 2'-F sugar moiety in the β-D-xylosyl configuration.

As used herein, "2'-substituted nucleoside" means a nucleoside comprising a 2'-substituted furanosyl sugar moiety. As used herein, "2'-substituted" in reference to a sugar moiety means a sugar moiety comprising at least one 2'-substituent group other than H or OH.

As used herein, "3' target site" refers to the 3'-most nucleotide of a target nucleic acid which is complementary to an antisense oligonucleotide, when the antisense oligonucleotide is hybridized to the target nucleic acid.

As used herein, "5' target site" refers to the 5'-most nucleotide of a target nucleic acid which is complementary to an antisense oligonucleotide, when the antisense oligonucleotide is hybridized to the target nucleic acid.

As used herein, "5-methylcytosine" means a cytosine modified with a methyl group attached to the 5 position. A 5-methylcytosine is a modified nucleobase.

As used herein, "abasic sugar moiety" means a sugar moiety of a nucleoside that is not attached to a nucleobase. Such abasic sugar moieties are sometimes referred to in the art as "abasic nucleosides."

As used herein, "administration" or "administering" means providing a pharmaceutical agent or composition to an animal.

As used herein, "ameliorate" in reference to a disease or condition means improvement in at least one symptom of the disease or condition relative to the same symptom in the absence of the treatment. In certain embodiments, amelioration is the reduction in the severity or frequency of the symptom or the delayed onset or slowing of progression in the severity or frequency of a symptom.

As used herein, "bicyclic nucleoside" or "BNA" means a nucleoside comprising a bicyclic sugar moiety.

As used herein, "bicyclic sugar" or "bicyclic sugar moiety" means a modified sugar moiety comprising two rings, wherein the second ring is formed via a bridge connecting two of the atoms in the first ring thereby forming a bicyclic structure. In certain embodiments, the first ring of the bicyclic sugar moiety is a furanosyl sugar moiety. In certain embodiments, the furanosyl sugar moiety is a ribosyl sugar moiety. In certain embodiments, the bicyclic sugar moiety does not comprise a furanosyl sugar moiety.

As used herein, "blunt" or "blunt ended" in reference to an oligomeric duplex formed by two oligonucleotides mean that there are no terminal unpaired nucleotides (i.e. no overhanging nucleotides). One or both ends of an oligomeric duplex can be blunt.

As used herein, "cell-targeting moiety" means a conjugate group or portion of a conjugate group that is capable of binding to a particular cell type or particular cell types.

As used herein, "cerebrospinal fluid" or "CSF" means the fluid filling the space around the brain and spinal cord. "Artificial cerebrospinal fluid" or "aCSF" means a prepared or manufactured fluid that has certain properties of cerebrospinal fluid.

As used herein, "cleavable moiety" means a bond or group of atoms that is cleaved under physiological conditions, for example, inside a cell, an animal, or a human.

As used herein, "complementary" in reference to an oligonucleotide means that at least 70% of the nucleobases of the oligonucleotide or one or more portions thereof and the nucleobases of another nucleic acid or

one or more portions thereof are capable of hydrogen bonding with one another when the nucleobase sequence of the oligonucleotide and the other nucleic acid are aligned in opposing directions. As used herein, "complementary nucleobases" means nucleobases that are capable of forming hydrogen bonds with one another. Complementary nucleobase pairs include adenine (A) and thymine (T), adenine (A) and uracil (U), cytosine (C) and guanine (G), 5-methylcytosine (^{m}C) and guanine (G). Certain modified nucleobases that pair with natural nucleobases or with other modified nucleobases are known in the art. For example, inosine can pair with adenosine, cytosine, or uracil. Complementary oligonucleotides and/or nucleic acids need not have nucleobase complementarity at each nucleoside. Rather, some mismatches are tolerated. As used herein, "fully complementary" or "100% complementary" in reference to an oligonucleotide, or a portion thereof, means that the oligonucleotide, or portion thereof, is complementary to another oligonucleotide or nucleic acid at each nucleobase of the shorter of the two oligonucleotides, or at each nucleoside if the oligonucleotides are the same length.

As used herein, "complementary region" in reference to an oligonucleotide is the range of nucleobases of the oligonucleotide that is complementary with a second oligonucleotide or target nucleic acid.

As used herein, "conjugate group" means a group of atoms that is directly or indirectly attached to an oligonucleotide. Conjugate groups include a conjugate moiety and a conjugate linker that attaches the conjugate moiety to the oligonucleotide.

As used herein, "conjugate linker" means a single bond or a group of atoms comprising at least one bond that connects a conjugate moiety to an oligonucleotide.

As used herein, "conjugate moiety" means a group of atoms that is attached to an oligonucleotide via a conjugate linker.

As used herein, "contiguous" in the context of an oligonucleotide refers to nucleosides, nucleobases, sugar moieties, or internucleoside linkages that are immediately adjacent to each other. For example, "contiguous nucleobases" means nucleobases that are immediately adjacent to each other in a sequence.

As used herein, "constrained ethyl" or "cEt" means a 4' to 2' bridge in place of the 2'OH-group of a ribosyl sugar moiety, wherein the bridge has the formula of 4'-CH(CH_3)-O-2', and wherein the methyl group of the bridge is in the S configuration. A "cEt sugar moiety" is a bicyclic sugar moiety with a 4' to 2' bridge in place of the 2'OH-group of a ribosyl sugar moiety, wherein the bridge has the formula of 4'-CH(CH_3)-O-2', and wherein the methyl group of the bridge is in the S configuration. "cEt" means constrained ethyl.

As used herein, "cEt nucleoside" means a nucleoside comprising a cEt sugar moiety.

As used herein, "chirally enriched population" means a plurality of molecules of identical molecular formula, wherein the number or percentage of molecules within the population that contain a particular stereochemical configuration at a particular chiral center is greater than the number or percentage of molecules expected to contain the same particular stereochemical configuration at the same particular chiral center within the population if the particular chiral center were stereorandom. Chirally enriched populations of molecules having multiple chiral centers within each molecule may contain one or more stereorandom chiral centers. In certain embodiments, the molecules are modified oligonucleotides. In certain embodiments, the molecules are compounds comprising modified oligonucleotides.

As used herein, "chirally controlled" in reference to an internucleoside linkage means chirality at that linkage is enriched for a particular stereochemical configuration.

As used herein, "deoxy region" means a region of 5-12 contiguous nucleotides, wherein at least 70% of the nucleosides are 2'-β-D-deoxynucleosides. In certain embodiments, each nucleoside is selected from a 2'-β-D-

deoxynucleoside, a bicyclic nucleoside, and a 2'-substituted nucleoside. In certain embodiments, a deoxy region supports RNase H activity. In certain embodiments, a deoxy region is the gap or internal region of a gapmer.

As used herein, "double-stranded" in reference to a region or an oligonucleotide, means a duplex formed by complementary strands of nucleic acids (including, but not limited to oligonucleotides) hybridized to one another. In certain embodiments, the two strands of a double-stranded region are separate molecules. In certain embodiments, the two strands are regions of the same molecule that has folded onto itself (e.g., a hairpin structure).

As used herein, "duplex" or "duplex region" means the structure formed by two oligonucleotides or portions thereof that are hybridized to one another.

As used herein, "gapmer" means a modified oligonucleotide comprising an internal region having a plurality of nucleosides that support RNase H cleavage positioned between external regions having one or more nucleosides, wherein the nucleosides comprising the internal region are chemically distinct from the nucleoside or nucleosides comprising the external regions. The internal region may be referred to as the "gap" and the external regions may be referred to as the "wings" or "wing segments." In certain embodiments, the internal region is a deoxy region. The positions of the internal region or gap refer to the order of the nucleosides of the internal region and are counted starting from the 5'-end of the internal region. Unless otherwise indicated, "gapmer" refers to a sugar motif. In certain embodiments, each nucleoside of the gap is a 2'-β-D-deoxynucleoside. In certain embodiments, the gap comprises one 2'-substituted nucleoside at position 1, 2, 3, 4, or 5 of the gap, and the remainder of the nucleosides of the gap are 2'-β-D-deoxynucleosides. As used herein, the term "MOE gapmer" indicates a gapmer having a gap comprising 2'-β-D-deoxynucleosides and wings comprising 2'-MOE nucleosides. As used herein, the term "mixed wing gapmer" indicates a gapmer having wings comprising modified nucleosides comprising at least two different sugar modifications. Unless otherwise indicated, a gapmer may comprise one or more modified internucleoside linkages and/or modified nucleobases and such modifications do not necessarily follow the gapmer pattern of the sugar modifications.

As used herein, "hotspot region" is a range of nucleobases on a target nucleic acid that is amenable to oligomeric compound-mediated reduction of the amount or activity of the target nucleic acid.

As used herein, "hybridization" means the pairing or annealing of complementary oligonucleotides and/or nucleic acids. While not limited to a particular mechanism, the most common mechanism of hybridization involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleobases. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an oligomeric duplex and a nucleic acid target. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an antisense oligonucleotide and a nucleic acid target.

As used herein, "internucleoside linkage" means the covalent linkage between contiguous nucleosides in an oligonucleotide. As used herein, "modified internucleoside linkage" means any internucleoside linkage other than a phosphodiester internucleoside linkage. "Phosphorothioate internucleoside linkage or "PS internucleoside linkage" is a modified internucleoside linkage in which one of the non-bridging oxygen atoms of a phosphodiester internucleoside linkage is replaced with a sulfur atom.

As used herein, "inverted nucleoside" means a nucleotide having a 3' to 3' and/or 5' to 5' internucleoside linkage, as shown herein.

As used herein, "inverted sugar moiety" means the sugar moiety of an inverted nucleoside or an abasic sugar moiety having a 3' to 3' and/or 5' to 5' internucleoside linkage.

As used herein, "linked nucleosides" are nucleosides that are connected in a contiguous sequence (i.e., no additional nucleosides are presented between those that are linked).

As used herein, “linker-nucleoside” means a nucleoside that links, either directly or indirectly, an oligonucleotide to a conjugate moiety. Linker-nucleosides are located within the conjugate linker of an oligomeric compound. Linker-nucleosides are not considered part of the oligonucleotide portion of an oligomeric compound even if they are contiguous with the oligonucleotide.

“Lipid nanoparticle” or “LNP” is a vesicle comprising a lipid layer encapsulating a pharmaceutically active molecule, such as a nucleic acid molecule, e.g., an RNAi or a plasmid from which an RNAi is transcribed. LNPs are described in, for example, U.S. Patent Nos. 6,858,225, 6,815,432, 8,158,601, and 8,058,069, the entire contents of which are hereby incorporated herein by reference.

As used herein, “mismatch” or “non-complementary” means a nucleobase of a first nucleic acid sequence that is not complementary with the corresponding nucleobase of a second nucleic acid sequence or target nucleic acid when the first and second nucleic acid sequences are aligned in opposing directions.

As used herein, “motif” means the pattern of unmodified and/or modified sugar moieties, nucleobases, and/or internucleoside linkages, in an oligonucleotide.

As used herein, “non-bicyclic modified sugar moiety” means a modified sugar moiety that comprises a modification, such as a substituent, that does not form a bridge between two atoms of the sugar to form a second ring.

As used herein, “motif” means the pattern of unmodified and/or modified sugar moieties, nucleobases, and/or internucleoside linkages, in an oligonucleotide.

As used herein, "nucleobase" means an unmodified nucleobase or a modified nucleobase. As used herein an “unmodified nucleobase” is adenine (A), thymine (T), cytosine (C), uracil (U), or guanine (G). As used herein, a “modified nucleobase” is a group of atoms other than unmodified A, T, C, U, or G capable of pairing with at least one unmodified nucleobase. A “5-methylcytosine” is a modified nucleobase. A universal base is a modified nucleobase that can pair with any one of the five unmodified nucleobases. As used herein, “nucleobase sequence” means the order of contiguous nucleobases in a target nucleic acid or oligonucleotide independent of any sugar or internucleoside linkage modification.

As used herein, “nucleoside” means a compound, or a fragment of a compound, comprising a nucleobase and a sugar moiety. The nucleobase and sugar moiety are each, independently, unmodified or modified. As used herein, “modified nucleoside” means a nucleoside comprising a modified nucleobase and/or a modified sugar moiety. Modified nucleosides include abasic nucleosides, which lack a nucleobase. “Linked nucleosides” are nucleosides that are connected in a contiguous sequence (i.e., no additional nucleosides are presented between those that are linked).

As used herein, “nucleoside overhang” refers to unpaired nucleotides at either or both ends of a duplex formed by hybridization of two oligonucleotides.

As used herein, "oligomeric agent" means an oligomeric compound and optionally one or more additional features, such as a second oligomeric compound. An oligomeric agent may be a single-stranded oligomeric compound or may be an oligomeric duplex formed by two complementary oligomeric compounds.

As used herein, "oligomeric compound" means an oligonucleotide and optionally one or more additional features, such as a conjugate group or terminal group. An oligomeric compound may be paired with a second oligomeric compound that is complementary to the first oligomeric compound or may be unpaired. A “singled-stranded oligomeric compound” is an unpaired oligomeric compound. The term “oligomeric duplex” means a duplex formed by two oligomeric compounds having complementary nucleobase sequences. Each oligomeric compound of an oligomeric duplex may be referred to as a “duplexed oligomeric compound.”

As used herein, "oligonucleotide" means a strand of linked nucleosides connected via internucleoside linkages, wherein each nucleoside and internucleoside linkage may be modified or unmodified. Unless otherwise indicated, oligonucleotides consist of 8-50 linked nucleosides. As used herein, "modified oligonucleotide" means an oligonucleotide, wherein at least one nucleoside or internucleoside linkage is modified. As used herein, "unmodified oligonucleotide" means an oligonucleotide that does not comprise any nucleoside modifications or internucleoside modifications. An oligonucleotide may be paired with a second oligonucleotide that is complementary to the oligonucleotide or it may be unpaired. A "single-stranded oligonucleotide" is an unpaired oligonucleotide. A "double-stranded oligonucleotide" is an oligonucleotide that is paired with a second oligonucleotide.

As used herein, an "oligonucleotide duplex" means a duplex formed by two paired oligonucleotides having complementary nucleobase sequences. Each oligo of an oligonucleotide duplex is a "duplexed oligonucleotide" or a "double-stranded oligonucleotide."

As used herein, "pharmaceutically acceptable carrier or diluent" means any substance suitable for use in administering to an animal. Certain such carriers enable pharmaceutical compositions to be formulated as, for example, tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspension and lozenges for the oral ingestion by an animal. In certain embodiments, a pharmaceutically acceptable carrier or diluent is sterile water, sterile saline, sterile buffer solution or sterile artificial cerebrospinal fluid.

As used herein, "pharmaceutically acceptable salts" means physiologically and pharmaceutically acceptable salts of compounds. Pharmaceutically acceptable salts retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

As used herein, "pharmaceutical composition" means a mixture of substances suitable for administering to an animal. For example, a pharmaceutical composition may comprise an oligomeric compound and a sterile aqueous solution. In certain embodiments, a pharmaceutical composition shows activity in free uptake assay in certain cell lines.

As used herein, "reducing the amount or activity" refers to a reduction or blockade of the transcriptional expression or activity relative to the transcriptional expression or activity in an untreated or control sample and does not necessarily indicate a total elimination of transcriptional expression or activity.

As used herein, "RNA" means an RNA transcript and includes pre-mRNA and mature mRNA unless otherwise specified.

As used herein, "RNAi agent" means an antisense agent that acts, at least in part, through RISC or Ago2 to modulate a target nucleic acid and/or protein encoded by a target nucleic acid. RNAi agents include, but are not limited to double-stranded siRNA, single-stranded RNAi (ssRNAi), and microRNA, including microRNA mimics. RNAi agents may comprise conjugate groups and/or terminal groups. In certain embodiments, an RNAi agent modulates the amount and/or activity, of a target nucleic acid. The term RNAi agent excludes antisense agents that act through RNase H.

As used herein, "RNase H agent" means an antisense agent that acts through RNase H to modulate a target nucleic acid and/or protein encoded by a target nucleic acid. In certain embodiments, RNase H agents are single-stranded. In certain embodiments, RNase H agents are double-stranded. RNase H agents may comprise conjugate groups and/or terminal groups. In certain embodiments, an RNase H agent modulates the amount and/or activity of a target nucleic acid. The term RNase H agent excludes antisense agents that act principally through RISC/Ago2.

As used herein, "self-complementary" in reference to an oligonucleotide means an oligonucleotide that at least partially hybridizes to itself.

As used herein, “single-stranded” means a nucleic acid (including but not limited to an oligonucleotide) that is unpaired and is not part of a duplex. Single-stranded compounds are capable of hybridizing with complementary nucleic acids to form duplexes, at which point they are no longer single-stranded.

As used herein, “stabilized phosphate group” means a 5’-phosphate analog that is metabolically more stable than a 5’-phosphate as naturally occurs on DNA or RNA.

As used herein, “standard cell assay” and “standard *in vitro* assay” are used interchangeably herein and the terms mean the assay described in Example 1 and reasonable variations thereof.

As used herein, “stereorandom chiral center” in the context of a population of molecules of identical molecular formula means a chiral center having a random stereochemical configuration. For example, in a population of molecules comprising a stereorandom chiral center, the number of molecules having the (*S*) configuration of the stereorandom chiral center may be but is not necessarily the same as the number of molecules having the (*R*) configuration of the stereorandom chiral center. The stereochemical configuration of a chiral center is considered random when it is the result of a synthetic method that is not designed to control the stereochemical configuration. In certain embodiments, a stereorandom chiral center is a stereorandom phosphorothioate internucleoside linkage.

As used herein, “subject” means a human or non-human animal. The terms “subject” “animal” and “individual” are used interchangeably. In certain embodiments, the subject is human.

As used herein, “sugar moiety” means an unmodified sugar moiety or a modified sugar moiety. As used herein, “unmodified sugar moiety” means a 2’-OH(H) β-D-ribosyl sugar moiety, as found in RNA (an “unmodified RNA sugar moiety”), or a 2’-H(H) β-D-deoxyribosyl sugar moiety, as found in DNA (an “unmodified DNA sugar moiety”). Unmodified sugar moieties have one hydrogen at each of the 1’, 3’, and 4’ positions, an oxygen at the 3’ position, and two hydrogens at the 5’ position. As used herein, “modified sugar moiety” or “modified sugar” means a modified furanosyl sugar moiety or a sugar surrogate.

As used herein, "sugar surrogate" means a modified sugar moiety having other than a furanosyl moiety that can link a nucleobase to another group, such as an internucleoside linkage, conjugate group, or terminal group in an oligonucleotide. Modified nucleosides comprising sugar surrogates can be incorporated into one or more positions within an oligonucleotide and such oligonucleotides are capable of hybridizing to complementary oligomeric compounds or target nucleic acids.

As used herein, “symptom or hallmark” means any physical feature or test result that indicates the existence or extent of a disease or disorder. In certain embodiments, a symptom is apparent to a subject or to a medical professional examining or testing said subject. In certain embodiments, a hallmark is apparent upon invasive diagnostic testing, including, but not limited to, post-mortem tests.

As used herein, “target nucleic acid” and “target RNA” mean a nucleic acid that an antisense compound is designed to affect. Target RNA means an RNA transcript and includes pre-mRNA and mature mRNA unless otherwise specified.

As used herein, “target region” means a portion of a target nucleic acid to which an oligomeric compound is designed to hybridize.

As used herein, "terminal group" means a chemical group or group of atoms that is covalently linked to a terminus of an oligonucleotide.

As used herein, “treating” means improving a subject’s disease or condition by administering an oligomeric agent or oligomeric compound described herein. In certain embodiments, treating a subject improves a symptom relative to the same symptom in the absence of the treatment. In certain embodiments, treatment reduces

in the severity or frequency of a symptom, or delays the onset of a symptom, slows the progression of a symptom, or slows the severity or frequency of a symptom.

As used herein, "therapeutically effective amount" means an amount of a pharmaceutical agent or composition that provides a therapeutic benefit to an animal. For example, a therapeutically effective amount improves a symptom of a disease.

As used herein, "antisense activity" means any detectable and/or measurable change attributable to the hybridization of an antisense compound to its target nucleic acid. In certain embodiments, antisense activity is a decrease in the amount or expression of a target nucleic acid or protein encoded by such target nucleic acid compared to target nucleic acid levels or target protein levels in the absence of the antisense compound. In certain embodiments, antisense activity is the modulation of splicing of a target pre-mRNA.

As used herein, "antisense agent" means an antisense compound and optionally one or more additional features, such as a sense compound.

As used herein, "antisense compound" means an antisense oligonucleotide and optionally one or more additional features, such as a conjugate group.

As used herein, "sense compound" means a sense oligonucleotide and optionally one or more additional features, such as a conjugate group.

As used herein, "antisense oligonucleotide" means an oligonucleotide, including the oligonucleotide portion of an antisense compound, that is capable of hybridizing to a target nucleic acid and is capable of at least one antisense activity. Antisense oligonucleotides include but are not limited to antisense RNAi oligonucleotides and antisense RNase H oligonucleotides.

As used herein, "sense oligonucleotide" means an oligonucleotide, including the oligonucleotide portion of a sense compound, that is capable of hybridizing to an antisense oligonucleotide.

CERTAIN EMBODIMENTS

The present disclosure provides the following non-limiting numbered embodiments:

Embodiment 1. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion of an PCDH19 nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar and a modified internucleoside linkage.

Embodiment 2. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of SEQ ID NOs: 15-482, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar and a modified internucleoside linkage.

Embodiment 3. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, or 16 contiguous nucleobases of any of SEQ ID NOs: 15-560, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar and a modified internucleoside linkage.

Embodiment 4. The oligomeric compound of embodiment 2 or embodiment 3, wherein the modified oligonucleotide has a nucleobase sequence consisting of the nucleobase sequence of any of SEQ ID NOs: 15-560.

Embodiment 5. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 contiguous nucleobases of any of SEQ ID NOs: 561-1028, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar and a modified internucleoside linkage.

Embodiment 6. The oligomeric compound of embodiment 5, wherein the modified oligonucleotide has a nucleobase sequence consisting of the nucleobase sequence of any of SEQ ID NOs: 561-1028.

Embodiment 7. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases complementary to:

an equal length portion of nucleobases 4,743-4,767 of SEQ ID NO: 1;

an equal length portion of nucleobases 12,319-12,346 of SEQ ID NO: 1;

an equal length portion of nucleobases 34,364-34,389 of SEQ ID NO: 1; or

an equal length portion of nucleobases 84,408-84,431 of SEQ ID NO: 1;

wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar and a modified internucleoside linkage.

Embodiment 8. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of a sequence selected from:

SEQ ID NO: 132, 228, 284, 330, or 440;

SEQ ID NO: 416, 72, 129, or 204;

SEQ ID NO: 371, 425, 20, or 111; or

SEQ ID NO: 367, 407, 24, 93, or 218;

wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar and a modified internucleoside linkage.

Embodiment 9. The oligomeric compound of any of embodiments 1-8, wherein the nucleobase sequence of the modified oligonucleotide is at least 80%, 85%, 90%, 95%, or 100% complementary to any of the nucleobase sequences of SEQ ID NO: 1 or SEQ ID NO: 2 when measured across the entire nucleobase sequence of the modified oligonucleotide.

Embodiment 10. The oligomeric compound of any of embodiments 1-9, wherein the modified oligonucleotide consists of 12 to 20, 12 to 25, 12 to 30, 12 to 50, 13 to 20, 13 to 25, 13 to 30, 13 to 50, 14 to 20, 14 to 25, 14 to 30, 14 to 50, 15 to 20, 15 to 25, 15 to 30, 15 to 50, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 16 to 50, 17 to 20, 17 to 25, 17 to 30, 17 to 50, 18 to 20, 18 to 25, 18 to 30, 18 to 50, 19 to 20, 19 to 25, 19 to 30, 19 to 50, 20 to 25, 20 to 30, 20 to 50, 21 to 25, 21 to 30, 21 to 50, 22 to 25, 22 to 30, 22 to 50, 23 to 25, 23 to 30, or 23 to 50 linked nucleosides.

Embodiment 11. The oligomeric compound of any of embodiments 1-10, wherein the modified oligonucleotide comprises at least one modified nucleoside.

Embodiment 12. The oligomeric compound of embodiment 11, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.

Embodiment 13. The oligomeric compound of embodiment 12, wherein the modified sugar moiety comprises a bicyclic sugar moiety.

Embodiment 14. The oligomeric compound of embodiment 13, wherein the bicyclic sugar moiety comprises a 2'-4' bridge selected from –O-CH_2-; and –O-CH(CH_3)-.

Embodiment 15. The oligomeric compound of any of embodiments 11-14, wherein at least one modified nucleoside of the modified oligonucleotide comprises a non-bicyclic modified sugar moiety.

Embodiment 16. The oligomeric compound of embodiment 15, wherein at least one modified nucleoside of the modified oligonucleotide comprises a bicyclic sugar moiety having a 2'-4' bridge and at least one nucleoside comprising a non-bicyclic modified sugar moiety.

Embodiment 17. The oligomeric compound of embodiment 15 or embodiment 16, wherein the non-bicyclic modified sugar moiety is a 2'-O(CH_2)$_2$-OCH_3 ribosyl sugar moiety, a 2'-OMe sugar moiety, or a 2'-F sugar moiety.

Embodiment 18. The oligomeric compound of any of embodiments 1-17, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.

Embodiment 19. The oligomeric compound of embodiment 18, wherein at least one modified nucleoside of the modified oligonucleotide comprises a sugar surrogate selected from morpholino and PNA.

Embodiment 20. The oligomeric compound of any of embodiments 1-19, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 21. The oligomeric compound of embodiment 20, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

Embodiment 22. The oligomeric compound of embodiment 20 or embodiment 21, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 23. The oligomeric compound of embodiment 20 or 22, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

Embodiment 24. The oligomeric compound of any of embodiments 20, 22, or 23, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.

Embodiment 25. The oligomeric compound of any of embodiments 20 or 22-24, wherein at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, or at least 19 internucleoside linkages of the modified oligonucleotide are phosphorothioate internucleoside linkages.

Embodiment 26. The oligomeric compound of any of embodiments 20-22, 24, or 25, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 27. The oligomeric compound of any of embodiments 20 or 22-26, wherein the internucleoside linkage motif of the modified oligonucleotide is selected from: 5'- sssssssssssssssssss -3', 5'- sssssssssssssss -3', 5'- soooosssssssssssooss-3', and ssooooooooooooooooooss; wherein each 'o' represents a phosphodiester internucleoside linkage and each 's' represents a phosphorothioate internucleoside linkage.

Embodiment 28. The oligomeric compound of any of embodiments 1-27, wherein the modified oligonucleotide comprises a modified nucleobase.

Embodiment 29. The oligomeric compound of embodiment 28, wherein the modified nucleobase is a 5-methylcytosine.

Embodiment 30. The oligomeric compound of any of embodiments 1-29, wherein the oligomeric compound comprises a modified oligonucleotide consisting of 12-22, 12-20, 14-18, 14-20, 15-17, 15-25, 16-20, 16-18, 18-22, 18-25, 18-20, 20-25, or 21-23 linked nucleosides, or a pharmaceutically acceptable salt thereof.

Embodiment 31. The oligomeric compound of embodiment 30, wherein the modified oligonucleotide is a pharmaceutically acceptable salt comprising one or more cations selected from sodium, potassium, calcium, and magnesium.

Embodiment 32. The oligomeric compound of any of embodiments 1-31, wherein the modified oligonucleotide consists of 16 linked nucleosides.

Embodiment 33. The oligomeric compound of any of embodiments 1-31, wherein the modified oligonucleotide consists of 18 linked nucleosides.

Embodiment 34. The oligomeric compound of any of embodiments 1-31, wherein the modified oligonucleotide consists of 20 linked nucleosides.

Embodiment 35. The oligomeric compound of any of embodiments 1-31, wherein the modified oligonucleotide consists of 21 linked nucleosides.

Embodiment 36. The oligomeric compound of any of embodiments 1-31, wherein the modified oligonucleotide consists of 23 linked nucleosides.

Embodiment 37. The oligomeric compound of any of embodiments 1-35, wherein the oligomeric compound activates RNase H.

Embodiment 38. The oligomeric compound of embodiment 37, wherein the modified oligonucleotide is a gapmer.

Embodiment 39. The oligomeric compound of any of embodiments 1-34, wherein the modified oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 1-6 linked 5'-region nucleosides;

a central region consisting of 6-10 linked central region nucleosides; and

a 3'-region consisting of 1-6 linked 3'-region nucleosides;

wherein the 3'-most nucleoside of the 5'-region and the 5'-most nucleoside of the 3'-region comprise modified sugar moieties, and

each of the central region nucleosides is selected from a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety and a nucleoside comprising a 2'-substituted sugar moiety, wherein the central region comprises at least six nucleosides comprising a 2'-β-D-deoxyribosyl sugar moiety and no more than two nucleosides comprising a 2'-substituted sugar moiety.

Embodiment 40. The oligomeric compound of any of embodiments 1-39, wherein the modified oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 1-6 linked 5'-region nucleosides;

a central region consisting of 6-10 linked central region nucleosides; and

a 3'-region consisting of 1-6 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a modified sugar moiety and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

Embodiment 41. The oligomeric compound of embodiment 40, wherein the modified oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 5 linked 5'-region nucleosides;

a central region consisting of 10 linked central region nucleosides; and

a 3'-region consisting of 5 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-$O(CH_2)_2$-OCH_3 ribosyl modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

Embodiment 42. The oligomeric compound of embodiment 40, wherein the modified oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 3 linked 5'-region nucleosides;

a central region consisting of 10 linked central region nucleosides; and

a 3'-region consisting of 3 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a cEt sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

Embodiment 43. A chirally enriched population of oligomeric compounds of any of embodiments 1-42, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

Embodiment 44. The chirally enriched population of embodiment 43, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the *(Sp)* or *(Rp)* configuration.

Embodiment 45. The chirally enriched population of embodiment 43, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

Embodiment 46. The chirally enriched population of embodiment 43, wherein the population is enriched for modified oligonucleotides having the *(Rp)* configuration at one particular phosphorothioate internucleoside linkage and the *(Sp)* configuration at each of the remaining phosphorothioate internucleoside linkages.

Embodiment 47. The chirally enriched population of embodiment 43, wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the *Sp*, *Sp*, and *Rp* configurations, in the 5' to 3' direction.

Embodiment 48. A population of oligomeric compounds of any of embodiments 1-42, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

Embodiment 49. An oligomeric duplex, comprising a first oligomeric compound and a second oligomeric compound comprising a second modified oligonucleotide, wherein the first oligomeric compound is an oligomeric compound of any of embodiments 1-42.

Embodiment 50. The oligomeric duplex of embodiment 49, wherein the second oligomeric compound comprises a second modified oligonucleotide consisting of 12 to 50 linked nucleosides, and wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 12 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

Embodiment 51. An oligomeric duplex comprising:

a first oligomeric compound comprising a first modified oligonucleotide consisting of 19 to 30 linked nucleosides wherein the nucleobase sequence of the first modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 contiguous nucleobases of the nucleobase sequence of any of SEQ ID NOs: 561-1028; and

a second oligomeric compound comprising a second modified oligonucleotide consisting of 15 to 30 linked nucleosides wherein the nucleobase sequence of the second modified oligonucleotide comprises a

complementary region of at least 12 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

Embodiment 52. An oligomeric duplex comprising:

a first oligomeric compound comprising a first modified oligonucleotide consisting of 19 to 30 linked nucleosides wherein the nucleobase sequence of the first modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 contiguous nucleobases of the nucleobase sequence of any of SEQ ID NOs: 561-1028; and

a second oligomeric compound comprising a second modified oligonucleotide consisting of 15 to 30 linked nucleosides wherein the nucleobase sequence of the second modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, or at least 21 contiguous nucleobases of the nucleobase sequence of any of SEQ ID NOs: 1029-1496, wherein the nucleobase sequence of the second modified oligonucleotide is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

Embodiment 53. An oligomeric duplex comprising:

a first oligomeric compound comprising a first modified oligonucleotide consisting of 23 linked nucleosides wherein the nucleobase sequence of the first modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 561-1028; and

a second oligomeric compound comprising a second modified oligonucleotide consisting of 21 linked nucleosides wherein the nucleobase sequence of the second modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 1029-1496, wherein the nucleobase sequence of the second modified oligonucleotide is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

Embodiment 54. The oligomeric duplex of any of embodiments 49-53, wherein the modified oligonucleotide of the first oligomeric compound comprises a 5'-stabilized phosphate group.

Embodiment 55. The oligomeric duplex of embodiment 54, wherein the 5'-stabilized phosphate group comprises a cyclopropyl phosphonate or a vinyl phosphonate.

Embodiment 56. The oligomeric duplex of any of embodiments 49-53, wherein the modified oligonucleotide of the first oligomeric compound comprises a glycol nucleic acid (GNA) sugar surrogate.

Embodiment 57. The oligomeric duplex of any of embodiments 49-55, wherein the modified oligonucleotide of the first oligomeric compound comprises a 2'-NMA sugar moiety.

Embodiment 58. The oligomeric duplex of any of embodiments 49-57, wherein at least one nucleoside of the second modified oligonucleotide comprises a modified sugar moiety.

Embodiment 59. The oligomeric duplex of embodiment 58, wherein the modified sugar moiety of the second modified oligonucleotide comprises a bicyclic sugar moiety.

Embodiment 60. The oligomeric duplex of embodiment 59, wherein the bicyclic sugar moiety of the second modified oligonucleotide comprises a 2'-4' bridge selected from –O-CH_2-; and –O-$CH(CH_3)$-.

Embodiment 61. The oligomeric duplex of embodiment 59 or embodiment 60, wherein the modified sugar moiety of the second modified oligonucleotide comprises a non-bicyclic modified sugar moiety.

Embodiment 62. The oligomeric duplex of embodiment 61, wherein the non-bicyclic modified sugar moiety of the second modified oligonucleotide is a 2'-MOE sugar moiety, a 2'-F sugar moiety, or 2'-OMe sugar moiety.

Embodiment 63. The oligomeric duplex of any of embodiments 49-62, wherein at least one nucleoside of the second modified oligonucleotide comprises a sugar surrogate.

Embodiment 64. The oligomeric duplex of any of embodiments 49-63, wherein the second modified oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 65. The oligomeric duplex of embodiment 64, wherein at least one modified internucleoside linkage of the second modified oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 66. The oligomeric duplex of any of embodiments 49-65, wherein the second modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

Embodiment 67. The oligomeric duplex of any of embodiments 49-66, wherein each internucleoside linkage of the second modified oligonucleotide is independently selected from a phosphodiester or a phosphorothioate internucleoside linkage.

Embodiment 68. The oligomeric duplex of any of embodiments 49-67, wherein the internucleoside linkage motif of the first modified oligonucleotide is ssooooooooooooooooooss and the internucleoside linkage motif of the second modified oligonucleotide is ssooooooooooooooooss, wherein each "o" represents a phosphodiester internucleoside linkage and each "s" represents a phosphorothioate internucleoside linkage.

Embodiment 69. The oligomeric duplex of any of embodiments 49-68, wherein the second modified oligonucleotide comprises at least one modified nucleobase.

Embodiment 70. The oligomeric duplex of embodiment 69, wherein the modified nucleobase of the second modified oligonucleotide is 5-methylcytosine.

Embodiment 71. The oligomeric duplex of any of embodiments 49-70, wherein the second modified oligonucleotide comprises a conjugate group.

Embodiment 72. The oligomeric duplex of embodiment 71, wherein the conjugate group comprises a conjugate linker and a conjugate moiety.

Embodiment 73. The oligomeric duplex of embodiment 71 or embodiment 72, wherein the conjugate group is attached to the second modified oligonucleotide at the 5'-end of the second modified oligonucleotide.

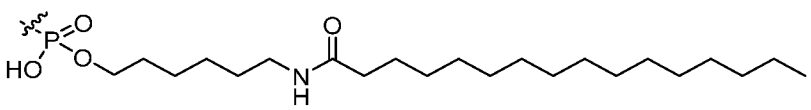
Embodiment 74. The oligomeric duplex of embodiment 71 or embodiment 72, wherein the conjugate group is attached to the second modified oligonucleotide at the 3'-end of the modified oligonucleotide.

Embodiment 75. The oligomeric duplex of embodiment 71 or embodiment 72, wherein the conjugate group is attached to the second modified oligonucleotide through a modified internucleoside linkage.

Embodiment 76. The oligomeric duplex of any of embodiments 71-75, wherein the conjugate group comprises a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, C5 alkyl, C22 alkenyl, C20 alkenyl, C16 alkenyl, C10 alkenyl, C21 alkenyl, C19 alkenyl, C18 alkenyl, C15 alkenyl, C14 alkenyl, C13 alkenyl, C12 alkenyl, C11 alkenyl, C9 alkenyl, C8 alkenyl, C7 alkenyl, C6 alkenyl, or C5 alkenyl.

Embodiment 77. The oligomeric duplex of any of embodiments 71-76, wherein the conjugate moiety is a 6-palmitamidohexyl conjugate moiety.

Embodiment 78. The oligomeric duplex of any of embodiments 71-74, wherein the conjugate group has the following structure:



Embodiment 79. The oligomeric duplex of any of embodiments 71-78, wherein the conjugate group comprises a cell-targeting moiety.

Embodiment 80. The oligomeric duplex of any of embodiments 49-79, wherein the second modified oligonucleotide comprises a terminal group.

Embodiment 81. The oligomeric duplex of embodiment 80, wherein the terminal group is an abasic sugar moiety.

Embodiment 82. The oligomeric duplex of any of embodiments 49-81, wherein the second modified oligonucleotide consists of 12 to 20, 12 to 25, 12 to 30, 12 to 50, 13 to 20, 13 to 25, 13 to 30, 13 to 50, 14 to 20, 14 to 25, 14 to 30, 14 to 50, 15 to 20, 15 to 25, 15 to 30, 15 to 50, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 16 to 50, 17 to 20, 17 to 25, 17 to 30, 17 to 50, 18 to 20, 18 to 25, 18 to 30, 18 to 50, 19 to 20, 19 to 25, 19 to 30, 19 to 50, 20 to 25, 20 to 30, 20 to 50, 21 to 25, 21 to 30, 21 to 50, 22 to 25, 22 to 30, 22 to 50, 23 to 25, 23 to 30, or 23 to 50 linked nucleosides.

Embodiment 83. The oligomeric duplex of any of embodiments 49-81, wherein the modified oligonucleotide of the first oligomeric compound consists of 23 linked nucleosides and the second modified oligonucleotide consists of 21 linked nucleosides.

Embodiment 84. The oligomeric duplex of embodiment 83, wherein the modified oligonucleotide of the first oligomeric compound has a sugar motif (from 5′ to 3′) of: yfyyyfyyyyyyyfyfyyyyyyy and the second modified oligonucleotide has a sugar motif (from 5′ to 3′) of: yyyyyyfyfffyyyyyyyyyy, wherein each “y” represents a 2’-OMe sugar moiety and each “f” represents a 2’-F sugar moiety.

Embodiment 85. An antisense agent comprising an antisense compound, wherein the antisense compound is the oligomeric compound of any of embodiments 1-42.

Embodiment 86. An antisense agent, wherein the antisense agent is the oligomeric duplex of any of embodiments 49-84.

Embodiment 87. The antisense agent of embodiment 85 or embodiment 86, wherein the antisense agent is:

i. an RNase H agent capable of reducing the amount of PCDH19 nucleic acid through the activation of RNase H; or
ii. an RNAi agent capable of reducing the amount of PCDH19 nucleic acid through the activation of RISC/Ago2.

Embodiment 88. The antisense agent of any of embodiments 85-87, wherein the conjugate group is a cell-targeting moiety.

Embodiment 89. A pharmaceutical composition comprising an oligomeric compound of any of embodiments 1-42, a population of any of embodiments 43-48, an oligomeric duplex of any of embodiments 49-84, or an antisense agent of any of embodiments 85-88, and a pharmaceutically acceptable diluent.

Embodiment 90. The pharmaceutical composition of embodiment 89, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or PBS.

Embodiment 91. The pharmaceutical composition of embodiment 90, wherein the pharmaceutical composition consists essentially of the oligomeric compound, the population, the oligomeric duplex, or the antisense agent, and aCSF.

Embodiment 92. The pharmaceutical composition of embodiment 90, wherein the pharmaceutical composition consists essentially of the oligomeric compound, the population, the oligomeric duplex, or the antisense agent, and PBS.

Embodiment 93. A method comprising administering to a subject an oligomeric compound of any of embodiments 1-42, a population of any of embodiments 43-48, an oligomeric duplex of any of embodiments 49-84, an antisense agent of any of embodiments 85-88, or a pharmaceutical composition of any of embodiments 89-92.

Embodiment 94. The method of embodiment 93, wherein the subject has a disease associated with PCDH19.

Embodiment 95. The method of embodiment 93, wherein the subject has PCDH19 Epilepsy.

Embodiment 96. A method of treating a disease associated with PCDH19 comprising administering to a subject having or at risk for developing a disease associated with PCDH19 a therapeutically effective amount of an oligomeric compound of any of embodiments 1-42, a population of any of embodiments 43-48, an oligomeric duplex of any of embodiments 49-84, an antisense agent of any of embodiments 85-88, or a pharmaceutical composition of any of embodiments 89-92; and thereby treating the disease associated with PCDH19.

Embodiment 97. The method of embodiment 96, wherein the disease associated with PCDH19 is a neurodevelopmental disease.

Embodiment 98. The method of embodiment 96 or embodiment 97, wherein the disease associated with PCDH19 is PCDH19 Epilepsy.

Embodiment 99. The method of any of embodiments 96-98, wherein at least one symptom or hallmark of the disease associated with PCDH19 is ameliorated.

Embodiment 100. The method of embodiment 99, wherein the symptom or hallmark is seizures, cognitive impairment, intellectual disabilities, autism spectrum disorder, behavioral problems, aggression, anxiety, obsessive-compulsive disorder, hyperactivity, attention deficit disorder (ADD), or attention deficit hyperactivity disorder (ADHD).

Embodiment 101. The method of embodiment 100, wherein the seizures are any of clusters of seizures, generalized tonic-clonic seiaures, focal seizures, or bilateral seizures.

Embodiment 102. The method of any of embodiments 96-101, wherein administering an oligomeric compound of any of embodiments 1-42, a population of any of embodiments 43-48, an oligomeric duplex of any of embodiments 49-84, an antisense agent of any of embodiments 85-88, or a pharmaceutical composition of any of embodiments 89-92 reduces seizures, reduces or delays cognitive impairment, reduces or delays intellectual disabilities, reduces or delays symptoms of autism spectrum disorder, reduces behavioral problems, reduces aggression, reduces anxiety, reduces obsessive-compulsive behavior, reduces hyperactivity, reduces symptoms of attention deficit disorder (ADD), or reduces symptoms of attention deficit hyperactivity disorder (ADHD) in the subject.

Embodiment 103. The method of any of embodiments 93-102, wherein the subject is human.

Embodiment 104. A method of reducing expression of PCDH19 in a cell comprising contacting the cell with an oligomeric compound of any of embodiments 1-42, a population of any of embodiments 43-48, an oligomeric duplex of any of embodiments 49-84, an antisense agent of any of embodiments 85-88, or a pharmaceutical composition of any of embodiments 89-92.

Embodiment 105. The method of embodiment 104, wherein the cell is a neuron.

Embodiment 106. The method of embodiment 104 or embodiment 105, wherein the cell is a human cell.

Embodiment 107. Use of an oligomeric compound of any of embodiments 1-42, a population of any of embodiments 43-48, an oligomeric duplex of any of embodiments 49-84, an antisense agent of any of embodiments 85-88, or a pharmaceutical composition of any of embodiments 89-92 for treating a disease associated with PCDH19.

Embodiment 108. Use of an oligomeric compound of any of embodiments 1-42, a population of any of embodiments 43-48, an oligomeric duplex of any of embodiments 49-84, or an antisense agent of any of embodiments 85-88in the manufacture of a medicament for treating a disease associated with PCDH19.

Embodiment 109. The use of embodiment 107 or embodiment 108, wherein the disease associated with PCDH19 is PCDH19 Epilepsy.

Certain Oligomeric Agents and Oligomeric Compounds

Certain embodiments provide oligomeric agents targeted to a PCDH19 nucleic acid. In certain embodiments, the PCDH19 nucleic acid has the sequence set forth in SEQ ID NO: 1 (ENSEMBL Accession No. ENSG00000165194.15 from version 104: May 2021), to SEQ ID NO: 2 (the cDNA of ENSEMBL Accession No. ENST00000373034.8 from version 104: May2021), or to both., each of which is incorporated by reference in its entirety. In certain embodiments, the oligomeric agent is a single-stranded oligomeric compound. In certain embodiments, the oligomeric agent is oligomeric duplex.

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion of a PCDH19 nucleic acid, and wherein the modified oligonucleotide has at least one modification selected from a modified sugar moiety and a modified internucleoside linkage. In certain embodiments, the PCDH19 nucleic acid has the nucleobase sequence of SEQ ID NOs: 1 or 2.

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 15-560.

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 15-482

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 16 to 50 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence of any of nucleobase sequences of SEQ ID NOs: 15-560.

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 20 linked nucleosides, wherein the modified oligonucleotide has a nucleobase sequence consisting of the nucleobase sequence of any of the nucleobase sequences of SEQ ID NOs: 15-482.

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 16 linked nucleosides, wherein the modified oligonucleotide has a nucleobase sequence consisting of the nucleobase sequence of any of the nucleobase sequences of SEQ ID NOs: 483-560.

In any of the oligomeric compounds provided herein, the nucleobase sequence of the modified oligonucleotide can be at least 85%, at least 90%, at least 95%, or 100% complementary to an equal length portion of a PCDH19 nucleic acid, wherein the PCDH19 nucleic acid has the nucleobase sequence of SEQ ID NOs: 1 or 2.

In any of the oligomeric compounds provided herein, the modified oligonucleotide can consist of 12 to 20, 12 to 25, 12 to 30, 12 to 50, 13 to 20, 13 to 25, 13 to 30, 13 to 50, 14 to 20, 14 to 25, 14 to 30, 14 to 50, 15 to 20, 15 to 25, 15 to 30, 15 to 50, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 16 to 50, 17 to 20, 17 to 25, 17 to 30, 17 to 50, 18 to

20, 18 to 25, 18 to 30, 18 to 50, 19 to 20, 19 to 25, 19 to 30, 19 to 50, 20 to 25, 20 to 30, 20 to 50, 21 to 25, 21 to 30, 21 to 50, 22 to 25, 22 to 30, 22 to 50, 23 to 25, 23 to 30, or 23 to 50 linked nucleosides.

In any of the oligomeric compounds provided herein, at least one nucleoside of the modified oligonucleotide can comprise a modified sugar moiety. In certain embodiments, the modified sugar moiety comprises a bicyclic sugar moiety, such as a 2'-4' bridge selected from –O-CH_2-; and –O-$CH(CH_3)$-. In certain embodiments, the modified sugar moiety comprises a non-bicyclic sugar moiety, such as a 2'-MOE sugar moiety or 2'-OMe sugar moiety.

In any of the oligomeric compounds provided herein, at least one nucleoside of the modified oligonucleotide compound can comprise a sugar surrogate.

In any of the oligomeric compounds provided herein, at least one internucleoside linkage of the modified oligonucleotide can comprise a modified internucleoside linkage, such as a phosphorothioate internucleoside linkage. In certain embodiments, each internucleoside linkage of the modified oligonucleotide can be a modified internucleoside linkage or each internucleoside linkage of the modified oligonucleotide can be a phosphorothioate internucleoside linkage. In certain embodiments, at least one internucleoside linkage of the modified oligonucleotide can be a phosphodiester internucleoside linkage. In certain embodiments, each internucleoside linkage of the modified oligonucleotide can be independently selected from a phosphodiester or a phosphorothioate internucleoside linkage. In certain embodiments, at least 2, at least 3, at least 4, at least 5, or at least 6 internucleoside linkages of the modified oligonucleotide can be phosphodiester internucleoside linkages. In certain embodiments, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 18 internucleoside linkages of the modified oligonucleotide can be phosphorothioate internucleoside linkages.

In any of the oligomeric compounds provided herein, at least one nucleobase of the modified oligonucleotide can be a modified nucleobase, such as 5-methylcytosine. In certain embodiments, each cytosine is 5-methylcytosine.

In any of the oligomeric compounds provided herein, the modified oligonucleotide can comprise a deoxy region consisting of 5-12 contiguous 2'-deoxynucleosides. In certain embodiments, each nucleoside of the deoxy region is a 2'-β-D-deoxynucleoside. In certain embodiments, the deoxy region consists of 7, 8, 9, 10, or 7-10 linked nucleosides. In certain embodiments, each nucleoside immediately adjacent to the deoxy region comprises a modified sugar moiety. In certain embodiments, the deoxy region is flanked on the 5'-side by a 5'-region consisting of 1-6 linked 5'-region nucleosides and on the 3'-side by a 3'-region consisting of 1-6 linked 3'-region nucleosides; wherein the 3'-most nucleoside of the 5'-region comprises a modified sugar moiety; and the 5'-most nucleoside of the 3'-region comprises a modified sugar moiety. In certain embodiments, each nucleoside of the 3'-region comprises a modified sugar moiety. In certain embodiments, each nucleoside of the 5'-region comprises a modified sugar moiety.

In certain embodiments, a compound comprises or consists of a modified oligonucleotide consisting of 16 to 50 linked nucleobases and having a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 483-560, wherein the modified oligonucleotide has:

a gap segment consisting of ten linked 2'-deoxynucleosides;

a 5' wing segment consisting of three linked nucleosides; and

a 3' wing segment consisting of three linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; wherein each nucleoside of each wing segment comprises a cEt nucleoside; wherein each internucleoside linkage is a phosphorothioate linkage; and wherein each cytosine is a 5-methylcytosine. In certain embodiments, the modified

oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

In certain embodiments, a compound comprises or consists of a modified oligonucleotide consisting of 16 to 50 linked nucleobases and having a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 15-482, wherein the modified oligonucleotide has:

a gap segment consisting of ten linked 2'-deoxynucleosides;

a 5' wing segment consisting of five linked nucleosides; and

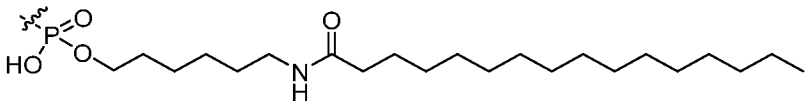
a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; wherein each nucleoside of each wing segment comprises a 2'-MOE nucleoside, and wherein each cytosine is a 5-methylcytosine. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 20 linked nucleosides wherein the internucleoside linkage motif for the modified oligonucleotide is (from 5' to 3'): soooosssssssssssooss ; wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

In certain embodiments, an oligomeric compound comprises a conjugate group. In certain embodiments, the conjugate group comprises a conjugate linker and a conjugate moiety. In certain embodiments, the conjugate linker consists of a single bond, the conjugate linker is cleavable, the conjugate linker comprises 1-3 linker-nucleosides, the conjugate linker does not comprise any linker nucleosides, the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide, or the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.

In certain embodiments, the conjugate group comprises a cell-targeting moiety having an affinity for transferrin receptor (TfR), also known as TfR1 and CD71. In certain embodiments, the conjugate group comprises an anti-TfR1 antibody or fragment thereof. In certain embodiments, the conjugate group comprises a protein or peptide capable of binding TfR1. In certain embodiments, the conjugate group comprises an aptamer capable of binding TfR1. In certain embodiments, conjugate groups may be selected from any of a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, C5 alkyl, C22 alkenyl, C20 alkenyl, C16 alkenyl, C10 alkenyl, C21 alkenyl, C19 alkenyl, C18 alkenyl, C15 alkenyl, C14 alkenyl, C13 alkenyl, C12 alkenyl, C11 alkenyl, C9 alkenyl, C8 alkenyl, C7 alkenyl, C6 alkenyl, or C5 alkenyl. In certain embodiments, conjugate groups may be selected from any of C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, and C5 alkyl, where the alkyl chain has one or more unsaturated bonds.

In certain embodiments, the conjugate group has the following structure:



Certain Oligomeric Duplexes

Certain embodiments are directed to oligomeric duplexes comprising a first oligomeric compound and a second oligomeric compound.

In certain embodiments, an oligomeric duplex comprises:

a first oligomeric compound comprising a first modified oligonucleotide consisting of 12 to 50 linked nucleosides wherein the nucleobase sequence of the first modified oligonucleotide comprises at least at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of the nucleobase sequence of any of SEQ ID NOs: 15-560; and

a second oligomeric compound comprising a second modified oligonucleotide consisting of 12 to 50 linked nucleosides wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 8 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

In certain embodiments, the first oligomeric compound is an antisense compound. In certain embodiments, the first modified oligonucleotide is an antisense oligonucleotide. In certain embodiments, the second oligomeric compound is a sense compound. In certain embodiments, the second modified oligonucleotide is a sense oligonucleotide.

In certain embodiments, an oligomeric duplex comprises:

a first oligomeric compound comprising a first modified oligonucleotide consisting of 16 to 50 linked nucleosides wherein the nucleobase sequence of the first modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 15-560; and

a second oligomeric compound comprising a second modified oligonucleotide consisting of 16 to 50 linked nucleosides wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 16 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

In certain embodiments, the first oligomeric compound is an antisense compound. In certain embodiments, the first modified oligonucleotide is an antisense oligonucleotide. In certain embodiments, the second oligomeric compound is a sense compound. In certain embodiments, the second modified oligonucleotide is a sense oligonucleotide.

In certain embodiments, an oligomeric duplex comprises:

a first oligomeric compound comprising a first modified oligonucleotide consisting of 19 to 30linked nucleosides wherein the nucleobase sequence of the first modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 contiguous nucleobases of the nucleobase sequence of any of SEQ ID NOs: 561-1028, and

a second oligomeric compound comprising a second modified oligonucleotide consisting of 15 to 30 linked nucleosides wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 8 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

In certain embodiments, the first oligomeric compound is an antisense compound. In certain embodiments, the first modified oligonucleotide is an antisense oligonucleotide. In certain embodiments, the second oligomeric compound is a sense compound. In certain embodiments, the second modified oligonucleotide is a sense oligonucleotide.

In certain embodiments, an oligomeric duplex comprises:

a first oligomeric compound comprising a first modified oligonucleotide consisting of 19 to 30 linked nucleosides wherein the nucleobase sequence of the first modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 contiguous nucleobases of the nucleobase sequence of any of SEQ ID NOs: 561-1028, and

a second oligomeric compound comprising a second modified oligonucleotide consisting of 15 to 30 linked nucleosides wherein the nucleobase sequence of the second modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, or at least 21 contiguous nucleobases of the nucleobase sequence of any of SEQ ID NOs: 1029-1496, wherein the nucleobase sequence of the second modified oligonucleotide is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

In certain embodiments, the first oligomeric compound is an antisense compound. In certain embodiments, the first modified oligonucleotide is an antisense oligonucleotide. In certain embodiments, the second oligomeric compound is a sense compound. In certain embodiments, the second modified oligonucleotide is a sense oligonucleotide.

In certain embodiments, an oligomeric duplex comprises:

a first oligomeric compound comprising a first modified oligonucleotide consisting of 23 linked nucleosides wherein the nucleobase sequence of the first modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 561-1028; and

a second oligomeric compound comprising a second modified oligonucleotide consisting of 21 linked nucleosides wherein the nucleobase sequence of the second modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 1029-1496, wherein the nucleobase sequence of the second modified oligonucleotide is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

In certain embodiments, the first oligomeric compound is an antisense compound. In certain embodiments, the first modified oligonucleotide is an antisense oligonucleotide. In certain embodiments, the second oligomeric compound is a sense compound. In certain embodiments, the second modified oligonucleotide is a sense oligonucleotide.

In certain embodiments, an oligomeric duplex comprises a first oligomeric compound comprising a first modified oligonucleotide consisting of 15 to 30 linked nucleosides and a second oligomeric compound comprising a second modified oligonucleotide consisting of 15 to 29 linked nucleosides, wherein the nucleobase sequence of the first modified oligonucleotide and the nucleobase sequence of the second modified oligonucleotide each comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 contiguous nucleobases of any of the following pairs of nucleobase sequences recited in SEQ ID NOs: 723/1029, 724/1030, 725/1031, 561/1032, 562/1033, 563/1034, 726/1035, 727/1036, 728/1037, 564/1038, 729/1039, 730/1040, 731/1041, 732/1042, 733/1043, 565/1044, 734/1045, 566/1046, 735/1047, 567/1048, 736/1049, 737/1050, 738/1051, 568/1052, 739/1053, 740/1054, 741/1055, 742/1056, 743/1057, 569/1058, 744/1059, 745/1060, 746/1061, 747/1062, 748/1063, 570/1064, 749/1065, 571/1066, 750/1067, 751/1068, 572/1069, 573/1070, 574/1071, 575/1072, 576/1073, 577/1074, 578/1075, 752/1076, 753/1077, 579/1078, 580/1079, 754/1080, 581/1081, 582/1082,

755/1083, 756/1084, 583/1085, 584/1086, 757/1087, 758/1088, 585/1089, 586/1090, 587/1091, 588/1092, 589/1093, 590/1094, 591/1095, 592/1096, 759/1097, 593/1098, 594/1099, 760/1100, 595/1101, 596/1102, 761/1103, 597/1104, 598/1105, 762/1106, 763/1107, 599/1108, 764/1109, 765/1110, 766/1111, 600/1112, 767/1113, 768/1114, 769/1115, 770/1116, 601/1117, 771/1118, 602/1119, 772/1120, 773/1121, 774/1122, 603/1123, 604/1124, 775/1125, 605/1126, 606/1127, 776/1128, 777/1129, 778/1130, 779/1131, 780/1132, 781/1133, 782/1134, 783/1135, 784/1136, 607/1137, 785/1138, 786/1139, 787/1140, 788/1141, 608/1142, 609/1143, 610/1144, 789/1145, 611/1146, 790/1147, 612/1148, 613/1149, 791/1150, 614/1151, 792/1152, 615/1153, 793/1154, 616/1155, 794/1156, 795/1157, 617/1158, 796/1159, 797/1160, 798/1161, 618/1162, 799/1163, 619/1164, 800/1165, 801/1166, 620/1167, 621/1168, 802/1169, 803/1170, 804/1171, 805/1172, 622/1173, 806/1174, 807/1175, 808/1176, 809/1177, 623/1178, 810/1179, 811/1180, 624/1181, 812/1182, 625/1183, 813/1184, 626/1185, 814/1186, 815/1187, 627/1188, 816/1189, 817/1190, 818/1191, 628/1192, 819/1193, 629/1194, 820/1195, 630/1196, 821/1197, 631/1198, 632/1199, 822/1200, 823/1201, 824/1202, 825/1203, 633/1204, 634/1205, 826/1206, 827/1207, 635/1208, 636/1209, 828/1210, 637/1211, 638/1212, 829/1213, 830/1214, 831/1215, 832/1216, 833/1217, 834/1218, 639/1219, 640/1220, 835/1221, 641/1222, 836/1223, 642/1224, 837/1225, 838/1226, 839/1227, 840/1228, 841/1229, 842/1230, 643/1231, 644/1232, 843/1233, 645/1234, 646/1235, 844/1236, 845/1237, 846/1238, 647/1239, 847/1240, 848/1241, 849/1242, 850/1243, 851/1244, 852/1245, 648/1246, 853/1247, 854/1248, 855/1249, 856/1250, 857/1251, 858/1252, 859/1253, 649/1254, 650/1255, 651/1256, 860/1257, 861/1258, 862/1259, 863/1260, 864/1261, 652/1262, 653/1263, 865/1264, 866/1265, 867/1266, 868/1267, 654/1268, 869/1269, 655/1270, 870/1271, 871/1272, 656/1273, 872/1274, 657/1275, 873/1276, 658/1277, 659/1278, 874/1279, 875/1280, 660/1281, 876/1282, 877/1283, 878/1284, 879/1285, 880/1286, 661/1287, 662/1288, 663/1289, 881/1290, 882/1291, 883/1292, 884/1293, 885/1294, 664/1295, 886/1296, 887/1297, 888/1298, 665/1299, 666/1300, 667/1301, 889/1302, 668/1303, 890/1304, 891/1305, 892/1306, 669/1307, 893/1308, 670/1309, 671/1310, 894/1311, 672/1312, 673/1313, 895/1314, 896/1315, 674/1316, 897/1317, 675/1318, 676/1319, 677/1320, 898/1321, 899/1322, 900/1323, 901/1324, 678/1325, 902/1326, 679/1327, 903/1328, 904/1329, 905/1330, 906/1331, 907/1332, 908/1333, 680/1334, 909/1335, 910/1336, 911/1337, 912/1338, 913/1339, 681/1340, 914/1341, 915/1342, 916/1343, 917/1344, 918/1345, 919/1346, 920/1347, 921/1348, 922/1349, 923/1350, 924/1351, 925/1352, 926/1353, 927/1354, 682/1355, 928/1356, 929/1357, 930/1358, 683/1359, 684/1360, 931/1361, 932/1362, 933/1363, 934/1364, 935/1365, 685/1366, 936/1367, 937/1368, 938/1369, 939/1370, 940/1371, 941/1372, 942/1373, 943/1374, 944/1375, 945/1376, 946/1377, 947/1378, 948/1379, 949/1380, 950/1381, 951/1382, 686/1383, 687/1384, 688/1385, 689/1386, 952/1387, 690/1388, 953/1389, 691/1390, 954/1391, 692/1392, 693/1393, 694/1394, 695/1395, 955/1396, 956/1397, 957/1398, 958/1399, 696/1400, 959/1401, 697/1402, 960/1403, 698/1404, 699/1405, 961/1406, 962/1407, 963/1408, 964/1409, 965/1410, 966/1411, 967/1412, 700/1413, 701/1414, 968/1415, 702/1416, 969/1417, 970/1418, 971/1419, 972/1420, 973/1421, 703/1422, 704/1423, 974/1424, 975/1425, 705/1426, 976/1427, 977/1428, 978/1429, 979/1430, 980/1431, 981/1432, 982/1433, 983/1434, 984/1435, 985/1436, 706/1437, 986/1438, 987/1439, 707/1440, 988/1441, 989/1442, 708/1443, 709/1444, 990/1445, 991/1446, 992/1447, 993/1448, 710/1449, 994/1450, 995/1451, 996/1452, 711/1453, 997/1454, 998/1455, 999/1456, 1000/1457, 712/1458, 1001/1459, 1002/1460, 713/1461, 1003/1462, 1004/1463, 1005/1464, 1006/1465, 1007/1466, 1008/1467, 1009/1468, 714/1469, 715/1470, 716/1471, 1010/1472, 717/1473, 718/1474, 1011/1475, 1012/1476, 719/1477, 720/1478, 1013/1479, 1014/1480, 1015/1481, 1016/1482, 1017/1483, 1018/1484, 1019/1485, 1020/1486, 1021/1487, 1022/1488, 721/1489, 1023/1490, 722/1491, 1024/1492, 1025/1493, 1026/1494, 1027/1495, or 1028/1496, wherein the nucleobase sequence of the first modified

oligonucleotide comprises the nucleobase sequence of the first SEQ ID NO recited in the pair and the nucleobase sequence of the second modified oligonucleotide comprises the nucleobase sequence of the second SEQ ID NO recited in the pair.

In certain embodiments, an oligomeric duplex comprises a first oligomeric compound comprising a first modified oligonucleotide consisting of 15 to 30 linked nucleosides and a second oligomeric compound comprising a second modified oligonucleotide consisting of 15 to 29 linked nucleosides, wherein the nucleobase sequence of the first modified oligonucleotide and the nucleobase sequence of the second modified oligonucleotide comprise any of the following pairs of nucleobase sequences recited in SEQ ID NOs: 723/1029, 724/1030, 725/1031, 561/1032, 562/1033, 563/1034, 726/1035, 727/1036, 728/1037, 564/1038, 729/1039, 730/1040, 731/1041, 732/1042, 733/1043, 565/1044, 734/1045, 566/1046, 735/1047, 567/1048, 736/1049, 737/1050, 738/1051, 568/1052, 739/1053, 740/1054, 741/1055, 742/1056, 743/1057, 569/1058, 744/1059, 745/1060, 746/1061, 747/1062, 748/1063, 570/1064, 749/1065, 571/1066, 750/1067, 751/1068, 572/1069, 573/1070, 574/1071, 575/1072, 576/1073, 577/1074, 578/1075, 752/1076, 753/1077, 579/1078, 580/1079, 754/1080, 581/1081, 582/1082, 755/1083, 756/1084, 583/1085, 584/1086, 757/1087, 758/1088, 585/1089, 586/1090, 587/1091, 588/1092, 589/1093, 590/1094, 591/1095, 592/1096, 759/1097, 593/1098, 594/1099, 760/1100, 595/1101, 596/1102, 761/1103, 597/1104, 598/1105, 762/1106, 763/1107, 599/1108, 764/1109, 765/1110, 766/1111, 600/1112, 767/1113, 768/1114, 769/1115, 770/1116, 601/1117, 771/1118, 602/1119, 772/1120, 773/1121, 774/1122, 603/1123, 604/1124, 775/1125, 605/1126, 606/1127, 776/1128, 777/1129, 778/1130, 779/1131, 780/1132, 781/1133, 782/1134, 783/1135, 784/1136, 607/1137, 785/1138, 786/1139, 787/1140, 788/1141, 608/1142, 609/1143, 610/1144, 789/1145, 611/1146, 790/1147, 612/1148, 613/1149, 791/1150, 614/1151, 792/1152, 615/1153, 793/1154, 616/1155, 794/1156, 795/1157, 617/1158, 796/1159, 797/1160, 798/1161, 618/1162, 799/1163, 619/1164, 800/1165, 801/1166, 620/1167, 621/1168, 802/1169, 803/1170, 804/1171, 805/1172, 622/1173, 806/1174, 807/1175, 808/1176, 809/1177, 623/1178, 810/1179, 811/1180, 624/1181, 812/1182, 625/1183, 813/1184, 626/1185, 814/1186, 815/1187, 627/1188, 816/1189, 817/1190, 818/1191, 628/1192, 819/1193, 629/1194, 820/1195, 630/1196, 821/1197, 631/1198, 632/1199, 822/1200, 823/1201, 824/1202, 825/1203, 633/1204, 634/1205, 826/1206, 827/1207, 635/1208, 636/1209, 828/1210, 637/1211, 638/1212, 829/1213, 830/1214, 831/1215, 832/1216, 833/1217, 834/1218, 639/1219, 640/1220, 835/1221, 641/1222, 836/1223, 642/1224, 837/1225, 838/1226, 839/1227, 840/1228, 841/1229, 842/1230, 643/1231, 644/1232, 843/1233, 645/1234, 646/1235, 844/1236, 845/1237, 846/1238, 647/1239, 847/1240, 848/1241, 849/1242, 850/1243, 851/1244, 852/1245, 648/1246, 853/1247, 854/1248, 855/1249, 856/1250, 857/1251, 858/1252, 859/1253, 649/1254, 650/1255, 651/1256, 860/1257, 861/1258, 862/1259, 863/1260, 864/1261, 652/1262, 653/1263, 865/1264, 866/1265, 867/1266, 868/1267, 654/1268, 869/1269, 655/1270, 870/1271, 871/1272, 656/1273, 872/1274, 657/1275, 873/1276, 658/1277, 659/1278, 874/1279, 875/1280, 660/1281, 876/1282, 877/1283, 878/1284, 879/1285, 880/1286, 661/1287, 662/1288, 663/1289, 881/1290, 882/1291, 883/1292, 884/1293, 885/1294, 664/1295, 886/1296, 887/1297, 888/1298, 665/1299, 666/1300, 667/1301, 889/1302, 668/1303, 890/1304, 891/1305, 892/1306, 669/1307, 893/1308, 670/1309, 671/1310, 894/1311, 672/1312, 673/1313, 895/1314, 896/1315, 674/1316, 897/1317, 675/1318, 676/1319, 677/1320, 898/1321, 899/1322, 900/1323, 901/1324, 678/1325, 902/1326, 679/1327, 903/1328, 904/1329, 905/1330, 906/1331, 907/1332, 908/1333, 680/1334, 909/1335, 910/1336, 911/1337, 912/1338, 913/1339, 681/1340, 914/1341, 915/1342, 916/1343, 917/1344, 918/1345, 919/1346, 920/1347, 921/1348, 922/1349, 923/1350, 924/1351, 925/1352, 926/1353, 927/1354, 682/1355, 928/1356, 929/1357, 930/1358, 683/1359, 684/1360, 931/1361, 932/1362, 933/1363, 934/1364, 935/1365, 685/1366, 936/1367, 937/1368, 938/1369, 939/1370, 940/1371,

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In certain embodiments, an oligomeric duplex comprises a first oligomeric compound comprising a first modified oligonucleotide consisting of 23 linked nucleosides and a second oligomeric compound comprising a second modified oligonucleotide consisting of 21 linked nucleosides, wherein the nucleobase sequence of the first modified oligonucleotide and the nucleobase sequence of the second modified oligonucleotide consist of any of the following pairs of nucleobase sequences recited in SEQ ID NOs: 723/1029, 724/1030, 725/1031, 561/1032, 562/1033, 563/1034, 726/1035, 727/1036, 728/1037, 564/1038, 729/1039, 730/1040, 731/1041, 732/1042, 733/1043, 565/1044, 734/1045, 566/1046, 735/1047, 567/1048, 736/1049, 737/1050, 738/1051, 568/1052, 739/1053, 740/1054, 741/1055, 742/1056, 743/1057, 569/1058, 744/1059, 745/1060, 746/1061, 747/1062, 748/1063, 570/1064, 749/1065, 571/1066, 750/1067, 751/1068, 572/1069, 573/1070, 574/1071, 575/1072, 576/1073, 577/1074, 578/1075, 752/1076, 753/1077, 579/1078, 580/1079, 754/1080, 581/1081, 582/1082, 755/1083, 756/1084, 583/1085, 584/1086, 757/1087, 758/1088, 585/1089, 586/1090, 587/1091, 588/1092, 589/1093, 590/1094, 591/1095, 592/1096, 759/1097, 593/1098, 594/1099, 760/1100, 595/1101, 596/1102, 761/1103, 597/1104, 598/1105, 762/1106, 763/1107, 599/1108, 764/1109, 765/1110, 766/1111, 600/1112, 767/1113, 768/1114, 769/1115, 770/1116, 601/1117, 771/1118, 602/1119, 772/1120, 773/1121, 774/1122, 603/1123, 604/1124, 775/1125, 605/1126, 606/1127, 776/1128, 777/1129, 778/1130, 779/1131, 780/1132, 781/1133, 782/1134, 783/1135, 784/1136, 607/1137, 785/1138, 786/1139, 787/1140, 788/1141, 608/1142, 609/1143, 610/1144, 789/1145, 611/1146, 790/1147, 612/1148, 613/1149, 791/1150, 614/1151, 792/1152, 615/1153, 793/1154, 616/1155, 794/1156, 795/1157, 617/1158, 796/1159, 797/1160, 798/1161, 618/1162, 799/1163, 619/1164, 800/1165, 801/1166, 620/1167, 621/1168, 802/1169, 803/1170, 804/1171, 805/1172, 622/1173, 806/1174, 807/1175, 808/1176, 809/1177, 623/1178, 810/1179, 811/1180, 624/1181, 812/1182, 625/1183, 813/1184, 626/1185, 814/1186, 815/1187, 627/1188, 816/1189, 817/1190, 818/1191, 628/1192, 819/1193, 629/1194, 820/1195, 630/1196, 821/1197, 631/1198, 632/1199, 822/1200, 823/1201, 824/1202, 825/1203, 633/1204, 634/1205, 826/1206, 827/1207, 635/1208, 636/1209, 828/1210, 637/1211, 638/1212, 829/1213, 830/1214, 831/1215, 832/1216, 833/1217, 834/1218, 639/1219, 640/1220, 835/1221, 641/1222, 836/1223, 642/1224, 837/1225, 838/1226, 839/1227, 840/1228, 841/1229, 842/1230, 643/1231, 644/1232, 843/1233, 645/1234, 646/1235, 844/1236, 845/1237, 846/1238, 647/1239, 847/1240, 848/1241, 849/1242,

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In any of the oligomeric duplexes described herein, at least one nucleoside of the first modified oligonucleotide and/or the second modified oligonucleotide can comprise a modified sugar moiety. Examples of suitable modified sugar moieties include, but are not limited to, a bicyclic sugar moiety, such as a 2'-4' bridge selected from –O-CH_2-; and –O-CH(CH_3)-, and a non-bicyclic sugar moiety, such as a 2'-MOE sugar moiety, a 2'-F sugar moiety, a 2'-OMe sugar moiety, or a 2'-NMA sugar moiety. In certain embodiments, at least 80%, at least 90%, or 100% of the nucleosides of the first modified oligonucleotide and/or the second modified oligonucleotide comprises a modified sugar moiety selected from 2'-F and 2'-OMe.

In any of the oligomeric duplexes described herein, at least one nucleoside of the first modified oligonucleotide and/or the second modified oligonucleotide can comprise a sugar surrogate. Examples of suitable sugar surrogates include, but are not limited to, morpholino, peptide nucleic acid (PNA), glycol nucleic acid (GNA), and unlocked nucleic acid (UNA). In certain embodiments, at least one nucleoside of the first modified oligonucleotide comprises a sugar surrogate, which can be a GNA.

In any of the oligomeric duplexes described herein, at least one internucleoside linkage of the first modified oligonucleotide and/or the second modified oligonucleotide can comprise a modified internucleoside linkage. In certain embodiments, the modified internucleoside linkage is a phosphorothioate internucleoside linkage. In certain embodiments, at least one of the first, second, or third internucleoside linkages from the 5' end and/or the 3' end of the first modified oligonucleotide comprises a phosphorothioate linkage. In certain embodiments, at least one of the first, second, or third internucleoside linkages from the 5' end and/or the 3' end of the second modified oligonucleotide comprises a phosphorothioate linkage.

In any of the oligomeric duplexes described herein, at least one internucleoside linkage of the first modified oligonucleotide and/or the second modified oligonucleotide can comprise a phosphodiester internucleoside linkage.

In any of the oligomeric duplexes described herein, each internucleoside linkage of the first modified oligonucleotide and/or the second modified oligonucleotide can be independently selected from a phosphodiester or a phosphorothioate internucleoside linkage.

In any of the oligomeric duplexes described herein, the internucleoside linkage motif of the second modified oligonucleotide can be ssooooooooooooooooss, wherein wherein each "o" represents a phosphodiester internucleoside linkage and each "s" represents a phosphorothioate internucleoside linkage.

In any of the oligomeric duplexes described herein, at least one nucleobase of the first modified oligonucleotide and/or the second modified oligonucleotide can be modified nucleobase. In certain embodiments, the modified nucleobase is 5-methylcytosine.

In any of the oligomeric duplexes described herein, the first modified oligonucleotide can comprise a stabilized phosphate group attached to the 5' position of the 5'-most nucleoside. In certain embodiments, the stabilized phosphate group comprises a cyclopropyl phosphonate or an *(E)*-vinyl phosphonate.

In any of the oligomeric duplexes described herein, the first modified oligonucleotide can comprise a conjugate group. In certain embodiments, the conjugate group comprises a conjugate linker and a conjugate moiety. In certain embodiments, the conjugate group is attached to the first modified oligonucleotide at the 5'-end of the first modified oligonucleotide. In certain embodiments, the conjugate group is attached to the first modified oligonucleotide at the 3'-end of the modified oligonucleotide. In certain embodiments, the conjugate group comprises N-acetyl galactosamine. In certain embodiments, the conjugate group comprises a cell-targeting moiety having an affinity for transferrin receptor (TfR), also known as TfR1 and CD71. In certain embodiments, the conjugate group comprises an anti-TfR1 antibody or fragment thereof. In certain embodiments, the conjugate group comprises a protein or peptide capable of binding TfR1. In certain embodiments, the conjugate group comprises an aptamer capable of binding TfR1. In certain embodiments, conjugate groups may be selected from any of a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, C5 alkyl, C22 alkenyl, C20 alkenyl, C16 alkenyl, C10 alkenyl, C21 alkenyl, C19 alkenyl, C18 alkenyl, C15 alkenyl, C14 alkenyl, C13 alkenyl, C12 alkenyl, C11 alkenyl, C9 alkenyl, C8 alkenyl, C7 alkenyl, C6 alkenyl, or C5 alkenyl. In certain embodiments, conjugate groups may be selected from any of C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, and C5 alkyl, where the alkyl chain has one or more unsaturated bonds.

In any of the oligomeric duplexes described herein, the second modified oligonucleotide can comprise a conjugate group. In certain embodiments, the conjugate group comprises a conjugate linker and a conjugate moiety. In certain embodiments, the conjugate group is attached to the second modified oligonucleotide at the 5'-

end of the second modified oligonucleotide. In certain embodiments, the conjugate group is attached to the second modified oligonucleotide at the 3'-end of the modified oligonucleotide. In certain embodiments, the conjugate group comprises N-acetyl galactosamine. In certain embodiments, the conjugate group comprises a cell-targeting moiety having an affinity for transferrin receptor (TfR), also known as TfR1 and CD71. In certain embodiments, the conjugate group comprises an anti-TfR1 antibody or fragment thereof. In certain embodiments, the conjugate group comprises a protein or peptide capable of binding TfR1. In certain embodiments, the conjugate group comprises an aptamer capable of binding TfR1. In certain embodiments, conjugate groups may be selected from any of a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, C5 alkyl, C22 alkenyl, C20 alkenyl, C16 alkenyl, C10 alkenyl, C21 alkenyl, C19 alkenyl, C18 alkenyl, C15 alkenyl, C14 alkenyl, C13 alkenyl, C12 alkenyl, C11 alkenyl, C9 alkenyl, C8 alkenyl, C7 alkenyl, C6 alkenyl, or C5 alkenyl. In certain embodiments, conjugate groups may be selected from any of C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, and C5 alkyl, where the alkyl chain has one or more unsaturated bonds.

In certain embodiments, an antisense agent comprises an antisense compound, which comprises an oligomeric compound or an oligomeric duplex described herein. In certain embodiments, an antisense agent, which can comprise an oligomeric compound or an oligomeric duplex described herein, is an RNAi agent capable of reducing the amount of PCDH19 nucleic acid through the activation of RISC/Ago2. In certain embodiments, an antisense agent, which can comprise an oligomeric compound or an oligomeric duplex described herein, is an RNAse H agent capable of reducing the amount of PCDH19 nucleic acid through the activation of RNAse H.

Certain embodiments provide an oligomeric agent comprising two or more oligomeric duplexes. In certain embodiments, an oligomeric agent comprises two or more of any of the oligomeric duplexes described herein. In certain embodiments, an oligomeric agent comprises two or more of the same oligomeric duplex, which can be any of the oligomeric duplexes described herein. In certain embodiments, the two or more oligomeric duplexes are linked together. In certain embodiments, the two or more oligomeric duplexes are covalently linked together. In certain embodiments, the second modified oligonucleotides of two or more oligomeric duplexes are covalently linked together. In certain embodiments, the second modified oligonucleotides of two or more oligomeric duplexes are covalently linked together at their 3' ends. In certain embodiments, the two or more oligomeric duplexes are covalently linked together by a glycol linker, such as a tetraethylene glycol linker.

I. Certain Oligonucleotides

In certain embodiments, provided herein are oligomeric compounds comprising oligonucleotides, which consist of linked nucleosides. Oligonucleotides may be unmodified oligonucleotides (RNA or DNA) or may be modified oligonucleotides. Modified oligonucleotides comprise at least one modification relative to unmodified RNA or DNA. That is, modified oligonucleotides comprise at least one modified nucleoside (comprising a modified sugar moiety and/or a modified nucleobase) and/or at least one modified internucleoside linkage. Certain modified nucleosides and modified internucleoside linkages suitable for use in modified oligonucleotides are described below.

A. Certain Modified Nucleosides

Modified nucleosides comprise a modified sugar moiety or a modified nucleobase or both a modified sugar moiety and a modified nucleobase. In certain embodiments, modified nucleosides comprising the following

modified sugar moieties and/or the following modified nucleobases may be incorporated into modified oligonucleotides.

1. **Certain Sugar Moieties**

In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties. In certain embodiments, modified sugar moieties are bicyclic or tricyclic sugar moieties. In certain embodiments, modified sugar moieties are sugar surrogates. Such sugar surrogates may comprise one or more substitutions corresponding to those of other types of modified sugar moieties.

In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties comprising a furanosyl ring with one or more substituent groups none of which bridges two atoms of the furanosyl ring to form a bicyclic structure. Such non bridging substituents may be at any position of the furanosyl, including but not limited to substituents at the 2', 3', 4', and/or 5' positions. In certain embodiments one or more non-bridging substituent of non-bicyclic modified sugar moieties is branched. Examples of 2'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 2'-F, 2'-OCH_3 ("OMe" or "O-methyl"), and 2'-$O(CH_2)_2OCH_3$ ("MOE" or "O-methoxyethyl"). In certain embodiments, 2'-substituent groups are selected from among: halo, allyl, amino, azido, SH, CN, OCN, CF_3, OCF_3, O-C_1-C_{10} alkoxy, O-C_1-C_{10} substituted alkoxy, O-C_1-C_{10} alkyl, O-C_1-C_{10} substituted alkyl, S-alkyl, N(R_m)-alkyl, O-alkenyl, S-alkenyl, N(R_m)-alkenyl, O-alkynyl, S-alkynyl, N(R_m)-alkynyl, O-alkylenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(R_m)(R_n)$ or $OCH_2C(=O)$-$N(R_m)(R_n)$, where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C_1-C_{10} alkyl, -$O(CH_2)_2ON(CH_3)_2$ ("DMAOE"), $O(CH_2)_2O(CH_2)_2N(CH_3)_2$ ("DMAEOE"), and the 2'-substituent groups described in Cook et al., U.S. 6,531,584; Cook et al., U.S. 5,859,221; and Cook et al., U.S. 6,005,087. Certain embodiments of these 2'-substituent groups can be further substituted with one or more substituent groups independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO_2), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl, alkenyl and alkynyl. In certain embodiments, non-bicyclic modified sugar moieties comprise a substituent group at the 3'-position. Examples of substituent groups suitable for the 3'-position of modified sugar moieties include but are not limited to alkoxy (e.g., methoxy), alkyl (e.g., methyl, ethyl). In certain embodiments, non-bicyclic modified sugar moieties comprise a substituent group at the 4'-position. Examples of 4'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to alkoxy (*e.g.*, methoxy), alkyl, and those described in Manoharan et al., WO 2015/106128. Examples of 5'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 5'-methyl (R or S), 5'-vinyl, ethyl, and 5'-methoxy. In certain embodiments, non-bicyclic modified sugar moieties comprise more than one non-bridging sugar substituent, for example, 2'-F-5'-methyl sugar moieties and the modified sugar moieties and modified nucleosides described in Migawa et al., WO 2008/101157 and Rajeev et al., US2013/0203836.

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, NH_2, N_3, OCF_3, OCH_3, $O(CH_2)_3NH_2$, $CH_2CH=CH_2$, $OCH_2CH=CH_2$, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(R_m)(R_n)$, $O(CH_2)_2O(CH_2)_2N(CH_3)_2$, and N-substituted acetamide ($OCH_2C(=O)$-$N(R_m)(R_n)$), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C_1-C_{10} alkyl.

In certain embodiments, a 2'-substituted nucleoside non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCF_3, OCH_3, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(CH_3)_2$, $O(CH_2)_2O(CH_2)_2N(CH_3)_2$, $O(CH_2)_2ON(CH_3)_2$ ("DMAOE"), $O(CH_2)2O(CH2)_2N(CH_3)_2$ ("DMAEOE") and $OCH_2C(=O)$-$N(H)CH_3$ ("NMA").

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCH_3, and $OCH_2CH_2OCH_3$.

In certain embodiments, modified furanosyl sugar moieties and nucleosides incorporating such modified furanosyl sugar moieties are further defined by isomeric configuration. For example, a 2'-deoxyfuranosyl sugar moiety may be in seven isomeric configurations other than the naturally occurring β-D-deoxyribosyl configuration. Such modified sugar moieties are described in, e.g., WO 2019/157531, incorporated by reference herein. A 2'-modified sugar moiety has an additional stereocenter at the 2'-position relative to a 2'-deoxyfuranosyl sugar moiety; therefore, such sugar moieties have a total of sixteen possible isomeric configurations. 2'-modified sugar moieties described herein are in the β-D-ribosyl isomeric configuration unless otherwise specified.

In naturally occurring nucleic acids, sugars are linked to one another 3' to 5'. In certain embodiments, oligonucleotides include one or more nucleoside or sugar moiety linked at an alternative position, for example at the 2' or inverted 5' to 3'. For example, where the linkage is at the 2' position, the 2'-substituent groups may instead be at the 3'-position.

Certain modified sugar moieties comprise a substituent that bridges two atoms of the furanosyl ring to form a second ring, resulting in a bicyclic sugar moiety. Nucleosides comprising such bicyclic sugar moieties have been referred to as bicyclic nucleosides (BNAs), locked nucleosides, or conformationally restricted nucleotides (CRN). Certain such compounds are described in US Patent Publication No. 2013/0190383; and PCT publication WO 2013/036868. In certain such embodiments, the bicyclic sugar moiety comprises a bridge between the 4' and the 2' furanose ring atoms. n certain such embodiments, the furanose ring is a ribose ring. Examples of such 4' to 2' bridging sugar substituents include but are not limited to: 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2' ("LNA"), 4'-CH_2-S-2', 4'-$(CH_2)_2$-O-2' ("ENA"), 4'-$CH(CH_3)$-O-2' (referred to as "constrained ethyl" or "cEt" when in the *S* configuration), 4'-CH_2-O-CH_2-2', 4'-CH_2-N(R)-2', 4'-$CH(CH_2OCH_3)$-O-2' ("constrained MOE" or "cMOE") and analogs thereof (*see, e.g.,* Seth et al., U.S. 7,399,845, Bhat et al., U.S. 7,569,686, Swayze et al., U.S. 7,741,457, and Swayze et al., U.S. 8,022,193), 4'-$C(CH_3)(CH_3)$-O-2' and analogs thereof (*see, e.g.,* Seth et al., U.S. 8,278,283), 4'-CH_2-$N(OCH_3)$-2' and analogs thereof (*see, e.g.,* Prakash et al., U.S. 8,278,425), 4'-CH_2-O-$N(CH_3)$-2' (*see, e.g.,* Allerson et al., U.S. 7,696,345 and Allerson et al., U.S. 8,124,745), 4'-CH_2-$C(H)(CH_3)$-2' (*see, e.g.,* Zhou, *et al., J. Org. Chem.*,2009, *74*, 118-134), 4'-CH_2-$C(=CH_2)$-2' and analogs thereof (*see e.g.*, Seth et al., U.S. 8,278,426), 4'-$C(R_aR_b)$-N(R)-O-2', 4'-$C(R_aR_b)$-O-N(R)-2', 4'-CH_2-O-N(R)-2', and 4'-CH_2-N(R)-O-2', wherein each R, R_a, and R_b is, independently, H, a protecting group, or C_1-C_{12} alkyl (*see, e.g.* Imanishi et al., U.S. 7,427,672).

In certain embodiments, such 4' to 2' bridges independently comprise from 1 to 4 linked groups independently selected from: -[C(Ra)(Rb)]n-, -[C(Ra)(Rb)]n-O-, C(Ra)=C(Rb)-, C(Ra)=N-, C(=NRa)-, -C(=O)-, -C(=S)-, -O-, -Si(Ra)2-, -S(=O)x-, and N(Ra)-;

wherein:

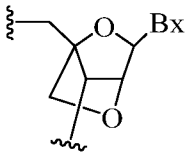
x is 0, 1, or 2;

n is 1, 2, 3, or 4;

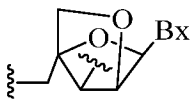
each Ra and Rb is, independently, H, a protecting group, hydroxyl, C1-C12 alkyl, substituted C1-C12 alkyl, C2-C12 alkenyl, substituted C2-C12 alkenyl, C2-C12 alkynyl, substituted C2-C12 alkynyl, C5-C20 aryl, substituted C5-C20 aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C5-C7 alicyclic radical, substituted C5-C7 alicyclic radical, halogen, OJ1, NJ1J2, SJ1, N3, COOJ1, acyl (C(=O)-H), substituted acyl, CN, sulfonyl (S(=O)2-J1), or sulfoxyl (S(=O)-J1); and each J1 and J2 is, independently, H, C1-C12 alkyl, substituted C1-C12 alkyl, C2-C12 alkenyl, substituted C2-C12 alkenyl, C2-C12 alkynyl, substituted C2-C12

alkynyl, C5-C20 aryl, substituted C5-C20 aryl, acyl (C(=O)-H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C1-C12 aminoalkyl, substituted C1-C12 aminoalkyl, or a protecting group.

Additional bicyclic sugar moieties are known in the art, see, for example: Freier et al., Nucleic Acids Research, 1997, 25(22), 4429-4443, Albaek et al., J. Org. Chem., 2006, 71, 7731-7740, Singh et al., Chem. Commun., 1998, 4, 455-456; Koshkin et al., Tetrahedron, 1998, 54, 3607-3630; Wahlestedt et al., Proc. Natl. Acad. Sci. U. S. A., 2000, 97, 5633-5638; Kumar et al., Bioorg. Med. Chem. Lett., 1998, 8, 2219-2222; Singh et al., J. Org. Chem., 1998, 63, 10035-10039; Srivastava et al., J. Am. Chem. Soc., 2007, 129, 8362-8379; Elayadi et al., Curr. Opinion Invens. Drugs, 2001, 2, 558-561; Braasch et al., Chem. Biol., 2001, 8, 1-7; Orum et al., Curr. Opinion Mol. Ther., 2001, 3, 239-243; Wengel et al., U.S. 7,053,207, Imanishi et al., U.S. 6,268,490, Imanishi et al. U.S. 6,770,748, Imanishi et al., U.S. RE44,779; Wengel et al., U.S. 6,794,499, Wengel et al., U.S. 6,670,461; Wengel et al., U.S. 7,034,133, Wengel et al., U.S. 8,080,644; Wengel et al., U.S. 8,034,909; Wengel et al., U.S. 8,153,365; Wengel et al., U.S. 7,572,582; and Ramasamy et al., U.S. 6,525,191, Torsten et al., WO 2004/106356, Wengel et al., WO 1999/014226; Seth et al.,WO 2007/134181; Seth et al., U.S. 7,547,684; Seth et al., U.S. 7,666,854; Seth et al., U.S. 8,088,746; Seth et al., U.S. 7,750,131; Seth et al., U.S. 8,030,467; Seth et al., U.S. 8,268,980; Seth et al., U.S. 8,546,556; Seth et al., U.S. 8,530,640; Migawa et al., U.S. 9,012,421; Seth et al., U.S. 8,501,805; Allerson et al., US2008/0039618; and Migawa et al., US2015/0191727. In certain embodiments, bicyclic sugar moieties and nucleosides incorporating such bicyclic sugar moieties are further defined by isomeric configuration. For example, an LNA nucleoside (described herein) may be in the α-L configuration or in the β-D configuration.



LNA (β-D-configuration)
bridge = 4'-CH_2-O-2'



α-*L*-LNA (α-*L*-configuration)
bridge = 4'-CH_2-O-2'

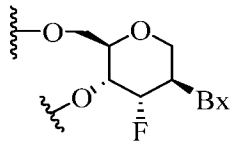
α-L-methyleneoxy (4'-CH_2-O-2') or α-L-LNA bicyclic nucleosides have been incorporated into oligonucleotides that showed antisense activity (Frieden et al., *Nucleic Acids Research,* 2003, *21*, 6365-6372). The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. et al., (2005) Nucleic Acids Research 33(1):439-447; Mook, OR. et al., (2007) Mal Cane Ther 6(3):833-843; Grunweller, A. et al., (2003) Nucleic Acids Research 31(12):3185-3193). Herein, general descriptions of bicyclic nucleosides include both isomeric configurations. When the positions of specific bicyclic nucleosides (*e.g.*, LNA or cEt) are identified in exemplified embodiments herein, they are in the β-D configuration, unless otherwise specified.

In certain embodiments, modified sugar moieties comprise one or more non-bridging sugar substituent and one or more bridging sugar substituent (e.g., 5'-substituted and 4'-2' bridged sugars).

In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the sugar moiety is replaced, *e.g.,* with a sulfur, carbon or nitrogen atom. In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents as described herein. For example, certain sugar surrogates comprise a 4'-sulfur atom and a substitution at the 2'-position (*see, e.g.,* Bhat et al., U.S. 7,875,733 and Bhat et al., U.S. 7,939,677) and/or the 5' position.

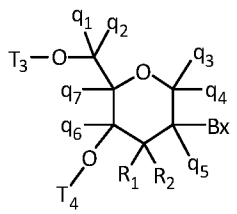
In certain embodiments, sugar surrogates comprise rings having other than 5 atoms. For example, in certain embodiments, a sugar surrogate comprises a six-membered tetrahydropyran ("THP"). Such

tetrahydropyrans may be further modified or substituted. Nucleosides comprising such modified tetrahydropyrans include but are not limited to hexitol nucleic acid ("HNA"), anitol nucleic acid ("ANA"), manitol nucleic acid ("MNA") (*see, e.g.,* Leumann, CJ. *Bioorg. & Med. Chem.* 2002, *10*, 841-854), fluoro HNA:



F-HNA

("F-HNA", *see e.g.* Swayze et al., U.S. 8,088,904; Swayze et al., U.S. 8,440,803; Swayze et al., U.S. 8,796,437; and Swayze et al., U.S. 9,005,906; F-HNA can also be referred to as a F-THP or 3'-fluoro tetrahydropyran), and nucleosides comprising additional modified THP compounds having the formula:



wherein, independently, for each of said modified THP nucleoside:

Bx is a nucleobase moiety;

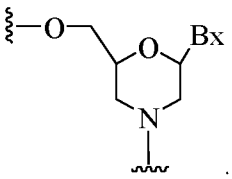
T_3 and T_4 are each, independently, an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide or one of T_3 and T_4 is an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide and the other of T_3 and T_4 is H, a hydroxyl protecting group, a linked conjugate group, or a 5' or 3'-terminal group;

q_1, q_2, q_3, q_4, q_5, q_6 and q_7 are each, independently, H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, or substituted C_2-C_6 alkynyl; and

each of R_1 and R_2 is independently selected from among: hydrogen, halogen, substituted or unsubstituted alkoxy, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$, and CN, wherein X is O, S or NJ_1, and each J_1, J_2, and J_3 is, independently, H or C_1-C_6 alkyl.

In certain embodiments, modified THP nucleosides are provided wherein q_1, q_2, q_3, q_4, q_5, q_6 and q_7 are each H. In certain embodiments, at least one of q_1, q_2, q_3, q_4, q_5, q_6 and q_7 is other than H. In certain embodiments, at least one of q_1, q_2, q_3, q_4, q_5, q_6 and q_7 is methyl. In certain embodiments, modified THP nucleosides are provided wherein one of R_1 and R_2 is F. In certain embodiments, R_1 is F and R_2 is H, in certain embodiments, R_1 is methoxy and R_2 is H, and in certain embodiments, R_1 is methoxyethoxy and R_2 is H.

In certain 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 oligonucleotides have been reported (*see, e.g.,* Braasch et al., Biochemistry, 2002, *41*, 4503-4510 and Summerton et al., U.S. 5,698,685; Summerton et al., U.S. 5,166,315; Summerton et al., U.S. 5,185,444; and Summerton et al., U.S. 5,034,506). As used here, the term "morpholino" means a sugar surrogate having the following structure:



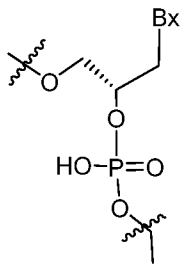
In certain embodiments, morpholinos may be modified, for example by adding or altering various substituent groups from the above morpholino structure. Such sugar surrogates are referred to herein as "modified morpholinos."

In certain embodiments, sugar surrogates comprise acyclic moieties. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include but are not limited to: peptide nucleic acid ("PNA"), acyclic butyl nucleic acid (*see, e.g.,* Kumar et al., *Org. Biomol. Chem.*, 2013, *11*, 5853-5865), and nucleosides and oligonucleotides described in Manoharan et al., WO2011/133876. In certain embodiments, sugar surrogates comprise acyclic moieties. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include, but are not limited to: peptide nucleic acid ("PNA"), acyclic butyl nucleic acid (*see, e.g.,* Kumar et al., *Org. Biomol. Chem.*, 2013, *11*, 5853-5865), and nucleosides and oligonucleotides described in Manoharan et al., US2013/130378. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262. Additional PNA compounds suitable for use in the oligonucleotides of the invention are described in, for example, in Nielsen *et al., Science,* 1991, 254, 1497-1500.

In certain embodiments, sugar surrogates are the "unlocked" sugar structure of UNA (unlocked nucleic acid) nucleosides. UNA is an unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked sugar surrogate. Representative U.S. publications that teach the preparation of UNA include, but are not limited to, US Patent No. 8,314,227; and US Patent Publication Nos. 2013/0096289; 2013/0011922; and 2011/0313020, the entire contents of each of which are hereby incorporated herein by reference.

In certain embodiments, sugar surrogates are the glycerol as found in GNA (glycol nucleic acid) nucleosides as depicted below:

(*S*)-GNA



where Bx represents any nucleobase.

Many other bicyclic and tricyclic sugar and sugar surrogates are known in the art that can be used in modified nucleosides.

2. Certain Modified Nucleobases

In certain embodiments, modified oligonucleotides comprise one or more nucleosides comprising an unmodified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleosides comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleosides that does not comprise a nucleobase, referred to as an abasic nucleoside. In certain embodiments,

modified oligonucleotides comprise one or more inosine nucleosides (i.e., nucleosides comprising a hypoxanthine nucleobase).

In certain embodiments, modified nucleobases are selected from: 5-substituted pyrimidines, 6-azapyrimidines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6 and O-6 substituted purines. In certain embodiments, modified nucleobases are selected from: 5-methylcytosine, 2-aminopropyladenine, 5-hydroxymethylcytosine, 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 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one and 9-(2-aminoethoxy)-1,3-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 Merigan et al., U.S. 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.

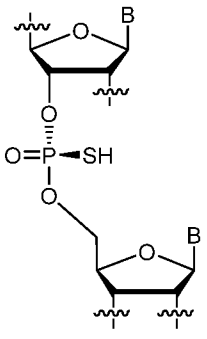
Publications that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include without limitation, Manoharan et al., US2003/0158403; Manoharan et al., US2003/0175906; Dinh et al., U.S. 4,845,205; Spielvogel et al., U.S. 5,130,302; Rogers et al., U.S. 5,134,066; Bischofberger et al., U.S. 5,175,273; Urdea et al., U.S. 5,367,066; Benner et al., U.S. 5,432,272; Matteucci et al., U.S. 5,434,257; Gmeiner et al., U.S. 5,457,187; Cook et al., U.S. 5,459,255; Froehler et al., U.S. 5,484,908; Matteucci et al., U.S. 5,502,177; Hawkins et al., U.S. 5,525,711; Haralambidis et al., U.S. 5,552,540; Cook et al., U.S. 5,587,469; Froehler et al., U.S. 5,594,121; Switzer et al., U.S. 5,596,091; Cook et al., U.S. 5,614,617; Froehler et al., U.S. 5,645,985; Cook et al., U.S. 5,681,941; Cook et al., U.S. 5,811,534; Cook et al., U.S. 5,750,692; Cook et al., U.S. 5,948,903; Cook et al., U.S. 5,587,470; Cook et al., U.S. 5,457,191; Matteucci et al., U.S. 5,763,588; Froehler et al., U.S. 5,830,653; Cook et al., U.S. 5,808,027; Cook et al., U.S. 6,166,199; and Matteucci et al., U.S. 6,005,096.

3. Certain Modified Internucleoside Linkages

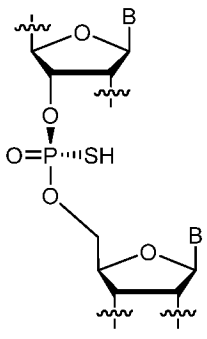
The naturally occurring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. In certain embodiments, nucleosides of modified oligonucleotides may be linked together using one or more modified internucleoside linkages. The two main classes of internucleoside linking groups are defined by the presence or absence of a phosphorus atom. Representative phosphorus-containing internucleoside linkages include but are not limited to phosphates, which contain a phosphodiester bond ("P=O") (also referred to as unmodified or naturally occurring linkages), phosphotriesters, methylphosphonates, phosphoramidates, and phosphorothioates ("P=S"), and phosphorodithioates ("HS-P=S"). Representative non-phosphorus containing internucleoside linking groups

include but are not limited to methylenemethylimino (-CH_2-N(CH_3)-O-CH_2-), thiodiester, thionocarbamate (-O-C(=O)(NH)-S-); siloxane (-O-SiH_2-O-); and N,N'-dimethylhydrazine (-CH_2-N(CH_3)-N(CH_3)-). Modified internucleoside linkages, compared to naturally occurring phosphate linkages, can be used to alter, typically increase, nuclease resistance of the oligonucleotide. In certain embodiments, internucleoside linkages having a chiral atom can be prepared as a racemic mixture, or as separate enantiomers. Methods of preparation of phosphorous-containing and non-phosphorous-containing internucleoside linkages are well known to those skilled in the art.

Representative internucleoside linkages having a chiral center include but are not limited to alkylphosphonates and phosphorothioates. Modified oligonucleotides comprising internucleoside linkages having a chiral center can be prepared as populations of modified oligonucleotides comprising stereorandom internucleoside linkages, or as populations of modified oligonucleotides comprising phosphorothioate linkages in particular stereochemical configurations. In certain embodiments, populations of modified oligonucleotides comprise phosphorothioate internucleoside linkages wherein all of the phosphorothioate internucleoside linkages are stereorandom. Such modified oligonucleotides can be generated using synthetic methods that result in random selection of the stereochemical configuration of each phosphorothioate linkage. Nonetheless, each individual phosphorothioate of each individual oligonucleotide molecule has a defined stereoconfiguration. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising one or more particular phosphorothioate internucleoside linkages in a particular, independently selected stereochemical configuration. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 65% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 70% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 80% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 90% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 99% of the molecules in the population. Such chirally enriched populations of modified oligonucleotides can be generated using synthetic methods known in the art, *e.g.*, methods described in Oka et al., *JACS* 125, 8307 (2003), Wan et al. *Nuc. Acid. Res.* 42, 13456 (2014), and WO 2017/015555. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one indicated phosphorothioate in the (*S*p) configuration. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one phosphorothioate in the (*R*p) configuration. In certain embodiments, modified oligonucleotides comprising (*R*p) and/or (*S*p) phosphorothioates comprise one or more of the following formulas, respectively, wherein "B" indicates a nucleobase:

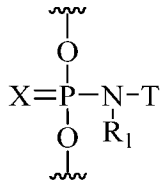


(R_p)



(S_p)

In certain embodiments, a modified internucleoside linkage comprises a linking group having a formula:



wherein independently for each internucleoside linking group of the modified oligonucleotide:

X is selected from O or S;

R_1 is selected from H, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl; and

T is selected from SO_2R_2, $C(=O)R_3$, and $P(=O)R_4R_5$, wherein:

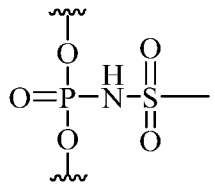
R_2 is selected from an aryl, a substituted aryl, a heterocycle, a substituted heterocycle, an aromatic heterocycle, a substituted aromatic heterocycle, a diazole, a substituted diazole, a C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_1-C_6 alkenyl substituted C_1-C_6 alkynyl, and a conjugate group;

R_3 is selected from an aryl, a substituted aryl, CH_3, $N(CH_3)_2$, OCH_3 and a conjugate group;

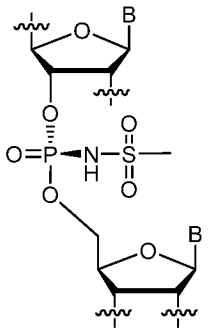
R_4 is selected from OCH_3, OH, C_1-C_6 alkyl, substituted C_1-C_6 alkyl and a conjugate group; and

R_5 is selected from OCH_3, OH, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl.

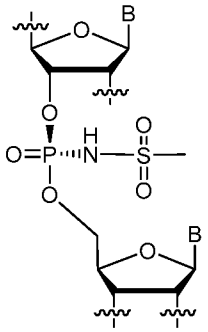
In certain embodiments, a modified internucleoside linkage comprises a mesyl phosphoramidate linking group having a formula:



In certain embodiments, a mesyl phosphoramidate internucleoside linkage may comprise a chiral center. In certain embodiments, modified oligonucleotides comprising (*R*p) and/or (*S*p) mesyl phosphoramidates comprise one or more of the following formulas, respectively, wherein "B" indicates a nucleobase:



(S_p)

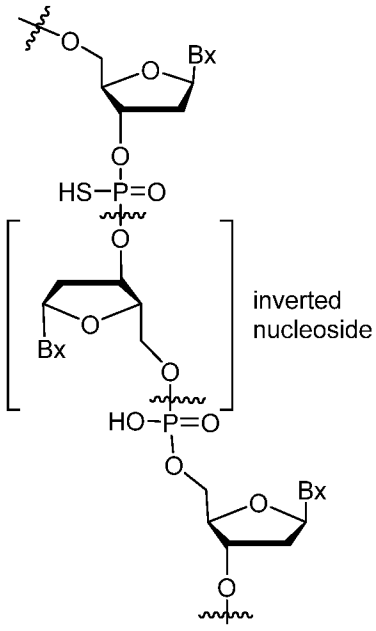


(R_p)

Unless otherwise indicated, chiral internucleoside linkages of modified oligonucleotides described herein can be stereorandom or in a particular stereochemical configuration.

Neutral internucleoside linkages include, without limitation, phosphotriesters, methylphosphonates, MMI (3'-CH_2-N(CH_3)-O-5'), amide-3 (3'-CH_2-C(=O)-N(H)-5'), amide-4 (3'-CH_2-N(H)-C(=O)-5'), formacetal (3'-O-CH_2-O-5'), methoxypropyl (MOP), and thioformacetal (3'-S-CH_2-O-5'). Further neutral internucleoside linkages include nonionic linkages comprising siloxane (dialkylsiloxane), carboxylate ester, carboxamide, sulfide, sulfonate ester and amides (See for example: *Carbohydrate Modifications in Antisense Research*; Y.S. Sanghvi and P.D. Cook, Eds., ACS Symposium Series 580; Chapters 3 and 4, 40-65). Further neutral internucleoside linkages include nonionic linkages comprising mixed N, O, S and CH_2 component parts.

In certain embodiments, modified oligonucleotides comprise one or more inverted nucleoside, as shown below:



,

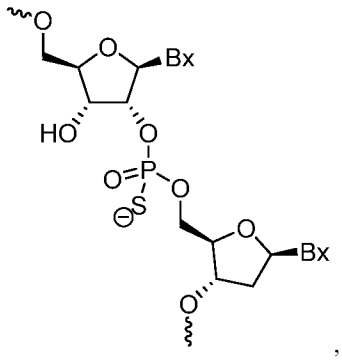
wherein each Bx independently represents any nucleobase.

In certain embodiments, an inverted nucleoside is terminal (i.e., the last nucleoside on one end of an oligonucleotide) and so only one internucleoside linkage depicted above will be present. In certain such

embodiments, additional features (such as a conjugate group) may be attached to the inverted nucleoside. Such terminal inverted nucleosides can be attached to either or both ends of an oligonucleotide.

In certain embodiments, such groups lack a nucleobase and are referred to herein as inverted sugar moieties. In certain embodiments, an inverted sugar moiety is terminal (i.e., attached to the last nucleoside on one end of an oligonucleotide) and so only one internucleoside linkage above will be present. In certain such embodiments, additional features (such as a conjugate group) may be attached to the inverted sugar moiety. Such terminal inverted sugar moieties can be attached to either or both ends of an oligonucleotide.

In certain embodiments, nucleic acids can be linked 2' to 5' rather than the standard 3' to 5' linkage. Such a linkage is illustrated below.



wherein each Bx represents any nucleobase.

B. Certain Motifs

In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more modified internucleoside linkage. In such embodiments, the modified, unmodified, and differently modified sugar moieties, nucleobases, and/or internucleoside linkages of a modified oligonucleotide define a pattern or motif. In certain embodiments, the patterns of sugar moieties, nucleobases, and internucleoside linkages are each independent of one another. Thus, a modified oligonucleotide may be described by its sugar motif, nucleobase motif and/or internucleoside linkage motif (as used herein, nucleobase motif describes the modifications to the nucleobases independent of the sequence of nucleobases).

1. Certain Sugar Motifs

In certain embodiments, oligonucleotides comprise one or more type of modified sugar and/or unmodified sugar moiety arranged along the oligonucleotide or region thereof in a defined pattern or sugar motif. In certain instances, such sugar motifs include but are not limited to any of the sugar modifications discussed herein.

Gapmer Oligonucleotides

In certain embodiments, modified oligonucleotides comprise or consist of a region having a gapmer motif, which is defined by two external regions or "wings" and a central or internal region or "gap." The three regions of a gapmer motif (the 5'-wing, the gap, and the 3'-wing) form a contiguous sequence of nucleosides wherein at least some of the sugar moieties of the nucleosides of each of the wings differ from at least some of the sugar moieties of the nucleosides of the gap. Specifically, at least the sugar moieties of the nucleosides of each wing that are closest to the gap (the 3'-most nucleoside of the 5'-wing and the 5'-most nucleoside of the 3'-wing) differ from the sugar moiety of the neighboring gap nucleosides, thus defining the boundary between the wings and the gap (i.e., the

wing/gap junction). In certain embodiments, the sugar moieties within the gap are the same as one another. In certain embodiments, the gap includes one or more nucleoside having a sugar moiety that differs from the sugar moiety of one or more other nucleosides of the gap. In certain embodiments, the sugar motifs of the two wings are the same as one another (symmetric gapmer). In certain embodiments, the sugar motif of the 5'-wing differs from the sugar motif of the 3'-wing (asymmetric gapmer).

In certain embodiments, the wings of a gapmer comprise 1-6 nucleosides. In certain embodiments, each nucleoside of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least one nucleoside of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least two nucleosides of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least three nucleosides of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least four nucleosides of each wing of a gapmer comprises a modified sugar moiety.

In certain embodiments, the gap of a gapmer comprises 7-12 nucleosides. In certain embodiments, each nucleoside of the gap of a gapmer comprises a 2'-β-D-deoxyribosyl sugar moiety. In certain embodiments, at least one nucleoside of the gap of a gapmer comprises a modified sugar moiety.

In certain embodiments, the gapmer is a deoxy gapmer. In certain embodiments, the nucleosides on the gap side of each wing/gap junction comprise 2'- deoxyribosyl sugar moieties and the nucleosides on the wing sides of each wing/gap junction comprise modified sugar moieties. In certain embodiments, each nucleoside of the gap comprises a 2'-β-D-deoxyribosyl sugar moiety. In certain embodiments, each nucleoside of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least one nucleoside of the gap of a gapmer comprises a modified sugar moiety. In certain embodiments, one nucleoside of the gap comprises a modified sugar moiety and each remaining nucleoside of the gap comprises a 2'-deoxyribosyl sugar moiety. In certain embodiments, at least one nucleoside of the gap of a gapmer comprises a 2'-OMe sugar moiety.

Herein, the lengths (number of nucleosides) of the three regions of a gapmer may be provided using the notation [# of nucleosides in the 5'-wing] – [# of nucleosides in the gap] – [# of nucleosides in the 3'-wing]. Thus, a 3-10-3 gapmer consists of 3 linked nucleosides in each wing and 10 linked nucleosides in the gap. Where such nomenclature is followed by a specific modification, that modification is the modification in each sugar moiety of each wing and the gap nucleosides comprise 2'-β-D-deoxyribosyl sugar moieties. A 3-10-3 cEt gapmer consists of 3 linked cEt nucleosides in the 5'-wing, 10 linked 2'- β-D-deoxynucleosides in the gap, and 3 linked cEt nucleosides in the 3'-wing. A 5-10-5 MOE gapmer consists of 5 linked 2'-MOE nucleosides in the 5'-wing, 10 linked 2'- β-D-deoxynucleosides in the gap, and 5 linked 2'-MOE nucleosides in the 3'-wing.

In certain embodiments, modified oligonucleotides have the sugar motif from 5' to 3': eeeeddddddddddeeeee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety and each "e" represents a 2'-MOE ribosyl sugar moiety.

In certain embodiments, modified oligonucleotides have the sugar motif from 5' to 3': kkkddddddddddkkk; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, and each "k" represents a cEt sugar moiety.

2. Certain Nucleobase Motifs

In certain embodiments, oligonucleotides comprise modified and/or unmodified nucleobases arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each nucleobase is modified. In certain embodiments, none of the nucleobases are modified. In certain embodiments, each purine or each pyrimidine is modified. In certain embodiments, each adenine is modified. In certain embodiments, each

guanine is modified. In certain embodiments, each thymine is modified. In certain embodiments, each uracil is modified. In certain embodiments, each cytosine is modified. In certain embodiments, some or all of the cytosine nucleobases in a modified oligonucleotide are 5-methylcytosines. In certain embodiments, all of the cytosine nucleobases are 5-methylcytosines and all of the other nucleobases of the modified oligonucleotide are unmodified nucleobases.

In certain embodiments, modified oligonucleotides comprise a block of modified nucleobases. In certain such embodiments, the block is at the 3'-end of the oligonucleotide. In certain embodiments the block is within 3 nucleosides of the 3'-end of the oligonucleotide. In certain embodiments, the block is at the 5'-end of the oligonucleotide. In certain embodiments the block is within 3 nucleosides of the 5'-end of the oligonucleotide.

In certain embodiments, oligonucleotides having a gapmer motif comprise a nucleoside comprising a modified nucleobase. In certain such embodiments, one nucleoside comprising a modified nucleobase is in the central gap of an oligonucleotide having a gapmer motif. In certain such embodiments, the sugar moiety of said nucleoside is a 2'-deoxyribosyl sugar moiety. In certain embodiments, the modified nucleobase is selected from: a 2-thiopyrimidine and a 5-propynepyrimidine.

3. Certain Internucleoside Linkage Motifs

In certain embodiments, oligonucleotides comprise modified and/or unmodified internucleoside linkages arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each internucleoside linking group is a phosphodiester internucleoside linkage (P=O). In certain embodiments, each internucleoside linking group of a modified oligonucleotide is a phosphorothioate internucleoside linkage (P=S). In certain embodiments, each internucleoside linkage of a modified oligonucleotide is independently selected from a phosphorothioate internucleoside linkage and phosphodiester internucleoside linkage. In certain embodiments, each phosphorothioate internucleoside linkage is independently selected from a stereorandom phosphorothioate a (*S*p) phosphorothioate, and a (*R*p) phosphorothioate.

In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer and the internucleoside linkages within the gap are all modified. In certain such embodiments, some or all of the internucleoside linkages in the wings are unmodified phosphodiester internucleoside linkages. In certain embodiments, the terminal internucleoside linkages are modified. In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer, and the internucleoside linkage motif comprises at least one phosphodiester internucleoside linkage in at least one wing, wherein the at least one phosphodiester linkage is not a terminal internucleoside linkage, and the remaining internucleoside linkages are phosphorothioate internucleoside linkages. In certain such embodiments, all of the phosphorothioate linkages are stereorandom. In certain embodiments, all of the phosphorothioate linkages in the wings are (Sp) phosphorothioates, and the gap comprises at least one Sp, Sp, Rp motif. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising such internucleoside linkage motifs.

C. Certain Lengths

It is possible to increase or decrease the length of an oligonucleotide without eliminating activity. For example, in Woolf et al. (Proc. Natl. Acad. Sci. USA 89:7305-7309, 1992), a series of oligonucleotides 13-25 nucleobases in length were tested for their ability to induce cleavage of a target RNA in an oocyte injection model. Oligonucleotides 25 nucleobases in length with 8 or 11 mismatch bases near the ends of the oligonucleotides were able to direct specific cleavage of the target RNA, albeit to a lesser extent than the oligonucleotides that contained

no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase oligonucleotides, including those with 1 or 3 mismatches.

In certain embodiments, oligonucleotides (including modified oligonucleotides) can have any of a variety of ranges of lengths. In certain embodiments, oligonucleotides consist of X to Y linked nucleosides, where X represents the fewest number of nucleosides in the range and Y represents the largest number nucleosides in the range. In certain such embodiments, X and Y are each independently selected from 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, and 50; provided that $X \leq Y$. For example, in certain embodiments, oligonucleotides consist of 12 to 13, 12 to 14, 12 to 15, 12 to 16, 12 to 17, 12 to 18, 12 to 19, 12 to 20, 12 to 21, 12 to 22, 12 to 23, 12 to 24, 12 to 25, 12 to 26, 12 to 27, 12 to 28, 12 to 29, 12 to 30, 13 to 14, 13 to 15, 13 to 16, 13 to 17, 13 to 18, 13 to 19, 13 to 20, 13 to 21, 13 to 22, 13 to 23, 13 to 24, 13 to 25, 13 to 26, 13 to 27, 13 to 28, 13 to 29, 13 to 30, 14 to 15, 14 to 16, 14 to 17, 14 to 18, 14 to 19, 14 to 20, 14 to 21, 14 to 22, 14 to 23, 14 to 24, 14 to 25, 14 to 26, 14 to 27, 14 to 28, 14 to 29, 14 to 30, 15 to 16, 15 to 17, 15 to 18, 15 to 19, 15 to 20, 15 to 21, 15 to 22, 15 to 23, 15 to 24, 15 to 25, 15 to 26, 15 to 27, 15 to 28, 15 to 29, 15 to 30, 16 to 17, 16 to 18, 16 to 19, 16 to 20, 16 to 21, 16 to 22, 16 to 23, 16 to 24, 16 to 25, 16 to 26, 16 to 27, 16 to 28, 16 to 29, 16 to 30, 17 to 18, 17 to 19, 17 to 20, 17 to 21, 17 to 22, 17 to 23, 17 to 24, 17 to 25, 17 to 26, 17 to 27, 17 to 28, 17 to 29, 17 to 30, 18 to 19, 18 to 20, 18 to 21, 18 to 22, 18 to 23, 18 to 24, 18 to 25, 18 to 26, 18 to 27, 18 to 28, 18 to 29, 18 to 30, 19 to 20, 19 to 21, 19 to 22, 19 to 23, 19 to 24, 19 to 25, 19 to 26, 19 to 27, 19 to 28, 19 to 29, 19 to 30, 20 to 21, 20 to 22, 20 to 23, 20 to 24, 20 to 25, 20 to 26, 20 to 27, 20 to 28, 20 to 29, 20 to 30, 21 to 22, 21 to 23, 21 to 24, 21 to 25, 21 to 26, 21 to 27, 21 to 28, 21 to 29, 21 to 30, 22 to 23, 22 to 24, 22 to 25, 22 to 26, 22 to 27, 22 to 28, 22 to 29, 22 to 30, 23 to 24, 23 to 25, 23 to 26, 23 to 27, 23 to 28, 23 to 29, 23 to 30, 24 to 25, 24 to 26, 24 to 27, 24 to 28, 24 to 29, 24 to 30, 25 to 26, 25 to 27, 25 to 28, 25 to 29, 25 to 30, 26 to 27, 26 to 28, 26 to 29, 26 to 30, 27 to 28, 27 to 29, 27 to 30, 28 to 29, 28 to 30, or 29 to 30 linked nucleosides.

D. Certain Modified Oligonucleotides

In certain embodiments, the above modifications (sugar, nucleobase, internucleoside linkage) are incorporated into a modified oligonucleotide. In certain embodiments, modified oligonucleotides are characterized by their modification motifs and overall lengths. In certain embodiments, such parameters are each independent of one another. Thus, unless otherwise indicated, each internucleoside linkage of an oligonucleotide having a gapmer sugar motif may be modified or unmodified and may or may not follow the gapmer modification pattern of the sugar modifications. For example, the internucleoside linkages within the wing regions of a sugar gapmer may be the same or different from one another and may be the same or different from the internucleoside linkages of the gap region of the sugar motif. Likewise, such sugar gapmer oligonucleotides may comprise one or more modified nucleobase independent of the gapmer pattern of the sugar modifications. Unless otherwise indicated, all modifications are independent of nucleobase sequence.

E. Certain Populations of Modified Oligonucleotides

Populations of modified oligonucleotides in which all of the modified oligonucleotides of the population have the same molecular formula can be stereorandom populations or chirally enriched populations. All of the chiral centers of all of the modified oligonucleotides are stereorandom in a stereorandom population. In a chirally enriched population, at least one particular chiral center is not stereorandom in the modified oligonucleotides of the population. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for

β-D ribosyl sugar moieties, and all of the phosphorothioate internucleoside linkages are stereorandom. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for both β-D ribosyl sugar moieties and at least one, particular phosphorothioate internucleoside linkage in a particular stereochemical configuration.

F. Nucleobase Sequence

In certain embodiments, oligonucleotides (unmodified or modified oligonucleotides) are further described by their nucleobase sequence. In certain embodiments oligonucleotides have a nucleobase sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain such embodiments, a region of an oligonucleotide has a nucleobase sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain embodiments, the nucleobase sequence of a region or entire length of an oligonucleotide is at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to the second oligonucleotide or nucleic acid, such as a target nucleic acid.

II. Certain Oligomeric Compounds

In certain embodiments, provided herein are oligomeric compounds, which consist of an oligonucleotide (modified or unmodified) and optionally one or more conjugate groups and/or terminal groups. Conjugate groups consist of one or more conjugate moiety and a conjugate linker which links the conjugate moiety to the oligonucleotide. Conjugate groups may be attached to either or both ends of an oligonucleotide and/or at any internal position. In certain embodiments, conjugate groups are attached to the 2'-position of a nucleoside of a modified oligonucleotide. In certain embodiments, conjugate groups that are attached to either or both ends of an oligonucleotide are terminal groups. In certain such embodiments, conjugate groups or terminal groups are attached at the 3' and/or 5'-end of oligonucleotides. In certain such embodiments, conjugate groups (or terminal groups) are attached at the 3'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 3'-end of oligonucleotides. In certain embodiments, conjugate groups (or terminal groups) are attached at the 5'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 5'-end of oligonucleotides.

Examples of terminal groups include but are not limited to conjugate groups, capping groups, phosphate moieties, protecting groups, modified or unmodified nucleosides, and two or more nucleosides that are independently modified or unmodified.

A. Certain Conjugate Groups

In certain embodiments, oligonucleotides are covalently attached to one or more conjugate groups. In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge and clearance.

In certain embodiments, conjugation of one or more carbohydrate moieties to a modified oligonucleotide can optimize one or more properties of the modified oligonucleotide. In certain embodiments, the carbohydrate moiety is attached to a modified subunit of the modified oligonucleotide. For example, the ribose sugar of one or more ribonucleotide subunits of a modified oligonucleotide can be replaced with another moiety, e.g. a non-carbohydrate (preferably cyclic) carrier to which is attached a carbohydrate ligand. A ribonucleotide subunit in which the ribose sugar of the subunit has been so replaced is referred to herein as a ribose replacement modification

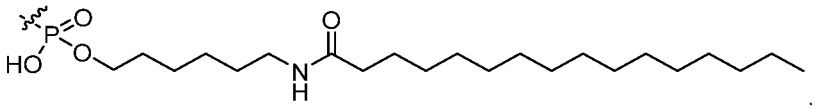
subunit (RRMS), which is a modified sugar moiety. A cyclic carrier may be a carbocyclic ring system, i.e., one or more ring atoms may be a heteroatom, e.g., nitrogen, oxygen, sulphur. The cyclic carrier may be a monocyclic ring system, or may contain two or more rings, e.g. fused rings. The cyclic carrier may be a fully saturated ring system, or it may contain one or more double bonds. In certain embodiments, the modified oligonucleotide is a gapmer.

In certain embodiments, conjugate groups impart a new property on the attached oligonucleotide, *e.g.*, fluorophores or reporter groups that enable detection of the oligonucleotide. Certain conjugate groups and conjugate moieties have been described previously, for example: cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1994, *4*, 1053-1060), a thioether, *e.g.,* hexyl-S-tritylthiol (Manoharan et al., *Ann. N.Y. Acad. Sci.*, 1992, *660*, 306-309; Manoharan et al., *Bioorg. Med. Chem. Lett.,* 1993, *3*, 2765-2770), a thiocholesterol (Oberhauser et al., *Nucl. Acids Res.*, 1992, *20*, 533-538), an aliphatic chain, *e.g.,* do-decan-diol or undecyl residues (Saison-Behmoaras et al., *EMBO J.,* 1991, *10*, 1111-1118; Kabanov et al., *FEBS Lett.*, 1990, *259*, 327-330; Svinarchuk et al., *Biochimie*, 1993, *75*, 49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., *Tetrahedron Lett.*, 1995, *36*, 3651-3654; Shea et al., *Nucl. Acids Res.*, 1990, *18*, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., *Nucleosides & Nucleotides*, 1995, *14*, 969-973), or adamantane acetic acid a palmityl moiety (Mishra et al., *Biochim. Biophys. Acta*, 1995, *1264,* 229-237), an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., *J. Pharmacol. Exp. Ther.,* 1996, *277*, 923-937), a tocopherol group (Nishina et al., *Molecular Therapy Nucleic Acids*, 2015**,** *4*, e220; and Nishina et al., *Molecular Therapy,* 2008, *16*, 734-740), or a GalNAc cluster (*e.g.*, WO2014/179620).

In certain embodiments, conjugate groups may be selected from any of a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, C5 alkyl, C22 alkenyl, C20 alkenyl, C16 alkenyl, C10 alkenyl, C21 alkenyl, C19 alkenyl, C18 alkenyl, C15 alkenyl, C14 alkenyl, C13 alkenyl, C12 alkenyl, C11 alkenyl, C9 alkenyl, C8 alkenyl, C7 alkenyl, C6 alkenyl, or C5 alkenyl.

In certain embodiments, conjugate groups may be selected from any of C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, and C5 alkyl, where the alkyl chain has one or more unsaturated bonds.

In certain embodiments, a conjugate group has the following structure:



1. **Conjugate Moieties**

Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates (e.g., GalNAc), vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterols, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, and dyes.

In certain embodiments, a conjugate moiety comprises an active drug substance, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fen-bufen, ketoprofen, (*S*)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, fingolimod, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indo-methicin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

2. **Conjugate Linkers**

Conjugate moieties are attached to oligonucleotides through conjugate linkers. In certain oligomeric compounds, the conjugate linker is a single chemical bond (i.e., the conjugate moiety is attached directly to an oligonucleotide through a single bond). In certain embodiments, the conjugate linker comprises a chain structure, such as a hydrocarbyl chain, or an oligomer of repeating units such as ethylene glycol, nucleosides, or amino acid units.

In certain embodiments, a conjugate linker comprises pyrrolidine.

In certain embodiments, a conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether, and hydroxylamino. In certain such embodiments, the conjugate linker comprises groups selected from alkyl, amino, oxo, amide and ether groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and amide groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and ether groups. In certain embodiments, the conjugate linker comprises at least one phosphorus moiety. In certain embodiments, the conjugate linker comprises at least one phosphate group. In certain embodiments, the conjugate linker includes at least one neutral linking group.

In certain embodiments, conjugate linkers, including the conjugate linkers described above, are bifunctional linking moieties, *e.g.,* those known in the art to be useful for attaching conjugate groups to compounds, such as the oligonucleotides provided herein. In general, a bifunctional linking moiety comprises at least two functional groups. One of the functional groups is selected to bind to a particular site on a compound and the other is selected to bind to a conjugate group. Examples of functional groups used in a bifunctional linking moiety include but are not limited to electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In certain embodiments, bifunctional linking moieties comprise one or more groups selected from amino, hydroxyl, carboxylic acid, thiol, alkyl, alkenyl, and alkynyl.

Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) and 6-aminohexanoic acid (AHEX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C_1-C_{10} alkyl, substituted or unsubstituted C_2-C_{10} alkenyl or substituted or unsubstituted C_2-C_{10} alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

In certain embodiments, conjugate linkers comprise 1-10 linker-nucleosides. In certain embodiments, conjugate linkers comprise 2-5 linker-nucleosides. In certain embodiments, conjugate linkers comprise exactly 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise the TCA motif. In certain embodiments, such linker-nucleosides are modified nucleosides. In certain embodiments such linker-nucleosides comprise a modified sugar moiety. In certain embodiments, linker-nucleosides are unmodified. In certain embodiments, linker-nucleosides comprise an optionally protected heterocyclic base selected from a purine, substituted purine, pyrimidine or substituted pyrimidine. In certain embodiments, a cleavable moiety is a nucleoside selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methylcytosine, 4-N-benzoyl-5-methylcytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. It is typically desirable for linker-nucleosides to be cleaved from the oligomeric compound after it reaches a target tissue. Accordingly, linker-nucleosides are typically linked to one another and to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are phosphodiester bonds.

Herein, linker-nucleosides are not considered to be part of the oligonucleotide. Accordingly, in embodiments in which an oligomeric compound comprises an oligonucleotide consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid and the oligomeric compound also comprises a conjugate group comprising a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid. For example, an oligomeric compound may comprise (1) a modified oligonucleotide consisting of 8-30 nucleosides and (2) a conjugate group comprising 1-10 linker-nucleosides that are contiguous with the nucleosides of the modified oligonucleotide. The total number of contiguous linked nucleosides in such an oligomeric compound is more than 30. Alternatively, an oligomeric compound may comprise a modified oligonucleotide consisting of 8-30 nucleosides and no conjugate group. The total number of contiguous linked nucleosides in such an oligomeric compound is no more than 30. Unless otherwise indicated conjugate linkers comprise no more than 10 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 5 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 2 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 1 linker-nucleoside.

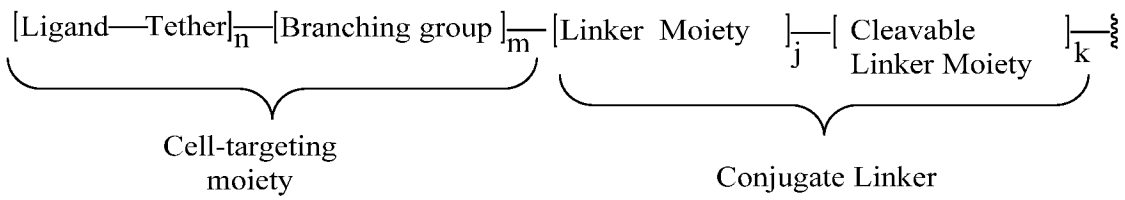
In certain embodiments, it is desirable for a conjugate group to be cleaved from the oligonucleotide. For example, in certain circumstances oligomeric compounds comprising a particular conjugate moiety are better taken up by a particular cell type, but once the oligomeric compound has been taken up, it is desirable that the conjugate group be cleaved to release the unconjugated or parent oligonucleotide. Thus, certain conjugate linkers may comprise one or more cleavable moieties. In certain embodiments, a cleavable moiety is a cleavable bond. In certain embodiments, a cleavable moiety is a group of atoms comprising at least one cleavable bond. In certain embodiments, a cleavable moiety comprises a group of atoms having one, two, three, four, or more than four cleavable bonds. In certain embodiments, a cleavable moiety is selectively cleaved inside a cell or subcellular compartment, such as a lysosome. In certain embodiments, a cleavable moiety is selectively cleaved by endogenous enzymes, such as nucleases.

In certain embodiments, a cleavable bond is selected from among: an amide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, or a disulfide. In certain embodiments, a cleavable bond is one or both of the esters of a phosphodiester. In certain embodiments, a cleavable moiety comprises a phosphate or phosphodiester. In certain embodiments, the cleavable moiety is a phosphate linkage between an oligonucleotide and a conjugate moiety or conjugate group.

In certain embodiments, a cleavable moiety comprises or consists of one or more linker-nucleosides. In certain such embodiments, the one or more linker-nucleosides are linked to one another and/or to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are unmodified phosphodiester bonds. In certain embodiments, a cleavable moiety is 2'-deoxynucleoside that is attached to either the 3' or 5'-terminal nucleoside of an oligonucleotide by a phosphate internucleoside linkage and covalently attached to the remainder of the conjugate linker or conjugate moiety by a phosphate or phosphorothioate linkage. In certain such embodiments, the cleavable moiety is 2'-deoxyadenosine.

3. **Cell-Targeting Moieties**

In certain embodiments, a conjugate group comprises a cell-targeting moiety. In certain embodiments, a conjugate group has the general formula:



wherein n is from 1 to about 3, m is 0 when n is 1, m is 1 when n is 2 or greater, j is 1 or 0, and k is 1 or 0.

In certain embodiments, n is 1, j is 1 and k is 0. In certain embodiments, n is 1, j is 0 and k is 1. In certain embodiments, n is 1, j is 1 and k is 1. In certain embodiments, n is 2, j is 1 and k is 0. In certain embodiments, n is 2, j is 0 and k is 1. In certain embodiments, n is 2, j is 1 and k is 1. In certain embodiments, n is 3, j is 1 and k is 0. In certain embodiments, n is 3, j is 0 and k is 1. In certain embodiments, n is 3, j is 1 and k is 1.

In certain embodiments, conjugate groups comprise cell-targeting moieties that have at least one tethered ligand. In certain embodiments, cell-targeting moieties comprise two tethered ligands covalently ligands covalently attached to a branching group.

In certain embodiments, each ligand of a cell-targeting moiety has an affinity for at least one type of receptor on a target cell. In certain embodiments, each ligand has an affinity for at least one type of receptor on the surface of a mammalian liver cell. In certain embodiments, each ligand has an affinity for the hepatic asialoglycoprotein receptor (ASGP-R). In certain embodiments, each ligand is a carbohydrate.

In certain embodiments, oligomeric compounds comprise a conjugate group comprising a cell-targeting moiety having an affinity for transferrin receptor (TfR), also known as TfR1 and CD71. In certain embodiments, the conjugate group comprises an anti-TfR1 antibody or fragment thereof. In certain embodiments, the anti-TfR1 antibody or fragment thereof can be any known in the art including but not limited to those described in WO1991/004753; WO2013/103800; WO2014/144060; WO2016/081643; WO2016/179257; WO2016/207240; WO2017/221883; WO2018/129384; WO2018/124121; WO2019/151539; WO2020/132584; WO2020/028864; US 7,208,174; US 9,034,329; and US 10,550,188. In certain embodiments, a fragment of an anti-TfR1 antibody is F(ab')2, Fab, Fab', Fv, or scFv.

In certain embodiments, the conjugate group comprises a protein or peptide capable of binding TfR1. In certain embodiments, the protein or peptide capable of binding TfR1 can be any known in the art including but not limited to those described in WO2019/140050; WO2020/037150; WO2020/124032; and US 10,138,483.

In certain embodiments, the conjugate group comprises an aptamer capable of binding TfR1. In certain embodiments, the aptamer capable of binding TfR1 can be any known in the art including but not limited to those described in WO2013/163303; WO2019/033051; and WO2020/245198.

B. Certain Terminal Groups

In certain embodiments, oligomeric compounds comprise one or more terminal groups. In certain such embodiments, oligomeric compounds comprise a stabilized 5'-phosphate. Stabilized 5'-phosphates include, but are not limited to 5'-phosphonates, including, but not limited to 5'-vinylphosphonates. In certain embodiments, terminal groups comprise one or more abasic sugar moieties and/or inverted nucleosides. In certain embodiments, terminal groups comprise one or more 2'-linked nucleosides or sugar moieties. In certain such embodiments, the 2'-linked group is an abasic sugar moiety.

III. **Antisense Activity**

In certain embodiments, oligomeric compounds and oligomeric duplexes are capable of hybridizing to a target nucleic acid, resulting in at least one antisense activity; such oligomeric compounds and oligomeric duplexes are antisense agents. In certain embodiments, antisense agents have antisense activity when they reduce or inhibit the amount or activity of a target nucleic acid by 25% or more in the standard cell assay. In certain embodiments, antisense agents selectively affect one or more target nucleic acid. Such antisense agents comprise a nucleobase sequence that hybridizes to one or more target nucleic acid, resulting in one or more desired antisense activity and does not hybridize to one or more non-target nucleic acid or does not hybridize to one or more non-target nucleic acid in such a way that results in significant undesired antisense activity.

In certain antisense activities, hybridization of an antisense agents or a portion or an antisense agentto a target nucleic acid results in recruitment of a protein that cleaves the target nucleic acid. For example, certain antisense agents result in RNase H mediated cleavage of the target nucleic acid. RNase H is a cellular endonuclease that cleaves the RNA strand of an RNA:DNA duplex. The DNA in such an RNA:DNA duplex need not be unmodified DNA. In certain embodiments, described herein are antisense agents comprising antisense oligomeric compounds comprising antisense oligonucleotidesthat are sufficiently "DNA-like" to elicit RNase H activity. In certain embodiments, one or more non-DNA-like nucleoside in the gap of a gapmer is tolerated.

In certain antisense activities, an antisense agent or a portion of an antisense agent is loaded into an RNA-induced silencing complex (RISC), ultimately resulting in cleavage of the target nucleic acid. For example, certain antisense agents result in cleavage of the target nucleic acid by Argonaute. Antisense agents that are loaded into RISC are RNAi agents. RNAi agents may be double-stranded (siRNA or dsRNAi) or single-stranded (ssRNAi).

In certain embodiments, hybridization of an antisense agent or portion thereof to a target nucleic acid does not result in recruitment of a protein that cleaves that target nucleic acid. In certain embodiments, hybridization of the antisense agent or portion thereof to the target nucleic acid results in alteration of splicing of the target nucleic acid. In certain embodiments, hybridization of an antisense agent or a portion thereof to a target nucleic acid results in inhibition of a binding interaction between the target nucleic acid and a protein or other nucleic acid. In certain embodiments, hybridization of an antisense agent or a portion thereof to a target nucleic acid results in alteration of translation of the target nucleic acid.

Antisense activities may be observed directly or indirectly. In certain embodiments, observation or detection of an antisense activity involves observation or detection of a change in an amount of a target nucleic acid or protein encoded by such target nucleic acid, a change in the ratio of splice variants of a nucleic acid or protein and/or a phenotypic change in a cell or animal.

IV. **Certain Target Nucleic Acids**

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid. In certain embodiments, the target nucleic acid is an endogenous RNA molecule. In certain embodiments, the target nucleic acid encodes a protein. In certain such embodiments, the target nucleic acid is selected from: a mature mRNA and a pre-mRNA, including intronic, exonic and untranslated regions. In certain embodiments, the target RNA is a mature mRNA. In certain embodiments, the target nucleic acid is a pre-mRNA. In certain embodiments, the target region is entirely within an intron. In certain embodiments, the target region spans an intron/exon junction. In certain embodiments, the target region is at least 50% within an intron.

A. **Complementarity/Mismatches to the Target Nucleic Acid and Duplex Complementarity**

In certain embodiments, oligonucleotides are complementary to the target nucleic acid over the entire length of the oligonucleotide. In certain embodiments, oligonucleotides are 99%, 95%, 90%, 85%, or 80% complementary to the target nucleic acid. In certain embodiments, oligonucleotides are at least 80% complementary to the target nucleic acid over the entire length of the oligonucleotide and comprise a region that is 100% or fully complementary to a target nucleic acid. In certain embodiments, the region of full complementarity is from 6 to 20, 10 to 18, or 18 to 20 nucleobases in length.

It is possible to introduce mismatch bases without eliminating activity. For example, Gautschi et al (J. Natl. Cancer Inst. 93:463-471, March 2001) demonstrated the ability of an oligonucleotide having 100% complementarity to the bcl-2 mRNA and having 3 mismatches to the bcl-xL mRNA to reduce the expression of both bcl-2 and bcl-xL in vitro and in vivo. Furthermore, this oligonucleotide demonstrated potent anti-tumor activity in vivo. Maher and Dolnick (Nuc. Acid. Res. 16:3341-3358, 1988) tested a series of tandem 14 nucleobase oligonucleotides, and 28 and 42 nucleobase oligonucleotides comprised of the sequence of two or three of the tandem oligonucleotides, respectively, for their ability to arrest translation of human DHFR in a rabbit reticulocyte assay. Each of the three 14 nucleobase oligonucleotides alone was able to inhibit translation, albeit at a more modest level than the 28 or 42 nucleobase oligonucleotides.

In certain embodiments, oligonucleotides comprise one or more mismatched nucleobases relative to the target nucleic acid. In certain embodiments, antisense activity against the target is reduced by such mismatch, but activity against a non-target is reduced by a greater amount. Thus, in certain embodiments selectivity of the oligonucleotide is improved. In certain embodiments, the mismatch is specifically positioned within an oligonucleotide having a gapmer motif. In certain embodiments, the mismatch is at position 1, 2, 3, 4, 5, 6, 7, or 8 from the 5'-end of the gap region. In certain embodiments, the mismatch is at position 9, 8, 7, 6, 5, 4, 3, 2, 1 from the 3'-end of the gap region. In certain embodiments, the mismatch is at position 1, 2, 3, or 4 from the 5'-end of the wing region. In certain embodiments, the mismatch is at position 4, 3, 2, or 1 from the 3'-end of the wing region.

B. **PCDH19**

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide that is complementary to a target nucleic acid, wherein the target nucleic acid is a PCDH19 nucleic acid. In certain embodiments, the PCDH19 nucleic acid has the nucleobase sequence set forth in SEQ ID NO: 1 (ENSEMBL Accession No. ENSG00000165194.15 from version 104: May 2021), to SEQ ID NO: 2 (the cDNA of ENSEMBL Accession No. ENST00000373034.8 from version 104: May2021), or to both. In certain embodiments, contacting a cell with an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 reduces the amount of PCDH19 RNA, and in certain embodiments reduces the amount of PCDH19 protein. In certain embodiments, contacting a cell with an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 reduces the amount of PCDH19 RNA in a cell, and in certain embodiments reduces the amount of PCDH19 protein in a cell. In certain embodiments, the cell is *in vitro*. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide. . In certain embodiments, the oligomeric compound consists of a modified oligonucleotide and a conjugate group. In certain embodiments, the oligomeric compound is paired with an additional oligomeric compound in an oligomeric duplex. In certain embodiments, the oligomeric duplex comprises a conjugate group.

In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 is capable of reducing the detectable amount of PCDH19 RNA *in vitro* by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% in the standard cell assay. In certain

embodiments, an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 is capable of reducing the detectable amount of PCDH19 protein *in vitro* by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 is capable of reducing the detectable amount of PCDH19 RNA *in vivo* by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 is capable of reducing the detectable amount of PCDH19 protein *in vivo* by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2, is capable of reducing the detectable amount of PCDH19 RNA in the CSF of an animal by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2, is capable of reducing the detectable amount of PCDH19 protein in the CSF of an animal by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%.

In certain embodiments, contacting a cell in an animal with the oligomeric compound ameliorates one or more symptom or hallmark of a neurodevelopmental disease or disorder. In certain embodiments, the neurodevelopmental disease or disorder is PCDH19 Epilepsy. In certain embodiments, the symptom or hallmark is any of seizures, cognitive impairment, intellectual disabilities, autism spectrum disorder, behavioral problems, aggression, anxiety, obsessive-compulsive disorder, hyperactivity, attention deficit disorder (ADD), and attention deficit hyperactivity disorder (ADHD). In certain embodiments, the seizures are any of clusters of seizures, generalized tonic-clonic seizures, or focal seizures, which may evolve to bilateral, tonic-clonic seizures.

C. Certain Target Nucleic Acids in Certain Tissues

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid, wherein the target nucleic acid is expressed in a pharmacologically relevant tissue. In certain embodiments, the pharmacologically relevant tissues are the cells and tissues that comprise the central nervous system. Such tissues include the brain and spinal cord.

IV. Certain Methods and Uses

Certain embodiments provided herein relate to methods of reducing or inhibiting PCDH19 expression or activity, which can be useful for treating, preventing, or ameliorating a disease associated with PCDH19. In certain embodiments, the disease associated with PCDH19 is a neurodevelopmental disease. In certain embodiments, the disease associated with PCDH19 is PCDH19 Epilepsy.

In certain embodiments, a method comprises administering to a subject an oligomeric compound, a modified oligonucleotide, an oligomeric duplex, or an antisense agent, any of which having a nucleobase sequence complementary to a PCDH19 nucleic acid. In certain embodiments, the subject has a neurodevelopmental disease. In certain embodiments, the subject has PCDH19 Epilepsy.

In certain embodiments, a method of treating a disease associated with PCDH19 comprises administering to a subject an oligomeric compound, a modified oligonucleotide, an oligomeric duplex, or an antisense agent, any of which having a nucleobase sequence complementary to a PCDH19 nucleic acid. In certain embodiments, the subject has or is a risk of developing a disease associated with PCDH19. In certain embodiments, the subject has a neurodevelopmental disease. In certain embodiments, the subject has PCDH19 Epilepsy. In certain embodiments, at

least one symptom or hallmark of the disease associated with PCDH19 is ameliorated. In certain embodiments, the at least one symptom or hallmark is seizures, cognitive impairment, intellectual disabilities, autism spectrum disorder, behavioral problems, aggression, anxiety, obsessive-compulsive disorder, hyperactivity, attention deficit disorder (ADD), or attention deficit hyperactivity disorder (ADHD). In certain embodiments, the seizures are any of clusters of seizures, generalized tonic-clonic seiaures, focal seizures, or bilateral seizures. In certain embodiments, administration of the oligomeric compound, the modified oligonucleotide, the oligomeric duplex, or the antisense agent to the subject reduces or delays the onset or progression of seizures, cognitive impairment, intellectual disabilities, autism spectrum disorder, behavioral problems, aggression, anxiety, obsessive-compulsive disorder, hyperactivity, attention deficit disorder (ADD), or attention deficit hyperactivity disorder (ADHD) in the subject.

In certain embodiments, a method of reducing expression of PCDH19 nucleic acid, for example RNA, or reducing expression of PCDH19 protein in a cell comprises contacting the cell with an oligomeric compound, a modified oligonucleotide, an oligomeric duplex, or an antisense agent, any of which having a nucleobase sequence complementary to a PCDH19 nucleic acid. In certain embodiments, the subject has or is a risk of developing a disease associated with PCDH19. In certain embodiments, the subject has a neurodevelopmental disease. In certain embodiments, the subject has PCDH19 Epilepsy. In certain embodiments, the cell is a neuron. In certain embodiments, the cell is a human cell.

Certain embodiments are drawn to an oligomeric compound, a modified oligonucleotide, an oligomeric duplex, or an antisense agent, any of which having a nucleobase sequence complementary to a PCDH19 nucleic acid, for use in treating a disease associated with PCDH19 or for use in the manufacture of a medicament for treating a disease associated with PCDH19. In certain embodiments, the disease associated with PCDH19 is a neurodevelopmental disease. In certain embodiments, the disease associated with PCDH19 is PCDH19 Epilepsy.

In any of the methods or uses described herein, the oligomeric compound, the modified oligonucleotide, the oligomeric duplex, or the antisense agent can be any described herein.

V. Certain Pharmaceutical Compositions

In certain embodiments, described herein are pharmaceutical compositions comprising one or more oligomeric compounds. In certain embodiments, the one or more oligomeric compounds each consists of a modified oligonucleotide. In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable diluent or carrier. In certain embodiments, a pharmaceutical composition comprises or consists of a sterile saline solution and one or more oligomeric compound. In certain embodiments, the sterile saline is pharmaceutical grade saline. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and sterile water. In certain embodiments, the sterile water is pharmaceutical grade water. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and phosphate-buffered saline (PBS). In certain embodiments, the sterile PBS is pharmaceutical grade PBS. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and artificial cerebrospinal fluid (“artificial CSF” or “aCSF”). In certain embodiments, the artificial cerebrospinal fluid is pharmaceutical grade.

In certain embodiments, a pharmaceutical composition comprises a modified oligonucleotide and artificial cerebrospinal fluid (aCSF). In certain embodiments, a pharmaceutical composition consists of a modified oligonucleotide and artificial cerebrospinal fluid. In certain embodiments, a pharmaceutical composition consists essentially of a modified oligonucleotide and artificial cerebrospinal fluid. In certain embodiments, the artificial cerebrospinal fluid is pharmaceutical grade.

In certain embodiments, aCSF comprises sodium chloride, potassium chloride, sodium dihydrogen phosphate dihydrate, sodium phosphate dibasic anhydrous, calcium chloride dihydrate, and magnesium chloride hexahydrate. In certain embodiments, the pH of an aCSF solution is modulated with a suitable pH-adjusting agent, for example, with acids such as hydrochloric acid and alkalis such as sodium hydroxide, to a range of from about 7.1-7.3, or to about 7.2.

In certain embodiments, pharmaceutical compositions comprise one or more oligomeric compound and one or more excipients. In certain embodiments, excipients are selected from water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose and polyvinylpyrrolidone.

In certain embodiments, oligomeric compounds may be admixed with pharmaceutically acceptable active and/or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions depend on a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

In certain embodiments, pharmaceutical compositions comprising an oligomeric compound encompass any pharmaceutically acceptable salts of the oligomeric compound, esters of the oligomeric compound, or salts of such esters. In certain embodiments, pharmaceutical compositions comprising oligomeric compounds comprising one or more oligonucleotide, upon administration to an animal, including a human, are capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of oligomeric compounds, prodrugs, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. In certain embodiments, pharmaceutically acceptable salts comprise inorganic salts, such as monovalent or divalent inorganic salts. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and, potassium, calcium, and magnesium salts. In certain embodiments, prodrugs comprise one or more conjugate group attached to an oligonucleotide, wherein the conjugate group is cleaved by endogenous nucleases within the body.

In certain embodiments, oligomeric compounds are lyophilized and isolated as sodium salts. In certain embodiments, the sodium salt of an oligomeric compound is mixed with a pharmaceutically acceptable diluent. In certain embodiments, the pharmaceutically acceptable diluent comprises sterile saline, sterile water, PBS, or aCSF. In certain embodiments, the sodium salt of an oligomeric compound is mixed with PBS. In certain embodiments, the sodium salt of an oligomeric compound is mixed with aCSF.

Lipid moieties have been used in nucleic acid therapies in a variety of methods. In certain such methods, the nucleic acid, such as an oligomeric compound, is introduced into preformed liposomes or lipoplexes made of mixtures of cationic lipids and neutral lipids. In certain methods, DNA complexes with mono- or poly-cationic lipids are formed without the presence of a neutral lipid. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to a particular cell or tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to fat tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to muscle tissue.

In certain embodiments, pharmaceutical compositions comprise a delivery system. Examples of delivery systems include, but are not limited to, liposomes and emulsions. Certain delivery systems are useful for preparing certain pharmaceutical compositions including those comprising hydrophobic compounds. In certain embodiments, certain organic solvents such as dimethylsulfoxide are used.

In certain embodiments, pharmaceutical compositions comprise one or more tissue-specific delivery molecules designed to deliver the one or more pharmaceutical agents comprising an oligomeric compound provided

herein to specific tissues or cell types. For example, in certain embodiments, pharmaceutical compositions include liposomes coated with a tissue-specific antibody.

In certain embodiments, pharmaceutical compositions comprise a co-solvent system. Certain of such co-solvent systems comprise, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. In certain embodiments, such co-solvent systems are used for hydrophobic compounds. A non-limiting example of such a co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™ and 65% w/v polyethylene glycol 300. The proportions of such co-solvent systems may be varied considerably without significantly altering their solubility and toxicity characteristics. Furthermore, the identity of co-solvent components may be varied: for example, other surfactants may be used instead of Polysorbate 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

In certain embodiments, pharmaceutical compositions are prepared for oral administration. In certain embodiments, pharmaceutical compositions are prepared for buccal administration. In certain embodiments, a pharmaceutical composition is prepared for administration by injection (e.g., intravenous, subcutaneous, intramuscular, intrathecal (IT), intracerebroventricular (ICV), intraneural, perineural, etc.). In certain of such embodiments, a pharmaceutical composition comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (e.g., ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical compositions for injection are presented in unit dosage form, e.g., in ampoules or in multi-dose containers. Certain pharmaceutical compositions for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in pharmaceutical compositions for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes.

Under certain conditions, certain compounds disclosed herein act as acids. Although such compounds may be drawn or described in protonated (free acid) form, or ionized and in association with a cation (salt) form, aqueous solutions of such compounds exist in equilibrium among such forms. For example, a phosphate linkage of an oligonucleotide in aqueous solution exists in equilibrium among free acid, anion and salt forms. Unless otherwise indicated, compounds described herein are intended to include all such forms. Moreover, certain oligonucleotides have several such linkages, each of which is in equilibrium. Thus, oligonucleotides in solution exist in an ensemble of forms at multiple positions all at equilibrium. The term "oligonucleotide" is intended to include all such forms. Drawn structures necessarily depict a single form. Nevertheless, unless otherwise indicated, such drawings are likewise intended to include corresponding forms. Herein, a structure depicting the free acid of a compound followed by the term "or salt thereof" or "or a pharmaceutically acceptable salt thereof" expressly includes all such forms that may be fully or partially protonated/de-protonated/in association with a cation or a combination of cations. In certain embodiments, one or more specific cation is identified. The cations include, but are not limited to, sodium, potassium, calcium, and magnesium. In certain embodiments, a structure depicting the free acid of a compound followed by the term "or a pharmaceutically acceptable salt thereof" expressly includes all such forms that may be fully or partially protonated/de-protonated/in association with one or more cations selected from sodium, potassium, calcium, and magnesium.

In certain embodiments, modified oligonucleotides or oligomeric compounds are in aqueous solution with sodium. In certain embodiments, modified oligonucleotides or oligomeric compounds are in aqueous solution with potassium. In certain embodiments, modified oligonucleotides or oligomeric compounds are in PBS. In certain embodiments, modified oligonucleotides or oligomeric compounds are in water. In certain such embodiments, the pH of the solution is adjusted with NaOH and/or HCl to achieve a desired pH.

Herein, certain specific doses are described. A dose may be in the form of a dosage unit. For clarity, a dose (or dosage unit) of a modified oligonucleotide or an oligomeric compound in milligrams indicates the mass of the free acid form of the modified oligonucleotide or oligomeric compound. As described above, in aqueous solution, the free acid is in equilibrium with anionic and salt forms. However, for the purpose of calculating dose, it is assumed that the modified oligonucleotide or oligomeric compound exists as a solvent-free, sodium-acetate free, anhydrous, free acid.

In certain embodiments, where a modified oligonucleotide or an oligomeric compound is in solution comprising sodium (e.g., saline), the modified oligonucleotide or oligomeric compound may be partially or fully de-protonated and in association with sodium ions. However, the mass of the protons is nevertheless counted toward the weight of the dose, and the mass of the sodium ions is not counted toward the weight of the dose. Thus, for example, a dose, or dosage unit, of 10 mg of a number of fully protonated molecules that weighs 10 mg. This would be equivalent to 10.59 mg of solvent-free, sodium acetate-free, anhydrous sodiated Compound No. 1549516.

In certain embodiments, where a modified oligonucleotide or oligomeric compound is in a solution, such as aCSF, comprising sodium, potassium, calcium, and magnesium, the modified oligonucleotide or oligomeric compound may be partially or fully de-protonated and in association with sodium, potassium, calcium, and/or magnesium. However, the mass of the protons is nevertheless counted toward the weight of the dose, and the mass of the sodium, potassium, calcium, and magnesium ions is not counted toward the weight of the dose.

In certain embodiments, when an oligomeric compound comprises a conjugate group, the mass of the conjugate group may be included in calculating the dose of such oligomeric compound. If the conjugate group also has an acid, the conjugate group is likewise assumed to be fully protonated for the purpose of calculating dose.

VI. Certain Hotspot Regions

In certain embodiments, nucleobases in the ranges specified below comprise a hotspot region of a PCDH19 nucleic acid. In certain embodiments, modified oligonucleotides that are complementary to a hotspot region of PCDH19 nucleic acid achieve an average of more than 50% reduction of PCDH19 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides that are complementary to a hotspot region of PCDH19 nucleic acid achieve an average of 50% or greater reduction of PCDH19 RNA *in vivo* in the standard *in vivo* assay.

1. Nucleobases 4743-4767 of SEQ ID NO: 1

In certain embodiments, nucleobases 4743-4767 of SEQ ID NO: 1 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 4743-4767 of SEQ ID NO: 1. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages.

The nucleobase sequences of SEQ ID NOs: 132, 228, 284, 330, and 440 are complementary to nucleobases 4743-4767 of SEQ ID NO: 1.

The nucleobase sequences of Compound Nos: 1549744, 1549855, 1549749, 1549523, and 1549712 are complementary to nucleobases 4743-4767 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 4743-4767 of SEQ ID NO: 1 achieve at least 81% reduction of PCDH19 mRNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 4743-4767 of SEQ ID NO: 1 achieve an average of 86% reduction of PCDH19 mRNA in the standard *in vitro* assay.

2. Nucleobases 12,319-12,346 of SEQ ID NO: 1

In certain embodiments, nucleobases 12,319-12,346 of SEQ ID NO: 1 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 12,319-12,346 of SEQ ID NO: 1. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages.

The nucleobase sequences of SEQ ID NOs: 416, 72, 129, and 204 are complementary to nucleobases 12,319-12,346 of SEQ ID NO: 1.

The nucleobase sequences of Compound Nos: 1549581, 1549876, 1549736, and 1549694 are complementary to nucleobases 12,319-12,346 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 12,319-12,346 of SEQ ID NO: 1 achieve at least 65% reduction of PCDH19 mRNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 12,319-12,346 of SEQ ID NO: 1 achieve an average of 69% reduction of PCDH19 mRNA in the standard *in vitro* assay.

3. Nucleobases 34364-34389 of SEQ ID NO: 1

In certain embodiments, nucleobases 34364-34389 of SEQ ID NO: 1 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 34364-34389 of SEQ ID NO: 1. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages.

The nucleobase sequences of SEQ ID NOs: 371, 425, 20, and 111 are complementary to nucleobases 34364-34389 of SEQ ID NO: 1.

The nucleobase sequences of Compound Nos: 1549753, 1549642, 1549562, and 1549613 are complementary to nucleobases 34364-34389 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 34364-34389 of SEQ ID NO: 1 achieve at least 64% reduction of 34389 of SEQ ID NO: 1 achieve an average of 80% reduction of PCDH19. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 34364-34389 of SEQ ID NO: 1 achieve an average of 80% reduction of PCDH19 mRNA in the standard *in vitro* assay.

4. Nucleobases 84,408-84,431 of SEQ ID NO: 1

In certain embodiments, nucleobases 84,408-84,431 of SEQ ID NO: 1 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 84,408-84,431 of SEQ ID NO: 1. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages.

The nucleobase sequences of SEQ ID NOs: 367, 407, 24, 93, and 218 are complementary to nucleobases 84,408-84,431 of SEQ ID NO: 1.

The nucleobase sequences of Compound Nos: 1549714, 1549528, 1549617, 1549514, and 1549790 are complementary to nucleobases 84,408-84,431 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 84,408-84,431 of SEQ ID NO: 1 achieve at least 65% reduction of PCDH19 mRNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 84,408-84,431 of SEQ ID NO: 1 achieve an average of 74% reduction of PCDH19 mRNA in the standard *in vitro* assay.

Nonlimiting disclosure and incorporation by reference

Each of the literature and patent publications listed herein is incorporated by reference in its entirety.

While certain compounds, compositions and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same. Each of the references, GenBank accession numbers, and the like recited in the present application is incorporated herein by reference in its entirety.

Although the sequence listing accompanying this filing identifies each sequence as either "RNA" or "DNA" as required, in reality, those sequences may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that such designation as "RNA" or "DNA" to describe modified oligonucleotides is, in certain instances, arbitrary. For example, an oligonucleotide comprising a nucleoside comprising a 2'-OH sugar moiety and a thymine base could be described as a DNA having a modified sugar moiety (2'-OH in place of one 2'-H of DNA) or as an RNA having a modified base (thymine (methylated uracil) in place of a uracil of RNA). Accordingly, nucleic acid sequences provided herein, including, but not limited to those in the sequence listing, are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, unless otherwise stated, including, but not limited to such nucleic acids having modified nucleobases. By way of further example and without limitation, an oligomeric compound having the nucleobase sequence "ATCGATCG" encompasses any oligomeric compounds having such nucleobase sequence, whether modified or unmodified, including, but not limited to, such compounds comprising RNA bases, such as those having sequence "AUCGAUCG" and those having some DNA bases and some RNA bases such as "AUCGATCG" and oligomeric compounds having other modified nucleobases, such as "AT^{m}CGAUCG," wherein ^{m}C indicates a cytosine base comprising a methyl group at the 5-position. Finally, for clarity, unless otherwise indicated, the phrase "nucleobase sequence of SEQ ID NO: X", refers only to the sequence of nucleobases in that SEQ ID NO: X, independent of any sugar or internucleoside linkage modifications also described in such SEQ ID.

While effort has been made to accurately describe compounds in the accompanying sequence listing, should there be any discrepancies between a description in this specification and in the accompanying sequence listing, the description in the specification and not in the sequence listing is the accurate description.

Certain compounds described herein (e.g., modified oligonucleotides) have one or more asymmetric center and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of absolute stereochemistry, as (*R*) or (*S*), as α or β such as for sugar anomers, or as (D) or (L), such as for amino acids, etc. Compounds provided herein that are drawn or described as having certain stereoisomeric configurations include only the indicated compounds. Compounds provided herein that are drawn or described with undefined stereochemistry include all such possible isomers, including their stereorandom and optically pure forms, unless specified otherwise. Likewise, all cis- and trans-isomers and tautomeric forms of the compounds herein are also included unless otherwise indicated. Oligomeric compounds described herein include chirally pure or enriched mixtures as well as racemic mixtures. For example, oligomeric compounds having a plurality of phosphorothioate internucleoside linkages include such compounds in which chirality of the phosphorothioate internucleoside linkages is controlled or is random. Unless otherwise indicated, compounds described herein are intended to include corresponding salt forms.

The compounds described herein include variations in which one or more atoms are replaced with a non-radioactive isotope or radioactive isotope of the indicated element. For example, compounds herein that comprise hydrogen atoms encompass all possible deuterium substitutions for each of the ^{1}H hydrogen atoms. Isotopic substitutions encompassed by the compounds herein include but are not limited to: ^{2}H or ^{3}H in place of ^{1}H, ^{13}C or ^{14}C in place of ^{12}C, ^{15}N in place of ^{14}N, ^{17}O or ^{18}O in place of ^{16}O, and ^{33}S, ^{34}S, ^{35}S, or ^{36}S in place of ^{32}S. In certain embodiments, non-radioactive isotopic substitutions may impart new properties on the oligomeric compound that are beneficial for use as a therapeutic or research tool. In certain embodiments, radioactive isotopic substitutions may make the compound suitable for research or diagnostic purposes such as imaging.

EXAMPLES

The following examples illustrate certain embodiments of the present disclosure and are not limiting. Moreover, where specific embodiments are provided, the inventors have contemplated generic application of those specific embodiments.

Example 1: Effect of 5-10-5 MOE modified oligonucleotides with mixed PS/PO internucleoside linkages complementary to a human PCDH19 RNA *in vitro*, single dose

Modified oligonucleotides complementary to human PCDH19 nucleic acid were designed and tested for their single dose effects on PCDH19 RNA *in vitro*. The modified oligonucleotides were tested in a series of experiments that had the same culture conditions.

The modified oligonucleotides in the table below are 5-10-5 MOE modified oligonucleotides with mixed PS/PO internucleoside linkages. The modified oligonucleotides are 20 nucleosides in length. The sugar motif for the modified oligonucleotides is (from 5' to 3'): eeeeeddddddddddeeeee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, and each "e" represents a 2'-MOE ribosyl sugar moiety. The internucleoside linkage motif for the modified oligonucleotides is (from 5' to 3'): soooosssssssssssooss; wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methylcytosine.

"Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the table below is

100% complementary to SEQ ID NO: 1 (ENSEMBL Accession No. ENSG00000165194.15 from version 104: May 2021), to SEQ ID NO: 2 (the cDNA of ENSEMBL Accession No. ENST00000373034.8 from version 104: May2021), or to both. "N/A" indicates that the modified oligonucleotide is not 100% complementary to that particular target nucleic acid sequence.

SHSY5Y cells, plated at a density of 15,000 cells/well, were differentiated in Neurobasal media supplemented with B27 (ThermoFisher), penicillin/streptomycin (ThermoFisher), and 10μM retinoic acid (Sigma) for 10 days. Differentiated SH-SY5Y cells were treated with modified oligonucleotide at a concentration of 15,000 nM by free uptake. After a treatment period of approximately 5 days, total RNA was isolated from the cells and PCDH19 RNA levels were measured by quantitative real-time RT-PCR using human primer-probe set RTS53390 (forward sequence GCTAACCACATCTACCATCACTC, designated herein as SEQ ID NO: 3; reverse sequence GCTATTCACGTAGTTGGAGTCA, designated herein as SEQ ID NO: 4; probe sequence TTTCAGTCTCAGGCAGAGGCACAC, designated herein as SEQ ID NO: 5). PCDH19 RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of PCDH19 RNA is presented in the table below as percent PCDH19 RNA relative to the amount in untreated control cells (% UTC).

Each separate experiment described in this example is identified by an Assay Identification letter in the table column labeled "AID".

Table 1

Reduction of PCDH19 RNA by 5-10-5 MOE modified oligonucleotides with mixed PS/PO internucleoside linkages at a concentration of 15,000 nM in differentiated SH-SY5Y cells

Compound No.	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	PCDH19 (% UTC)	AID	SEQ ID NO
1549516	21259	21278	N/A	N/A	GCTTCTTTATTAATTACCCA	36	A	15
1549535	117328	117347	8454	8473	ACTGCTATTATGTACAATAA	74	A	16
1549542	60204	60223	N/A	N/A	TTCTTTTTCTCTCTCATCTA	17	A	17
1549557	52717	52736	N/A	N/A	CCCACTATTTTCATCACATC	27	A	18
1549558	41754	41773	N/A	N/A	GCTTGTTTTCTTCCTCTCCT	3	A	19
1549562	34367	34386	N/A	N/A	GCTGTCACTTTTCCATACTA	8	A	20
1549589	25522	25541	N/A	N/A	ACATCATTTTTCATGTGGTC	9	A	21
1549605	72604	72623	N/A	N/A	ATTCTCTCTCATTTCCACCC	9	A	22
1549612	18035	18054	N/A	N/A	GTTAGCTTTCTTTCCATTTC	27	A	23
1549617	84410	84429	N/A	N/A	TTGTTTTTTTCATATCCCTA	13	A	24
1549620	6722	6741	3936	3955	CTTAGGCTCACTTTCTCCTC	80	A	25
1549626	68244	68263	4397	4416	GGTCACTCTCCTCATGTCCA	10	A	26
1549632	59780	59799	N/A	N/A	GTTTATTTACTTTTTTATGC	52	A	27
1549640	80014	80033	N/A	N/A	CATCATTCCTCTTTTTCCTC	11	A	28
1549647	45631	45650	N/A	N/A	GCTTAGTTATATCTCACCCC	47	A	29
1549651	114228	114247	5354	5373	TCTCTGTTTCCCCAACATCA	11	A	30
1549652	11035	11054	N/A	N/A	GCACTTATCATTCTATGCTA	22	A	31
1549659	54750	54769	N/A	N/A	TTTGATGCTTTTACTCTACT	13	A	32
1549660	114366	114385	5492	5511	CCAGAGCTTTTTTTTTTCAC	27	A	33
1549665	29518	29537	N/A	N/A	GCCTGCTTTCTGCTTCAATC	52	A	34
1549672	19426	19445	N/A	N/A	GCTCTTTTCTGATAACCTAT	34	A	35

1549682	4951	4970	N/A	N/A	GCATCATTCATTTTCAGCAA	29	A	36
1549684	64160	64179	N/A	N/A	CCATGTTTCTATTACTGCTC	66	A	37
1549688	82577	82596	N/A	N/A	ATTTTTATCTTATTTCATTC	114	A	38
1549704	6274	6293	N/A	N/A	ACTGTGCCTTATTCTCACTC	11	A	39
1549705	30259	30278	N/A	N/A	GCTGCTTCTTTCTTTACTTT	18	A	40
1549708	82507	82526	N/A	N/A	TTCTGATTTTGATCCTCACT	62	A	41
1549720	39476	39495	N/A	N/A	TGCATTTTTTCCTATAATCT	38	A	42
1549724	95382	95401	N/A	N/A	CATCTTGTCTCCATTCCATA	31	A	43
1549725	93272	93291	N/A	N/A	CTTTGTTTCCTACTGCCATA	13	A	44
1549727	115538	115557	6664	6683	TGACATATTTCTTTAGTTTA	35	A	45
1549728	23346	23365	N/A	N/A	TCATAGTCTCCATTTATCCA	34	A	46
1549733	118288	118307	9414	9433	GCATCCCTCTAAATTTCCAC	14	A	47
1549735	98283	98302	N/A	N/A	AGCAGTTTTAATCCTTCCTC	59	A	48
1549740	33164	33183	N/A	N/A	ATGTTTATTTCTCTATGCCT	48	A	49
1549743	76485	76504	N/A	N/A	GTTTGTTTTTTTCCTCTTCA	12	A	50
1549750	95898	95917	N/A	N/A	GCTTGCCTTTTTTTCTTCCC	31	A	51
1549755	12335	12354	N/A	N/A	CCTACTATCTTTCTTCTCCA	11	A	52
1549764	55287	55306	N/A	N/A	CTTTTTTATTTCATCTCAGT	71	A	53
1549775	111784	111803	N/A	N/A	ATGGACACTTTCATCCCCCT	32	A	54
1549781	412	431	412	431	CTTGATTTCATCTTCCCGGA	20	A	55
1549782	64802	64821	N/A	N/A	CTGCTTTGTCTTCACTTCTC	48	A	56
1549814	12310	12329	N/A	N/A	CTTCTTTTTCAACCTCCTTT	103	A	57
1549821	43462	43481	N/A	N/A	ACTTTATTAGTCTACTTCTT	97	A	58
1549824	25784	25803	N/A	N/A	CCTATTTATTCTTCCATACA	88	A	59
1549834	78893	78912	N/A	N/A	GAGTCTGTTTTATCTATCCA	20	A	60
1549838	15892	15911	N/A	N/A	GTGATTTTTCTCCCTCCCCA	54	A	61
1549839	70900	70919	N/A	N/A	TCTATTTTCCCTTCTCACCT	86	A	62
1549841	4534	4553	N/A	N/A	GCTATTTTTACTGAAACATC	7	A	63
1549843	114008	114027	5134	5153	GGTTTCTTTCTCTTCTTCCT	33	A	64
1549851	43971	43990	N/A	N/A	TTCTCATTTTTACTGCCTCA	38	A	65
1549852	25734	25753	N/A	N/A	ATATTCTCTTTTTCCCTCCC	17	A	66
1549860	7476	7495	4018	4037	GCGGATGTCATTCTTACTGA	36	A	67
1549862	118347	118366	9473	9492	AACAATTTTATCTTCATATA	107	A	68
1549864	115868	115887	6994	7013	GTTCTTTTTCAGAAATGTTC	55	A	69
1549868	115178	115197	6304	6323	ACTGCTTACTCTATCCCTAC	68	A	70
1549873	52791	52810	N/A	N/A	CCTTGTGTCATTTTTTTCTC	26	A	71
1549876	12320	12339	N/A	N/A	CTCCATTTTCCTTCTTTTTC	30	A	72
1549880	17979	17998	N/A	N/A	CTTCTTTTTCTATTTCTAAA	120	A	73
1549884	38627	38646	N/A	N/A	TGCCTTATTTTTCTCCATAT	62	A	74
1549887	10648	10667	N/A	N/A	GTGTCATTTTCCCTACGCAG	1	A	75
1549895	25884	25903	N/A	N/A	ACTCATTTTCCATCTATGAA	32	A	76
1549896	49308	49327	N/A	N/A	GCTTCTCATTTTATTTGGGA	33	A	77
1549908	20421	20440	N/A	N/A	GCTGGTATTTTTCTTTGTGC	64	A	78
1549910	13019	13038	N/A	N/A	CTGATGTTTTATTTTCATTA	62	A	79
1549911	36819	36838	N/A	N/A	GCTTCAGTTTTTAACCTCTC	11	A	80
1549912	63480	63499	N/A	N/A	GTTCATTTCCTATTTCATTT	27	A	81

1549915	115316	115335	6442	6461	GTTCACATTTTTAATCAAAA	6	A	82
1549918	107500	107519	N/A	N/A	TCTATATTTTCTGCTACCTT	88	A	83
1549923	47992	48011	N/A	N/A	GTACACCCTTTCCTCATCCT	65	A	84
1549930	117940	117959	9066	9085	GCATCATCAGTTTTCCCTAA	54	A	85
1549937	85958	85977	N/A	N/A	ACTTGTTTGATTTTCATCCT	11	A	86
1549944	73355	73374	N/A	N/A	CCAATCTCATATCAGGATTA	55	A	87
	75767	75786						
1549950	72467	72486	N/A	N/A	AAGAGGATCTTAAAAGCTAT	26	A	88
	75978	75997						
1549973	73148	73167	N/A	N/A	CTTGTCAATCACTCTTTTTA	14	A	89
	75560	75579						
1549980	73316	73335	N/A	N/A	TGGGATATCCACATCATCAA	4	A	90
	75728	75747						
1549990	73218	73237	N/A	N/A	AAATTCAAGCCCCATGATAC	152	A	91
	75630	75649						
1549991	73210	73229	N/A	N/A	GCCCCATGATACCCCTAATC	39	A	92
	75622	75641						
1549514	84411	84430	N/A	N/A	GTTGTTTTTTTCATATCCCT	32	B	93
1549520	17980	17999	N/A	N/A	ACTTCTTTTTCTATTTCTAA	10	B	94
1549526	59851	59870	N/A	N/A	CGTACATTTTCATACCAAGA	10	B	95
1549532	118348	118367	9474	9493	CAACAATTTTATCTTCATAT	59	B	96
1549538	114367	114386	5493	5512	TCCAGAGCTTTTTTTTTTCA	71	B	97
1549543	95396	95415	N/A	N/A	CCCACTCCTCTTCTCATCTT	165	B	98
1549546	46229	46248	N/A	N/A	CCATTTTCTTCCTTCATCAT	25	B	99
1549553	87014	87033	N/A	N/A	ACCAGCTATTTCCTTCCATC	53	B	100
1549569	78959	78978	N/A	N/A	GCTTTATATTCTCTCTACCT	62	B	101
1549577	31478	31497	N/A	N/A	CTGCACACTTCTTCACTCCC	21	B	102
1549582	82580	82599	N/A	N/A	GATATTTTTATCTTATTTCA	102	B	103
1549586	52767	52786	N/A	N/A	GCATTTGTTCTACCTCATTC	91	B	104
1549591	38630	38649	N/A	N/A	TTCTGCCTTATTTTTCTCCA	50	B	105
1549594	27059	27078	N/A	N/A	ACTCACATTGAATCCTCACA	51	B	106
1549601	13020	13039	N/A	N/A	ACTGATGTTTTATTTTCATT	75	B	107
1549604	12311	12330	N/A	N/A	CCTTCTTTTTCAACCTCCTT	43	B	108
1549610	114009	114028	5135	5154	TGGTTTCTTTCTCTTCTTCC	26	B	109
1549611	112143	112162	N/A	N/A	CTTCCTTGTATACTTGTATT	50	B	110
1549613	34370	34389	N/A	N/A	GTTGCTGTCACTTTTCCATA	5	B	111
1549618	60582	60601	N/A	N/A	GTTTCATTTCTATTATTTTA	58	B	112
1549629	39477	39496	N/A	N/A	ATGCATTTTTTCCTATAATC	30	B	113
1549631	18217	18236	N/A	N/A	GTACGGATTTTTCTCCACCT	135	B	114
1549643	25735	25754	N/A	N/A	TATATTCTCTTTTTCCCTCC	26	B	115
1549653	70901	70920	N/A	N/A	TTCTATTTTCCCTTCTCACC	17	B	116
1549654	21405	21424	N/A	N/A	ACTTTTGTTTTACACATTCC	12	B	117
1549655	76652	76671	N/A	N/A	GTGCTCCTTTTACATATCCT	29	B	118
1549664	43972	43991	N/A	N/A	TTTCTCATTTTTACTGCCTC	32	B	119
1549675	51765	51784	N/A	N/A	GCACTTTTCTTTGCTCTCAT	114	B	120
1549679	10719	10738	N/A	N/A	GCTCTTCTATAGATTTCATT	78	B	121

1549687	33294	33313	N/A	N/A	ACTTTTGGTTCCCTCTCTTT	142	B	122
1549691	5397	5416	N/A	N/A	CCCACATTTTTCTCCTATAA	18	B	123
1549700	7441	7460	3983	4002	TTGATTTCTTTTGATGCCCA	6	B	124
1549706	6393	6412	N/A	N/A	GTCATTTATTACTTTGCACA	23	B	125
1549721	15893	15912	N/A	N/A	AGTGATTTTTCTCCCTCCCC	112	B	126
1549723	11811	11830	N/A	N/A	GCTATCTTCCATTCAGCACT	84	B	127
1549730	64162	64181	N/A	N/A	GCCCATGTTTCTATTACTGC	13	B	128
1549736	12323	12342	N/A	N/A	CTTCTCCATTTTCCTTCTTT	35	B	129
1549737	25785	25804	N/A	N/A	TCCTATTTATTCTTCCATAC	12	B	130
1549742	68853	68872	N/A	N/A	GTTTGGTATTTTCTATCCTC	42	B	131
1549744	4743	4762	N/A	N/A	GTTTCTTCTTTTCTCCCTTT	12	B	132
1549754	63481	63500	N/A	N/A	TGTTCATTTCCTATTTCATT	89	B	133
1549758	12547	12566	N/A	N/A	TGCATTTTCTTCCTCCAATA	38	B	134
1549762	20492	20511	N/A	N/A	GCTTATTTTTTAATTTAGTT	76	B	135
1549763	80015	80034	N/A	N/A	ACATCATTCCTCTTTTTCCT	34	B	136
1549765	64905	64924	N/A	N/A	GTTAATTTCTTCTAACATTA	75	B	137
1549771	415	434	415	434	CGTCTTGATTTCATCTTCCC	42	B	138
1549772	20106	20125	N/A	N/A	ACTTATGCTTTCTCTATGTC	19	B	139
1549783	93274	93293	N/A	N/A	TTCTTTGTTTCCTACTGCCA	38	B	140
1549785	117943	117962	9069	9088	TCAGCATCATCAGTTTTCCC	53	B	141
1549799	118292	118311	9418	9437	ACTTGCATCCCTCTAAATTT	99	B	142
1549804	41756	41775	N/A	N/A	ATGCTTGTTTTCTTCCTCTC	6	B	143
1549810	29593	29612	N/A	N/A	TCTGATTCTTATTCCTCCCA	72	B	144
1549827	38616	38635	N/A	N/A	TCTCCATATCACTTATCTTC	84	B	145
1549828	107642	107661	N/A	N/A	GTCACCTTTTCATTTATCCA	121	B	146
1549833	43468	43487	N/A	N/A	GCACAGACTTTATTAGTCTA	21	B	147
1549840	7508	7527	4050	4069	TTGTCTGTCTCCTCCACATC	95	B	148
1549846	56043	56062	N/A	N/A	GTATATTTTTTCACACTTCT	77	B	149
1549853	115539	115558	6665	6684	GTGACATATTTCTTTAGTTT	39	B	150
1549867	25672	25691	N/A	N/A	TCTTCCTTTTATTTAGTTAA	70	B	151
1549871	106274	106293	N/A	N/A	TCCACATTTTTCATTCATCT	47	B	152
1549879	23738	23757	N/A	N/A	CTGCTTTATCACATTAACTT	51	B	153
1549882	96204	96223	N/A	N/A	GTTTATATTTTTAACACCCT	131	B	154
1549900	114229	114248	5355	5374	GTCTCTGTTTCCCCAACATC	66	B	155
1549901	117464	117483	8590	8609	ATGCCAGTTTTTCAAAGTCA	15	B	156
1549909	72607	72626	N/A	N/A	GTCATTCTCTCTCATTTCCA	92	B	157
1549913	54769	54788	N/A	N/A	GCTTTTCTTCCATTTCAAGT	93	B	158
1549924	115944	115963	7070	7089	GCCACACCAATATTTTGCAT	66	B	159
1549931	82561	82580	N/A	N/A	ATTCTCTCTTATCACCTCAT	28	B	160
1549932	115179	115198	6305	6324	TACTGCTTACTCTATCCCTA	27	B	161
1549934	48128	48147	N/A	N/A	ATGTGTCCTTTCCTTTCCCC	49	B	162
1549939	53228	53247	N/A	N/A	ATTCATTTATCTATCCAGTA	144	B	163
1549940	115317	115336	6443	6462	TGTTCACATTTTTAATCAAA	56	B	164
1549945	73219	73238	N/A	N/A	GAAATTCAAGCCCCATGATA	227	B	165
	75631	75650						
1549948	72468	72487	N/A	N/A	AAAGAGGATCTTAAAAGCTA	17	B	166

	75979	75998						
1549977	73317	73336	N/A	N/A	ATGGGATATCCACATCATCA	12	B	167
	75729	75748						
1549988	73211	73230	N/A	N/A	AGCCCCATGATACCCCTAAT	328	B	168
	75623	75642						
1550004	73149	73168	N/A	N/A	ACTTGTCAATCACTCTTTTT	107	B	169
	75561	75580						
1550006	73356	73375	N/A	N/A	CCCAATCTCATATCAGGATT	30	B	170
	75768	75787						
1549513	43411	43430	N/A	N/A	GCATTTCTTTTCTACCAGTA	6	C	171
1549525	48667	48686	N/A	N/A	TTGCCTTTTCTTTTTCTCAA	29	C	172
1549533	114010	114029	5136	5155	GTGGTTTCTTTCTCTTCTTC	50	C	173
1549537	46230	46249	N/A	N/A	CCCATTTTCTTCCTTCATCA	37	C	174
1549540	117980	117999	9106	9125	AGGTCATCTTGAATTGCCAA	66	C	175
1549541	118295	118314	9421	9440	TGTACTTGCATCCCTCTAAA	64	C	176
1549544	21079	21098	N/A	N/A	CATACTTCCTTATTTTTCTT	39	C	177
1549547	112166	112185	N/A	N/A	GCATCAGTCTATATATAACA	62	C	178
1549552	93360	93379	N/A	N/A	GCTACAATTTCAATAGATAT	71	C	179
1549556	52221	52240	N/A	N/A	GTTCACTGTTATCACTCCCA	46	C	180
1549559	38646	38665	N/A	N/A	ACTCATTATCTTCCTTTTCT	46	C	181
1549560	38617	38636	N/A	N/A	TTCTCCATATCACTTATCTT	97	C	182
1549564	12312	12331	N/A	N/A	TCCTTCTTTTTCAACCTCCT	26	C	183
1549584	20160	20179	N/A	N/A	CTTAACTTCTATCTTGTCTC	50	C	184
1549585	78961	78980	N/A	N/A	CTGCTTTATATTCTCTCTAC	96	C	185
1549587	87648	87667	N/A	N/A	GTATTGTTTTTTCTAATCCT	40	C	186
1549588	29869	29888	N/A	N/A	GCTCTTTTCTTTCATAGCAT	35	C	187
1549596	76868	76887	N/A	N/A	GCATAATTTTATCTAGCATA	18	C	188
1549609	6716	6735	3930	3949	CTCACTTTCTCCTCTGTCTT	49	C	189
1549614	36674	36693	N/A	N/A	GCCTATTTTCCTTTCTTCGA	36	C	190
1549635	107970	107989	N/A	N/A	GCATCTTTATTACTAGCGGT	52	C	191
1549636	33582	33601	N/A	N/A	CTTAGATTTTTTTCTTTATC	122	C	192
1549637	106275	106294	N/A	N/A	TTCCACATTTTTCATTCATC	90	C	193
1549639	96731	96750	N/A	N/A	AGTACTTTCTTATCCCCTTA	50	C	194
1549644	44572	44591	N/A	N/A	TCTATTATCTCTCTTGCACA	49	C	195
1549650	7446	7465	3988	4007	CTTGCTTGATTTCTTTTGAT	76	C	196
1549662	1369	1388	1369	1388	ACTCAGTTTTACCCCTTCAA	33	C	197
1549667	40586	40605	N/A	N/A	ACTTTTTGCCTCTCTCATAA	86	C	198
1549677	114230	114249	5356	5375	TGTCTCTGTTTCCCCAACAT	26	C	199
1549680	70902	70921	N/A	N/A	ATTCTATTTTCCCTTCTCAC	94	C	200
1549683	82980	82999	N/A	N/A	ATTTCTATCATTACTCCCAT	52	C	201
1549686	63487	63506	N/A	N/A	GTGCTTTGTTCATTTCCTAT	97	C	202
1549693	118350	118369	9476	9495	TACAACAATTTTATCTTCAT	86	C	203
1549694	12327	12346	N/A	N/A	CTTTCTTCTCCATTTTCCTT	32	C	204
1549696	13041	13060	N/A	N/A	GCTATTTTTTTTCAAAGCCT	80	C	205
1549716	32171	32190	N/A	N/A	TTGTTCATTTATACCACACA	32	C	206
1549719	115679	115698	6805	6824	CCTCTTTTGCATTCTAGTGC	54	C	207

1549729	82564	82583	N/A	N/A	TTCATTCTCTCTTATCACCT	39	C	208
1549734	53934	53953	N/A	N/A	CTTCTTTTTTTAACTGCTGA	39	C	209
1549738	72609	72628	N/A	N/A	CTGTCATTCTCTCTCATTTC	72	C	210
1549746	95645	95664	N/A	N/A	CCATCTGTTCTATCCGCTTT	69	C	211
1549747	64957	64976	N/A	N/A	ACACTTCTATATCTTCTGTA	53	C	212
1549766	25685	25704	N/A	N/A	GCTTTTTTTTGAATCTTCCT	17	C	213
1549773	43528	43547	N/A	N/A	CATCATTCTTATTTATTCAT	47	C	214
1549777	25786	25805	N/A	N/A	TTCCTATTTATTCTTCCATA	74	C	215
1549784	80720	80739	N/A	N/A	GCATCAGTTTTTCTTCTAAA	8	C	216
1549786	25736	25755	N/A	N/A	ATATATTCTCTTTTTCCCTC	79	C	217
1549790	84412	84431	N/A	N/A	AGTTGTTTTTTTCATATCCC	23	C	218
1549796	18277	18296	N/A	N/A	ACATTTATTTGATCCCATAT	81	C	219
1549803	15925	15944	N/A	N/A	ACTCTCATTCTCATTTTTTC	61	C	220
1549812	114463	114482	5589	5608	GCTCAATTTCACATCACTGA	74	C	221
1549819	5398	5417	N/A	N/A	CCCCACATTTTTCTCCTATA	20	C	222
1549820	17981	18000	N/A	N/A	CACTTCTTTTTCTATTTCTA	35	C	223
1549822	8230	8249	N/A	N/A	CTATCCATATTCTCTCACCA	54	C	224
1549829	115181	115200	6307	6326	TGTACTGCTTACTCTATCCC	67	C	225
1549831	21617	21636	N/A	N/A	GTGTATTGCCAAATTGCCCC	27	C	226
1549835	23741	23760	N/A	N/A	ACTCTGCTTTATCACATTAA	24	C	227
1549855	4745	4764	N/A	N/A	GTGTTTCTTCTTTTCTCCCT	13	C	228
1549856	28043	28062	N/A	N/A	GCTTTTGTTCTCCCCCTCCC	32	C	229
1549861	12548	12567	N/A	N/A	TTGCATTTTCTTCCTCCAAT	12	C	230
1549863	11921	11940	N/A	N/A	TGTTCCATTCCCTTTACCTT	19	C	231
1549870	54873	54892	N/A	N/A	CTGTGGTTTTTTTCTTGTCT	33	C	232
1549872	116325	116344	7451	7470	GTTCCCACTTTCCACAATCT	28	C	233
1549874	115319	115338	6445	6464	CTTGTTCACATTTTTAATCA	23	C	234
1549891	117478	117497	8604	8623	TCTTAAGCTCATTTATGCCA	50	C	235
1549916	69476	69495	N/A	N/A	GTACATTTTTTCCTTTGGAC	17	C	236
1549919	59998	60017	N/A	N/A	TATATTTCTAATATCACATT	145	C	237
1549922	52784	52803	N/A	N/A	TCATTTTTTTCTCACCTGCA	57	C	238
1549926	56190	56209	N/A	N/A	GCCTCATTAGTACTACATTC	75	C	239
1549935	64264	64283	N/A	N/A	CTTGCTTTATTACCTGCATA	120	C	240
1549938	10817	10836	N/A	N/A	CTTGTCTTTTTCATCTCTCT	2	C	241
1549943	60699	60718	N/A	N/A	TTTATTCCTTGAATTCTACT	81	C	242
1549946	73213	73232	N/A	N/A	CAAGCCCCATGATACCCCTA	58	C	243
	75625	75644						
1549951	72469	72488	N/A	N/A	AAAAGAGGATCTTAAAAGCT	102	C	244
	75980	75999						
1549965	73357	73376	N/A	N/A	CCCCAATCTCATATCAGGAT	31	C	245
	75769	75788						
1549985	73312	73331	N/A	N/A	ATATCCACATCATCAAAAAT	100	C	246
	75724	75743						
1550005	73318	73337	N/A	N/A	AATGGGATATCCACATCATC	25	C	247
	75730	75749						
1550010	73150	73169	N/A	N/A	TACTTGTCAATCACTCTTTT	61	C	248

	75562	75581						
1549515	46231	46250	N/A	N/A	ACCCATTTTCTTCCTTCATC	47	D	249
1549517	21747	21766	N/A	N/A	TCCGATGTTTTATCCTCATA	2	D	250
1549518	5510	5529	N/A	N/A	GCTGATTTCTTTTTCATCAA	7	D	251
1549527	69709	69728	N/A	N/A	ACTGTTTAATTTTTTTCATC	111	D	252
1549549	25687	25706	N/A	N/A	ACGCTTTTTTTTGAATCTTC	78	D	253
1549550	29895	29914	N/A	N/A	CCCATTTTACTCTTTCATAA	65	D	254
1549551	59718	59737	N/A	N/A	ATTCATTTTAAAATCCCCCA	98	D	255
1549563	93856	93875	N/A	N/A	CTTGACATTCATATCCAGTA	71	D	256
1549575	118146	118165	9272	9291	GCTGATTTCTAGCTCGAGCT	83	D	257
1549576	77602	77621	N/A	N/A	GTTTAGATTTATCATTTCCC	43	D	258
1549578	52552	52571	N/A	N/A	CTTAGCATTTTCTCAGCACT	53	D	259
1549590	25787	25806	N/A	N/A	TTTCCTATTTATTCTTCCAT	67	D	260
1549593	38943	38962	N/A	N/A	TCTACTACTTCCATCACACT	92	D	261
1549599	95893	95912	N/A	N/A	CCTTTTTTTCTTCCCCACTC	69	D	262
1549602	16836	16855	N/A	N/A	ATGTTCATTTTATTCCCTCC	17	D	263
1549619	33728	33747	N/A	N/A	ACTATTTTCTTTTTAAATCA	146	D	264
1549625	12549	12568	N/A	N/A	GTTGCATTTTCTTCCTCCAA	23	D	265
1549627	70908	70927	N/A	N/A	GTGCAGATTCTATTTTCCCT	30	D	266
1549628	17984	18003	N/A	N/A	GCACACTTCTTTTTCTATTT	6	D	267
1549634	12281	12300	N/A	N/A	TCACTCTTTTCTACGCCCTC	62	D	268
1549641	115711	115730	6837	6856	TGACTTATCTACCTAAACTT	122	D	269
1549658	6717	6736	3931	3950	GCTCACTTTCTCCTCTGTCT	71	D	270
1549669	23833	23852	N/A	N/A	TTCGATCTTCTTATCACCTT	36	D	271
1549670	48669	48688	N/A	N/A	ACTTGCCTTTTCTTTTTCTC	47	D	272
1549674	117686	117705	8812	8831	CTGGAATATTTCATTATCAA	30	D	273
1549676	115185	115204	6311	6330	ACTTTGTACTGCTTACTCTA	59	D	274
1549690	32172	32191	N/A	N/A	GTTGTTCATTTATACCACAC	69	D	275
1549692	115320	115339	6446	6465	TCTTGTTCACATTTTTAATC	29	D	276
1549695	116331	116350	7457	7476	ATTAATGTTCCCACTTTCCA	84	D	277
1549699	12331	12350	N/A	N/A	CTATCTTTCTTCTCCATTTT	120	D	278
1549707	114258	114277	5384	5403	AATACATAATACTTTTCACA	71	D	279
1549717	87649	87668	N/A	N/A	AGTATTGTTTTTTCTAATCC	84	D	280
1549732	18279	18298	N/A	N/A	ACACATTTATTTGATCCCAT	24	D	281
1549741	25737	25756	N/A	N/A	TATATATTCTCTTTTTCCCT	101	D	282
1549745	78962	78981	N/A	N/A	ACTGCTTTATATTCTCTCTA	53	D	283
1549749	4746	4765	N/A	N/A	TGTGTTTCTTCTTTTCTCCC	19	D	284
1549756	43413	43432	N/A	N/A	TTGCATTTCTTTTCTACCAG	16	D	285
1549760	13364	13383	N/A	N/A	GCATTGTTTCTCATTGCTTT	107	D	286
1549767	85361	85380	N/A	N/A	ACTACCAGTATCCTCCATTC	87	D	287
1549768	60704	60723	N/A	N/A	GCTTGTTTATTCCTTGAATT	45	D	288
1549776	1998	2017	1998	2017	ACGCAGATTTCCATTGAGCT	40	D	289
1549778	118458	118477	9584	9603	CTGCTTTATCATCTTCATAA	33	D	290
1549788	28085	28104	N/A	N/A	ACACATTTCACATTCAGGTT	12	D	291
1549789	114011	114030	5137	5156	TGTGGTTTCTTTCTCTTCTT	40	D	292
1549792	43529	43548	N/A	N/A	ACATCATTCTTATTTATTCA	59	D	293

1549806	97116	97135	N/A	N/A	GATCATGTATCTTTACACTC	95	D	294
1549807	114609	114628	5735	5754	GCCTTTTGCCATCACCACAC	69	D	295
1549809	55222	55241	N/A	N/A	ATTCTTTTTCTAATTCGAAT	107	D	296
1549811	20192	20211	N/A	N/A	TCTGCTTTTCTCATTGACTT	30	D	297
1549816	64669	64688	N/A	N/A	TCATCTTTTTCATAGGCATC	33	D	298
1549817	82565	82584	N/A	N/A	TTTCATTCTCTCTTATCACC	127	D	299
1549818	106548	106567	N/A	N/A	CTACTTGTCTCTTTCTCACT	159	D	300
1549825	59999	60018	N/A	N/A	GTATATTTCTAATATCACAT	183	D	301
1549845	12315	12334	N/A	N/A	TTTTCCTTCTTTTTCAACCT	69	D	302
1549848	113900	113919	5026	5045	ATGCATGACTTTCTCGCTAT	85	D	303
1549859	7460	7479	4002	4021	CTGATTTTTTTCTTCTTGCT	17	D	304
1549865	8975	8994	N/A	N/A	CCATCATCCATATACCACTC	47	D	305
1549878	82447	82466	N/A	N/A	ATGCTTGTCTCTCCCTTTCA	51	D	306
1549883	108229	108248	N/A	N/A	TTGTCTTTATTCCTTCCTGC	57	D	307
1549886	21083	21102	N/A	N/A	GCTTCATACTTCCTTATTTT	33	D	308
1549888	83231	83250	N/A	N/A	AATGCATTTTCTCTCCCCAT	32	D	309
1549889	74722	74741	N/A	N/A	CAGTCTTTTCATATTGCTTC	21	D	310
1549894	118314	118333	9440	9459	ACTGCTTAATGAGACATACT	64	D	311
1549897	53937	53956	N/A	N/A	CTGCTTCTTTTTTTAACTGC	50	D	312
1549899	52785	52804	N/A	N/A	GTCATTTTTTTCTCACCTGC	20	D	313
1549907	63654	63673	N/A	N/A	CTTCCATTTCTCTCATGCAT	92	D	314
1549914	65069	65088	N/A	N/A	GTTATTGTTTAATACCATCA	23	D	315
1549925	36678	36697	N/A	N/A	GCTAGCCTATTTTCCTTTCT	71	D	316
1549927	38624	38643	N/A	N/A	CTTATTTTTCTCCATATCAC	74	D	317
1549928	40644	40663	N/A	N/A	TCTCTTCATTTCAACACATT	131	D	318
1549929	45391	45410	N/A	N/A	ATTTCTTTCAACATTTCCCA	80	D	319
1549941	10818	10837	N/A	N/A	TCTTGTCTTTTTCATCTCTC	6	D	320
1549952	73319	73338	N/A	N/A	TAATGGGATATCCACATCAT	91	D	321
	75731	75750						
1549964	73358	73377	N/A	N/A	ACCCCAATCTCATATCAGGA	53	D	322
	75770	75789						
1549975	73151	73170	N/A	N/A	CTACTTGTCAATCACTCTTT	86	D	323
	75563	75582						
1549995	73313	73332	N/A	N/A	GATATCCACATCATCAAAAA	37	D	324
	75725	75744						
1550000	73214	73233	N/A	N/A	TCAAGCCCCATGATACCCCT	50	D	325
	75626	75645						
1550008	72479	72498	N/A	N/A	AGATAGCTAAAAAAGAGGAT	100	D	326
	75990	76009						
1549511	52787	52806	N/A	N/A	GTGTCATTTTTTTCTCACCT	34	E	327
1549512	18969	18988	N/A	N/A	GTGCATCTCCTATTCATCCC	13	E	328
1549519	78891	78910	N/A	N/A	GTCTGTTTTATCTATCCACT	9	E	329
1549523	4747	4766	N/A	N/A	CTGTGTTTCTTCTTTTCTCC	15	E	330
1549524	115191	115210	6317	6336	ATATACACTTTGTACTGCTT	35	E	331
1549530	43414	43433	N/A	N/A	ATTGCATTTCTTTTCTACCA	55	E	332
1549534	12550	12569	N/A	N/A	AGTTGCATTTTCTTCCTCCA	8	E	333

1549536	115331	115350	6457	6476	TTTTAGTATTTTCTTGTTCA	40	E	334
1549539	15628	15647	N/A	N/A	CTGTCATATTTTATTTCATT	21	E	335
1549545	12332	12351	N/A	N/A	ACTATCTTTCTTCTCCATTT	104	E	336
1549548	36733	36752	N/A	N/A	ACTTGGACTTTTATCCTTTA	53	E	337
1549554	5751	5770	N/A	N/A	ACCAATTATTTAATTATACT	72	E	338
1549555	12316	12335	N/A	N/A	ATTTTCCTTCTTTTTCAACC	75	E	339
1549561	9742	9761	N/A	N/A	CTCTCACTTTCTATTGCTGA	45	E	340
1549566	32756	32775	N/A	N/A	GCACTCATTTTTGTAAACTC	5	E	341
1549567	24150	24169	N/A	N/A	GTGTATCTATATCTCCCTAC	15	E	342
1549570	4111	4130	N/A	N/A	TCTCTGTTTTTCCTACCATA	53	E	343
1549572	59762	59781	N/A	N/A	GCTTTTCTCAATTTTCCAAA	15	E	344
1549580	75143	75162	N/A	N/A	TTTTAGTGATTATTTTTCCA	66	E	345
1549592	93859	93878	N/A	N/A	TGTCTTGACATTCATATCCA	72	E	346
1549597	107051	107070	N/A	N/A	GCACTATTATCAATCCCATC	87	E	347
1549600	25690	25709	N/A	N/A	CCTACGCTTTTTTTTGAATC	133	E	348
1549606	54367	54386	N/A	N/A	GTCATTTTGCATTACTTTTA	21	E	349
1549615	52594	52613	N/A	N/A	CCTCATTTCTAATATATCTC	158	E	350
1549616	92012	92031	N/A	N/A	GTGCCTTTTTTCCCTTCCAT	32	E	351
1549621	29896	29915	N/A	N/A	CCCCATTTTACTCTTTCATA	54	E	352
1549622	60000	60019	N/A	N/A	TGTATATTTCTAATATCACA	85	E	353
1549623	109643	109662	N/A	N/A	GTGTCTTTAATTTAAACATA	98	E	354
1549633	79186	79205	N/A	N/A	CCTATTTTACACACCATCCT	174	E	355
1549638	45396	45415	N/A	N/A	CTTGTATTTCTTTCAACATT	53	E	356
1549645	70084	70103	N/A	N/A	CTTATTATCCAATCTACACA	105	E	357
1549648	113937	113956	5063	5082	CTTTGTTGCGACCTTCCTTC	114	E	358
1549649	118337	118356	9463	9482	TCTTCATATAATCAGCAACA	75	E	359
1549656	38625	38644	N/A	N/A	CCTTATTTTTCTCCATATCA	95	E	360
1549657	114012	114031	5138	5157	GTGTGGTTTCTTTCTCTTCT	54	E	361
1549663	118459	118478	9585	9604	GCTGCTTTATCATCTTCATA	73	E	362
1549668	46232	46251	N/A	N/A	GACCCATTTTCTTCCTTCAT	35	E	363
1549689	21089	21108	N/A	N/A	ATGTATGCTTCATACTTCCT	79	E	364
1549710	12282	12301	N/A	N/A	TTCACTCTTTTCTACGCCCT	33	E	365
1549711	7461	7480	4003	4022	ACTGATTTTTTTCTTCTTGC	31	E	366
1549714	84408	84427	N/A	N/A	GTTTTTTTCATATCCCTAAT	35	E	367
1549722	20323	20342	N/A	N/A	ATGATTTTATTATTTGAGTT	76	E	368
1549739	21748	21767	N/A	N/A	TTCCGATGTTTTATCCTCAT	7	E	369
1549752	18030	18049	N/A	N/A	CTTTCTTTCCATTTCAGAAA	128	E	370
1549753	34364	34383	N/A	N/A	GTCACTTTTCCATACTAATA	30	E	371
1549759	95894	95913	N/A	N/A	GCCTTTTTTTCTTCCCCACT	26	E	372
1549770	82566	82585	N/A	N/A	ATTTCATTCTCTCTTATCAC	89	E	373
1549774	118198	118217	9324	9343	GCCTATTGCAACTAATACCT	55	E	374
1549779	55252	55271	N/A	N/A	CTTTCTTATTATTTAGTATA	77	E	375
1549787	38950	38969	N/A	N/A	AGTACTTTCTACTACTTCCA	56	E	376
1549794	115712	115731	6838	6857	CTGACTTATCTACCTAAACT	79	E	377
1549795	117886	117905	9012	9031	TTGTGGGTTATTCTTTACCA	22	E	378
1549800	43531	43550	N/A	N/A	GCACATCATTCTTATTTATT	9	E	379

1549805	28829	28848	N/A	N/A	GCTTTTTTCTCTGCTACTCA	13	E	380
1549808	6718	6737	3932	3951	GGCTCACTTTCTCCTCTGTC	36	E	381
1549813	85694	85713	N/A	N/A	CTCTCATTTTACATTTTTAA	50	E	382
1549815	48821	48840	N/A	N/A	GCTACATTTTCTCAGATCTC	68	E	383
1549823	76482	76501	N/A	N/A	TGTTTTTTTCCTCTTCATTT	44	E	384
1549826	63655	63674	N/A	N/A	TCTTCCATTTCTCTCATGCA	63	E	385
1549830	40647	40666	N/A	N/A	TAGTCTCTTCATTTCAACAC	54	E	386
1549832	97202	97221	N/A	N/A	ATGCATTTTCATTCACAAAT	74	E	387
1549837	17353	17372	N/A	N/A	CTGTCCATTCTTCTCACTTA	79	E	388
1549844	114265	114284	5391	5410	AACACTTAATACATAATACT	81	E	389
1549849	25738	25757	N/A	N/A	ATATATATTCTCTTTTTCCC	86	E	390
1549866	10821	10840	N/A	N/A	ATTTCTTGTCTTTTTCATCT	9	E	391
1549881	67873	67892	N/A	N/A	ACTTTTCTCTTCCTATAAAA	68	E	392
1549885	64799	64818	N/A	N/A	CTTTGTCTTCACTTCTCAAA	112	E	393
1549892	60993	61012	N/A	N/A	GGTTATTTTTTTCTTTCTAA	32	E	394
1549902	114701	114720	5827	5846	GCTCATTCATTTGCTGTCTC	76	E	395
1549903	25788	25807	N/A	N/A	ATTTCCTATTTATTCTTCCA	52	E	396
1549933	70964	70983	N/A	N/A	ACTAGTTTTTTTCTCCTCAA	34	E	397
1549936	116789	116808	7915	7934	CTTGTAGCTTTTCACCAGAC	73	E	398
1549942	82505	82524	N/A	N/A	CTGATTTTGATCCTCACTAT	90	E	399
1549947	73215	73234	N/A	N/A	TTCAAGCCCCATGATACCCC	92	E	400
	75627	75646						
1549966	73153	73172	N/A	N/A	CTCTACTTGTCAATCACTCT	43	E	401
	75565	75584						
1549969	73361	73380	N/A	N/A	TAAACCCCAATCTCATATCA	97	E	402
	75773	75792						
1549984	73344	73363	N/A	N/A	TCAGGATTACATATTTAAGT	35	E	403
	75756	75775						
1549994	73314	73333	N/A	N/A	GGATATCCACATCATCAAAA	70	E	404
	75726	75745						
1549521	43415	43434	N/A	N/A	AATTGCATTTCTTTTCTACC	54	F	405
1549522	61905	61924	N/A	N/A	CACATTTTACATTTAACACA	114	F	406
1549528	84409	84428	N/A	N/A	TGTTTTTTTCATATCCCTAA	28	F	407
1549529	25883	25902	N/A	N/A	CTCATTTTCCATCTATGAAA	61	F	408
1549531	10103	10122	N/A	N/A	GCATCTTTCACCTCTATTGT	12	F	409
1549565	78892	78911	N/A	N/A	AGTCTGTTTTATCTATCCAC	47	F	410
1549568	5888	5907	N/A	N/A	GTTGATTTTCTATTCTAATC	26	F	411
1549571	114741	114760	5867	5886	GTGAGTATTCTCCAAGTACT	72	F	412
1549573	21234	21253	N/A	N/A	GTTCATTTTACATTTTTTAT	44	F	413
1549574	64800	64819	N/A	N/A	GCTTTGTCTTCACTTCTCAA	35	F	414
1549579	49307	49326	N/A	N/A	CTTCTCATTTTATTTGGGAA	101	F	415
1549581	12319	12338	N/A	N/A	TCCATTTTCCTTCTTTTTCA	27	F	416
1549583	45397	45416	N/A	N/A	ACTTGTATTTCTTTCAACAT	78	F	417
1549595	36818	36837	N/A	N/A	CTTCAGTTTTTAACCTCTCC	58	F	418
1549598	118239	118258	9365	9384	TCATCAGGCTCATTCCCCTC	69	F	419
1549603	92926	92945	N/A	N/A	GCTTCATTCTGAATTTAATC	51	F	420

1549607	115536	115555	6662	6681	ACATATTTCTTTAGTTTATT	74	F	421
1549608	76483	76502	N/A	N/A	TTGTTTTTTTCCTCTTCATT	41	F	422
1549624	40903	40922	N/A	N/A	GCATCTGTTTTTTAATGATT	55	F	423
1549630	60001	60020	N/A	N/A	TTGTATATTTCTAATATCAC	89	F	424
1549642	34366	34385	N/A	N/A	CTGTCACTTTTCCATACTAA	36	F	425
1549646	118460	118479	9586	9605	AGCTGCTTTATCATCTTCAT	103	F	426
1549661	39475	39494	N/A	N/A	GCATTTTTTCCTATAATCTT	16	F	427
1549666	114003	114022	5129	5148	CTTTCTCTTCTTCCTGGAGA	78	F	428
1549671	114341	114360	5467	5486	GCTTTTTTAAATGTAATCCT	64	F	429
1549673	32841	32860	N/A	N/A	CGCACATAATTCTTCATCTT	54	F	430
1549678	115853	115872	6979	6998	TGTTCTCCCCTACCTAACCC	72	F	431
1549681	52714	52733	N/A	N/A	ACTATTTTCATCACATCACT	77	F	432
1549685	47269	47288	N/A	N/A	ACTCTTGATTTCCTAATCTA	110	F	433
1549697	70250	70269	N/A	N/A	TCTCATTATTGATTATGCCA	13	F	434
1549698	7468	7487	4010	4029	CATTCTTACTGATTTTTTTC	52	F	435
1549701	72415	72434	N/A	N/A	CTGGATATACTAACCACCCC	89	F	436
1549702	21806	21825	N/A	N/A	GCATATGTATATATCATAAT	52	F	437
1549703	95896	95915	N/A	N/A	TTGCCTTTTTTTCTTCCCCA	56	F	438
1549709	12334	12353	N/A	N/A	CTACTATCTTTCTTCTCCAT	58	F	439
1549712	4748	4767	N/A	N/A	ACTGTGTTTCTTCTTTTCTC	12	F	440
1549713	80007	80026	N/A	N/A	CCTCTTTTTCCTCTTTTCCA	25	F	441
1549715	68235	68254	4388	4407	CCTCATGTCCACTATCCTTC	86	F	442
1549718	97754	97773	N/A	N/A	TCTTTTTCCATTTGTCCGCT	24	F	443
1549726	94071	94090	N/A	N/A	CCTAGCATTTCTCTTTTTCA	61	F	444
1549731	115315	115334	6441	6460	TTCACATTTTTAATCAAAAA	137	F	445
1549748	18031	18050	N/A	N/A	GCTTTCTTTCCATTTCAGAA	36	F	446
1549751	43670	43689	N/A	N/A	GCTGCTGTTTCTATTTTTAT	40	F	447
1549757	116938	116957	8064	8083	GTCACACTTCAACACCAACT	40	F	448
1549761	29227	29246	N/A	N/A	TTTGATCTATTTCTGACCTT	69	F	449
1549769	82506	82525	N/A	N/A	TCTGATTTTGATCCTCACTA	72	F	450
1549780	54744	54763	N/A	N/A	GCTTTTACTCTACTGTGTTC	88	F	451
1549791	25732	25751	N/A	N/A	ATTCTCTTTTTCCCTCCCTT	35	F	452
1549793	117937	117956	9063	9082	TCATCAGTTTTCCCTAATGA	66	F	453
1549797	63665	63684	N/A	N/A	GCTAAGATTTTCTTCCATTT	15	F	454
1549798	18970	18989	N/A	N/A	CGTGCATCTCCTATTCATCC	11	F	455
1549801	24152	24171	N/A	N/A	TTGTGTATCTATATCTCCCT	30	F	456
1549802	12283	12302	N/A	N/A	CTTCACTCTTTTCTACGCCC	28	F	457
1549836	30256	30275	N/A	N/A	GCTTCTTTCTTTACTTTGAA	13	F	458
1549842	15629	15648	N/A	N/A	GCTGTCATATTTTATTTCAT	11	F	459
1549847	52788	52807	N/A	N/A	TGTGTCATTTTTTTCTCACC	70	F	460
1549850	107289	107308	N/A	N/A	ACTATTTTATCATAAATACT	134	F	461
1549854	114132	114151	5258	5277	GTCACAGAATGATAATCACC	67	F	462
1549857	82572	82591	N/A	N/A	TATCTTATTTCATTCTCTCT	110	F	463
1549858	4112	4131	N/A	N/A	CTCTCTGTTTTTCCTACCAT	26	F	464
1549869	59764	59783	N/A	N/A	ATGCTTTTCTCAATTTTCCA	44	F	465
1549875	10888	10907	N/A	N/A	ATTAGCATTTATTACTCTAT	17	F	466

1549877	38626	38645	N/A	N/A	GCCTTATTTTTCTCCATATC	56	F	467
1549890	25763	25782	N/A	N/A	TTTCATGTATATATAAACCA	77	F	468
1549893	13012	13031	N/A	N/A	TTTATTTTCATTATTTCCAC	63	F	469
1549898	6719	6738	3933	3952	AGGCTCACTTTCTCCTCTGT	36	F	470
1549904	20420	20439	N/A	N/A	CTGGTATTTTTCTTTGTGCT	8	F	471
1549905	85957	85976	N/A	N/A	CTTGTTTGATTTTCATCCTA	67	F	472
1549906	118341	118360	9467	9486	TTTATCTTCATATAATCAGC	41	F	473
1549917	110199	110218	N/A	N/A	GCCACTTTATATATGAAATA	53	F	474
1549920	17751	17770	N/A	N/A	CCACTGTGTTCTCTCCCCTA	32	F	475
1549921	55257	55276	N/A	N/A	AGTCACTTTCTTATTATTTA	60	F	476
1549949	73144	73163	N/A	N/A	TCAATCACTCTTTTTAGAGA	63	F	477
	75556	75575						
1549953	73315	73334	N/A	N/A	GGGATATCCACATCATCAAA	98	F	478
	75727	75746						
1549968	73217	73236	N/A	N/A	AATTCAAGCCCCATGATACC	120	F	479
	75629	75648						
1549971	73209	73228	N/A	N/A	CCCCATGATACCCCTAATCA	114	F	480
	75621	75640						
1549986	73362	73381	N/A	N/A	ATAAACCCCAATCTCATATC	111	F	481
	75774	75793						
1549998	73347	73366	N/A	N/A	ATATCAGGATTACATATTTA	160	F	482
	75759	75778						

Example 2: Effect of modified oligonucleotides on human PCDH19 *in vitro,* multiple doses

SHSY5Y cells, plated at a density of 10,000 cells/well, were differentiated in Neurobasal media supplemented with B27 (ThermoFisher), penicillin/streptomycin (ThermoFisher), and 10μM retinoic acid (Sigma) for 10 days. Differentiated SH-SY5Y cells were treated with modified oligonucleotides at concentrations indicated in the tables below by free uptake. After a treatment period of approximately 5 days, total RNA was isolated from the cells and PCDH19 RNA levels were measured by quantitative real-time RT-PCR using human PCDH19 primer-probe set RTS53390 (described herein above) was used to measure RNA levels. PCDH19 RNA levels were normalized to total RNA content, as measured by GAPDH. Human GAPDH was measured using the human primer-probe set RTS104 (forward sequence GAAGGTGAAGGTCGGAGTC, designated herein as SEQ ID NO: 6; reverse sequence GAAGATGGTGATGGGATTTC, designated herein as SEQ ID NO: 7; probe sequence CAAGCTTCCCGTTCTCAGCC, designated herein as SEQ ID NO: 8). Reduction of PCDH19 RNA is presented in the tables below as percent PCDH19 RNA, relative to untreated control cells (% UTC). "N.C." refers to values that were not calculated.

The half maximal inhibitory concentration (IC_{50}) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in Excel and is also presented in the table below.

Table 2

Dose-dependent reduction of human PCDH19 RNA in differentiated SH-SY5Y cells by modified oligonucleotides

Compound No.	PCDH19 RNA (% UTC) RTS53390				IC_{50} (μM)
	240 nM	1200 nM	6000 nM	30000 nM	
1549513	41	12	6	3	<0.24
1549558	42	16	9	1	<0.24

1549562	64	34	13	5	0.50
1549589	23	12	4	4	<0.24
1549605	68	54	32	27	1.44
1549626	75	70	60	19	4.73
1549697	37	16	7	5	<0.24
1549712	38	22	11	5	<0.24
1549784	22	7	4	3	<0.24
1549798	35	21	6	5	<0.24
1549841	59	31	17	5	0.36
1549842	33	11	5	3	<0.24
1549855	23	8	5	5	<0.24
1549887	69	32	10	5	0.56
1549904	73	28	13	5	0.60
1549911	47	26	16	4	<0.24
1549915	57	31	39	13	0.36
1549938	23	9	4	3	<0.24
1549980	81	52	29	10	1.65

Table 3

Dose-dependent reduction of human PCDH19 RNA in differentiated SH-SY5Y cells by modified oligonucleotides

Compound No.	**PCDH19 RNA (% UTC) RTS53390**				**IC_{50} (μM)**
	240 nM	**1200 nM**	**6000 nM**	**30000 nM**	
1549517	35	13	11	4	<0.24
1549518	28	14	8	5	<0.24
1549519	42	19	9	6	<0.24
1549520	56	39	25	6	0.44
1549526	43	22	7	8	<0.24
1549534	35	15	6	2	<0.24
1549566	26	15	4	2	<0.24
1549572	38	15	6	3	<0.24
1549613	52	25	10	N.C	0.24
1549628	23	9	4	5	<0.24
1549654	69	35	19	7	0.67
1549700	50	33	27	N.C	<0.24
1549737	62	36	20	7	0.51
1549739	32	11	6	4	<0.24
1549800	32	13	7	4	<0.24
1549804	51	31	14	3	0.22
1549866	33	8	7	4	<0.24
1549887	45	19	9	9	<0.24
1549941	33	14	8	7	<0.24

Example 3: Effect of 3-10-3 cEt modified oligonucleotides with uniform phosphorothioate internucleoside linkages complementary to a human PCDH19 RNA *in vitro*, single dose

Modified oligonucleotides complementary to human PCDH19 nucleic acid were designed and tested for their single dose effects on PCDH19 RNA *in vitro*. The modified oligonucleotides were tested in a series of experiments that had the same culture conditions.

The modified oligonucleotides in the table below are 3-10-3 cEt modified oligonucleotides with uniform phosphorothioate internucleoside linkages. The modified oligonucleotides are 16 nucleosides in length. The sugar motif for the modified oligonucleotides is (from 5' to 3'): kkkddddddddddkkk; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, and each "k" represents a cEt sugar moiety. The internucleoside linkage motif for the modified oligonucleotides is (from 5' to 3'): sssssssssssssss; wherein each "s" represents a phosphorothioate internucleoside linkage. Each cytosine residue is a 5-methylcytosine.

"Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the table below is 100% complementary to SEQ ID NO: 1 (described herein above), to SEQ ID NO: 2 (described herein above), or to both. "N/A" indicates that the modified oligonucleotide is not 100% complementary to that particular target nucleic acid sequence.

SHSY5Y cells, plated at a density of 10,000 cells/well, were differentiated in Neurobasal media supplemented with B27 (ThermoFisher), penicillin/streptomycin (ThermoFisher), and 10μM retinoic acid (Sigma) for 10 days. Differentiated SH-SY5Y cells were treated with modified oligonucleotide at a concentration of 6,000 nM by free uptake. After a treatment period of approximately 5 days, total RNA was isolated from the cells and PCDH19 RNA levels were measured by quantitative real-time RT-PCR using human primer-probe set RTS53390 (described herein above). PCDH19 RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of PCDH19 RNA is presented in the table below as percent PCDH19 RNA relative to the amount in untreated control cells (% UTC).

Each separate experiment described in this example is identified by an Assay Identification letter in the table column labeled "AID".

Table 4

Reduction of PCDH19 RNA by 3-10-3 cEt modified oligonucleotides with uniform phosphorothioate internucleoside linkages at a concentration of 6,000 nM in differentiated SH-SY5Y cells

Compound No.	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	PCDH19 (% UTC)	AID	SEQ ID NO
1626338	31494	31509	N/A	N/A	GACTATACTAAGCTGC	46	G	483
1626339	80695	80710	N/A	N/A	AGATATTTACACGCAG	11	G	484
1626340	82939	82954	N/A	N/A	CGAACAAATAAGGTCA	30	G	485
1626341	61843	61858	N/A	N/A	TAGGTATTATGCTTCA	18	G	486
1626342	38804	38819	N/A	N/A	GGATATAAAGGTAGGT	7	G	487
1626343	108445	108460	N/A	N/A	ATAACTAATTGCCTGC	77	G	488
1626344	17864	17879	N/A	N/A	TAGTATTTGAGATTCG	3	G	489
1626345	21721	21736	N/A	N/A	AGATTAACAACCCTGT	37	G	490
1626346	38972	38987	N/A	N/A	CCATATGTAGTATGTG	70	G	491
1626347	31852	31867	N/A	N/A	GTCAATACGGTTCTTT	18	G	492
1626348	96905	96920	N/A	N/A	GAATTTGAAGCTCCGT	24	G	493
1626349	100640	100655	N/A	N/A	CTGAATAAGGGTATCC	93	G	494
1626350	73501	73516	N/A	N/A	GAGCAATTAGAGTCAT	24	G	495
1626351	107870	107885	N/A	N/A	GACTAAGGTAGATCTC	70	G	496

1626352	109959	109974	N/A	N/A	ATTGTATAGGACTTGT	65	G	497
1626353	72416	72431	N/A	N/A	GATATACTAACCACCC	51	G	498
1626354	100639	100654	N/A	N/A	TGAATAAGGGTATCCA	65	G	499
1626355	9559	9574	N/A	N/A	GCAGAATACCATCAGT	16	G	500
1626356	47246	47261	N/A	N/A	GAAATAATATCAGCCG	49	G	501
1626357	29081	29096	N/A	N/A	TCTTACTAGTAGGTGA	47	G	502
	63965	63980						
1626358	21701	21716	N/A	N/A	GAATTTTTACGCTGAT	17	G	503
1626359	94399	94414	N/A	N/A	ACTAATAGGCATCCCA	39	G	504
1626360	116339	116354	7465	7480	GACAATTAATGTTCCC	33	G	505
1626361	117452	117467	8578	8593	GTCAATAAGGGTCTTA	13	G	506
1626362	86726	86741	N/A	N/A	GTAGATAAGAACTGCC	70	G	507
1626363	64064	64079	N/A	N/A	GACGAATGAACATCAC	66	G	508
1626364	32404	32419	N/A	N/A	CCAAATAGGGTTCGAT	30	G	509
1626365	106683	106698	N/A	N/A	ATCCGTAAAACATTCA	39	G	510
1626366	98758	98773	N/A	N/A	TACTATACATGAGTCC	39	G	511
1626367	18811	18826	N/A	N/A	GAATATGCTGCCCTCA	63	G	512
1626368	97739	97754	N/A	N/A	TTAATTATACTAGTCG	75	G	513
1626369	93924	93939	N/A	N/A	GCATTACAATCCCCAG	25	G	514
1626370	115090	115105	6216	6231	CTAATCATGATTGGGA	30	G	515
1626371	50677	50692	N/A	N/A	CCCATATAAGATCTCC	38	G	516
1626372	29082	29097	N/A	N/A	ATCTTACTAGTAGGTG	65	G	517
	63966	63981						
1626373	98771	98786	N/A	N/A	GTAGAATAGGCCATAC	86	G	518
1626374	60537	60552	N/A	N/A	GCAGAATAACCACTGG	67	G	519
1626375	73355	73370	N/A	N/A	TCTCATATCAGGATTA	16	G	520
	75767	75782						
1626376	116212	116227	7338	7353	CATAATATCAGGATGG	28	G	521
1626377	73354	73369	N/A	N/A	CTCATATCAGGATTAC	5	G	522
	75766	75781						
1626378	29479	29494	N/A	N/A	CCAAATCAAAACCCGT	25	G	523
1626379	35977	35992	N/A	N/A	GATAATTACCAGTCTA	65	G	524
1626380	92752	92767	N/A	N/A	CCAATAAAAGTTCGGT	75	G	525
1626381	18505	18520	N/A	N/A	CTAGTAATAACAGGCT	67	G	526
1626382	67011	67026	N/A	N/A	GATTATGAGATTCCTC	62	G	527
1626383	82952	82967	N/A	N/A	AAAATTGAGGATTCGA	43	G	528
1626384	20228	20243	N/A	N/A	ACCAATTACATGGCAC	28	G	529
1626385	4425	4440	N/A	N/A	CACTTTATATAGCCAG	10	G	530
1626386	18927	18942	N/A	N/A	AAGGTTAGAATACCCA	101	G	531
1626387	57855	57870	N/A	N/A	CATCTACGATATTCAG	37	G	532
1626388	73500	73515	N/A	N/A	AGCAATTAGAGTCATC	7	G	533
1626389	94401	94416	N/A	N/A	GCACTAATAGGCATCC	78	G	534
1626390	93953	93968	N/A	N/A	GAATATCATTGATTGG	23	G	535
1626391	68433	68448	N/A	N/A	AAGTAGTATAGTGTGC	31	G	536
1626392	9470	9485	N/A	N/A	ATCAATGTAAGTGGTC	36	G	537
1626393	84590	84605	N/A	N/A	GGACTATAATGATCTT	76	G	538

	84903	84918						
1626394	98651	98666	N/A	N/A	GCATTAGTAAATCTCC	47	G	539
1626395	23090	23105	N/A	N/A	GTTTATACAGCCATCA	28	G	540
1626396	28923	28938	N/A	N/A	CTATAGTATATGTCTG	65	G	541
1626397	107970	107985	N/A	N/A	CTTTATTACTAGCGGT	47	G	542
1626398	6356	6371	N/A	N/A	GGAAATTCGATTTCTG	61	G	543
1626399	94944	94959	N/A	N/A	GAAAATTTCGAGTCTT	55	G	544
1626400	28468	28483	N/A	N/A	GATGTAATATGGGCAA	5	G	545
1626401	97740	97755	N/A	N/A	CTTAATTATACTAGTC	76	G	546
1626402	50676	50691	N/A	N/A	CCATATAAGATCTCCC	84	G	547
1626403	114384	114399	5510	5525	CTTATTAAAGGTGTCC	29	G	548
1626404	73836	73851	N/A	N/A	AAGCATAGTACGCAGC	32	G	549
1626405	68430	68445	N/A	N/A	TAGTATAGTGTGCCTA	47	G	550
1626406	68165	68180	N/A	N/A	GATAATTTACGACCGT	77	G	551
1626407	9325	9340	N/A	N/A	GCAGTATAGAGTCCTT	6	G	552
1626408	69088	69103	N/A	N/A	CTCGATAAAGCATGTG	18	G	553
1626409	26542	26557	N/A	N/A	GACTTAACATGACTCC	48	G	554
1626410	11934	11949	N/A	N/A	CTTGATTAGTGTTCCA	8	G	555
1626411	68289	68304	4442	4457	ACAATACAGGCTCCGC	51	G	556
1626412	61423	61438	N/A	N/A	TAAGATGCAAGGGTCC	29	G	557
1626413	93017	93032	N/A	N/A	GATACTTAAGTTCTGC	18	G	558
1626414	50392	50407	N/A	N/A	ACAGTATGAGCTCTCC	74	G	559
1626415	63951	63966	N/A	N/A	GATACTACATACCCAG	43	G	560

Example 4: Effect of modified oligonucleotides on human PCDH19 *in vitro,* multiple doses

SHSY5Y cells, plated at a density of 8,000 cells/well, were differentiated in Neurobasal media supplemented with B27 (ThermoFisher), penicillin/streptomycin (ThermoFisher), and 10µM retinoic acid (Sigma) for 10 days. Differentiated SH-SY5Y cells were treated with modified oligonucleotides at concentrations indicated in the table below by free uptake. After a treatment period of approximately 5 days, total RNA was isolated from the cells and PCDH19 RNA levels were measured by quantitative real-time RT-PCR using human PCDH19 primer-probe set RTS53390 (described herein above) was used to measure RNA levels. PCDH19 RNA levels were normalized to total RNA content, as measured by GAPDH. Human GAPDH was measured using the human primer-probe set RTS104 (described herein above). Reduction of PCDH19 RNA is presented in the tables below as percent PCDH19 RNA, relative to untreated control cells (% UTC).

The half maximal inhibitory concentration (IC_{50}) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in Excel and is also presented in the table below.

Table 5

Dose-dependent reduction of human PCDH19 RNA in differentiated SH-SY5Y cells by modified oligonucleotides

Compound No.	PCDH19 RNA (% UTC) RTS53390				IC_{50} (µM)
	46 nM	278 nM	1667 nM	10000 nM	
1626339	47	16	8	2	<0.046
1626341	135	71	20	1	0.88
1626342	91	19	6	3	0.19
1626344	16	5	1	0.4	<0.046

1626347	134	47	26	5	0.78
1626348	128	58	29	15	1.00
1626355	72	41	17	2	0.18
1626358	119	54	12	4	0.54
1626361	18	13	7	7	<0.046
1626375	125	52	17	4	0.66
1626377	16	6	2	0.2	<0.046
1626383	152	72	42	19	1.64
1626385	48	21	7	1	<0.046
1626388	48	27	8	5	<0.046
1626395	133	45	19	3	0.68
1626400	49	9	2	0.1	<0.046
1626407	15	2	0.2	0	<0.046
1626408	132	69	30	14	1.13
1626410	70	5	2	1	0.05

Example 5: Design of 5-10-5 MOE gapmer modified oligonucleotides with PS internucleoside linkages that target a human PCDH19 nucleic acid

Modified oligonucleotides complementary to a human PCDH19 nucleic acid were designed, as described in the table below. "Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the table below is 100% complementary to SEQ ID NO: 1 (described herein above), to SEQ ID NO: 2 (described herein above), or to both. 'N/A' indicates that the modified oligonucleotide has two or more mismatches to that particular target nucleic acid sequence.

The modified oligonucleotides in the table below are 5-10-5 MOE modified oligonucleotides with uniform phosphorothioate internucleoside linkages. The modified oligonucleotides are 20 nucleosides in length, wherein the central gap segment consists of ten 2'-β-D-deoxynucleosides, and wherein the 5' and 3' wing segments each consist of five 2'-MOE nucleosides. The sugar motif for the modified oligonucleotides is (from 5' to 3'): eeeeeddddddddddeeeee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, and each "e" represents a 2'-MOE ribosyl sugar moiety. The internucleoside linkage motifs for the modified oligonucleotides is (from 5' to 3'): sssssssssssssssss; wherein each "s" represents a phosphorothioate internucleoside linkage. All cytosine nucleobases are 5-methylcytosines.

Table 6

5-10-5 MOE modified oligonucleotides with uniform phosphorothioate internucleoside linkages complementary to human PCDH19

Compound No.	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SEQ ID NO
1653805	10648	10667	N/A	N/A	GTGTCATTTTCCCTACGCAG	75
1653806	10817	10836	N/A	N/A	CTTGTCTTTTTCATCTCTCT	241
1653807	73316	73335	N/A	N/A	TGGGATATCCACATCATCAA	90
	75728	75747				

1653808	32756	32775	N/A	N/A	GCACTCATTTTTGTAAACTC	341
1653809	43411	43430	N/A	N/A	GCATTTCTTTTCTACCAGTA	171
1653810	115316	115335	6442	6461	GTTCACATTTTTAATCAAAA	82
1653811	17984	18003	N/A	N/A	GCACACTTCTTTTTCTATTT	267
1653812	10818	10837	N/A	N/A	TCTTGTCTTTTTCATCTCTC	320
1653813	7441	7460	3983	4002	TTGATTTCTTTTGATGCCCA	124
1653814	41756	41775	N/A	N/A	ATGCTTGTTTTCTTCCTCTC	143
1653815	5510	5529	N/A	N/A	GCTGATTTCTTTTTCATCAA	251
1653816	21748	21767	N/A	N/A	TTCCGATGTTTTATCCTCAT	369
1653817	4534	4553	N/A	N/A	GCTATTTTTACTGAAACATC	63
1653818	12550	12569	N/A	N/A	AGTTGCATTTTCTTCCTCCA	333
1653819	20420	20439	N/A	N/A	CTGGTATTTTTCTTTGTGCT	471
1653820	80720	80739	N/A	N/A	GCATCAGTTTTTCTTCTAAA	216
1653821	34367	34386	N/A	N/A	GCTGTCACTTTTCCATACTA	20
1653822	78891	78910	N/A	N/A	GTCTGTTTTATCTATCCACT	329
1653823	25522	25541	N/A	N/A	ACATCATTTTTCATGTGGTC	21
1653824	43531	43550	N/A	N/A	GCACATCATTCTTATTTATT	379
1653825	10821	10840	N/A	N/A	ATTTCTTGTCTTTTTCATCT	391
1653826	72604	72623	N/A	N/A	ATTCTCTCTCATTTCCACCC	22
1653827	59851	59870	N/A	N/A	CGTACATTTTCATACCAAGA	95
1653828	17980	17999	N/A	N/A	ACTTCTTTTTCTATTTCTAA	94

Example 6: Design of RNAi compounds that target a human PCDH19 nucleic acid

RNAi compounds comprising antisense RNAi oligonucleotides complementary to a human PCDH19 nucleic acid, and sense RNAi oligonucleotides complementary to the antisense RNAi oligonucleotides were designed as follows.

The antisense RNAi oligonucleotide in each case is 23 nucleosides in length; has a sugar motif (from 5' to 3') of: yfyyyfyyyyyyyfyfyyyyyyy; wherein each 'y' represents a 2′-O-methylribosyl sugar moiety and each "f" represents a 2'-fluororibosyl sugar; and an internucleoside linkage motif (from 5' to 3') of: ssooooooooooooooooooss; wherein 'o' represents a phosphodiester internucleoside linkage and 's' represents a phosphorothioate internucleoside linkage. Each cytosine residue is a non-methylated cytosine. Each antisense RNAi oligonucleotide has a terminal phosphate at the 5'-end. The antisense RNAi oligonucleotides are listed below in Tables 7 and 8.

"Start site" indicates the 5'-most nucleoside to which the antisense RNAi oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the antisense RNAi oligonucleotide is complementary in the target nucleic acid sequence. Each antisense RNAi oligonucleoside listed in the Table 7 below is 100% complementary to SEQ ID NO: 1 (ENSEMBL Accession No. ENSG00000165194.15 from version 104: May 2021), to SEQ ID NO: 2 (ENSEMBL Accession No. ENST00000373034.8 from version 104: May 2021), or to both. 'N/A' indicates that the antisense RNAi oligonucleotide is not 100% complementary to that particular target nucleic acid sequence in Table 7 below.

Table 7

Design of antisense strand modified oligonucleotides targeted to human PCDH19

Antisense Strand Compound No.	SEQ ID NO: 1 Antisense Strand Start Site	SEQ ID NO: 1 Antisense Strand Stop Site	SEQ ID NO: 2 Antisense Strand Start Site	SEQ ID NO: 2 Antisense Strand Stop Site	Antisense Strand Sequence (5' to 3')	SEQ ID NO
1688321	327	349	327	349	UGUCUCGCUUUCUCUGUCUGUCU	561
1688324	329	351	329	351	UCUGUCUCGCUUUCUCUGUCUGU	562
1688327	408	430	408	430	UUGAUUUCAUCUUCCCGGAGAGG	563
1688339	697	719	697	719	UCAAAGCCCCGGUCUUUCUAAUG	564
1688357	785	807	785	807	UUCGUCUAGGAAAUCAAAGUUAA	565
1688363	1254	1276	1254	1276	UACUUGAGGCGAAGGUAAAGAGG	566
1688369	1359	1381	1359	1381	UUUACCCCUUCAAAGUUAGCCGG	567
1688381	1752	1774	1752	1774	UGCUCCUCUUCUACCGAGUACUU	568
1688399	1987	2009	1987	2009	UUCCAUUGAGCUGGACAUGACCU	569
1688417	2235	2257	2235	2257	UUUUCCACCACGAGUUCGGCAAA	570
1688423	2352	2374	2352	2374	UCAUUGGAGUCGGUCACCUUGAU	571
1688432	2493	2515	2493	2515	UAGCCAUAGAAGGAGUAGACCAC	572
1688435	2502	2524	2502	2524	UCGUUGACGUAGCCAUAGAAGGA	573
1688438	2571	2593	2571	2593	UAGUCUAAAGCGCCAGUGACAGU	574
1688441	2577	2599	2577	2599	UCUUCGUAGUCUAAAGCGCCAGU	575
1688444	2694	2716	2694	2716	UUGAUGACCGGCGGAUUGUCAUU	576
1688447	2709	2731	2709	2731	UUGACUGACAGCAGGUUGAUGAC	577
1688450	2724	2746	2724	2746	UCCACAAGCUCACUGUUGACUGA	578
1688459	2877	2899	2877	2899	UCCACCAGAAUAGUGGAGAAGCU	579
1688462	2920	2942	2920	2942	UGUGAGGUUGUAUUGGUCGUGCU	580
1688468	2984	3006	2984	3006	UGAUGAGCACGGUAAAGGACUUG	581
1688471	2999	3021	2999	3021	UGUCAUUUUCGUCAGUGAUGAGC	582
1688480	3030	3052	3030	3052	UGGUAGUAGGGCUUGGAAAAGUG	583
1688483	3045	3067	3045	3067	UCCUGCACAAUGACCUGGUAGUA	584
1688492	3186	3208	3186	3208	UUGGGAUUGAUGGAGACAUAGGU	585
1688495	3201	3223	3201	3223	UAGAUGUCGCCUGAGUUGGGAUU	586
1688498	3219	3241	3219	3241	UUAAAGGAUCGCAGCGCGUAGAU	587
1688501	3234	3256	3234	3256	UUGGUCUGCUCGUGGUUAAAGGA	588
1688504	3249	3271	3249	3271	UUGAAUUCGAACGCCUUGGUCUG	589
1688507	3261	3283	3261	3283	UUGGCCAGCACCUUGAAUUCGAA	590
1688510	3330	3352	3330	3352	UUGUCGUUGACGUCGAGGAUGAU	591
1688513	3363	3385	3363	3385	UUAAUCAGAGGUGGGGCUGUGAU	592
1688519	3438	3460	3438	3460	UAGUCUUCUGCCUUGACAACAGU	593
1688522	3453	3475	3453	3475	UUUUCGCCCUCAUCGUAGUCUUC	594
1688528	3507	3529	3507	3529	UCUAUUUCAAAGAAGCCGCGGUC	595
1688531	3522	3544	3522	3544	UCGCCAUUGACCUGGUCUAUUUC	596
1688537	3575	3597	3575	3597	UAAGCUCAUAGGAGGACUUGGAG	597
1688540	3588	3610	3588	3610	UGAGCCACCACGAUAAGCUCAUA	598
1688549	3681	3703	3681	3703	UUCACAGAGCCCAUUGACUCUUG	599
1688561	3737	3759	3737	3759	UUACAAAGAGGAUGCCCGCAAUG	600
1688576	N/A	N/A	3811	3833	UAAACAAUUACUGCAGUUGUAGG	601

1688582	6627	6649	3841	3863	UAUAAAACAGCCGAGGAGACAAG	602
1688594	6680	6702	3894	3916	UCGCUAAUGGGAGAAACCGAGAU	603
1688597	6695	6717	3909	3931	UUUUUGUCUUGCUCCUCGCUAAU	604
1688603	6725	6747	3939	3961	UUUCCCCUUAGGCUCACUUUCUC	605
1688606	N/A	N/A	3954	3976	UACUCAGCAAUUCUCUUUCCCCU	606
1688953	7568	7590	4110	4132	UGCUGGUGGUAGUCAAAAUAGUU	607
1688968	7649	7671	4191	4213	UUAGCACUGGUGUUGCGGGUAUU	608
1688971	7664	7686	4206	4228	UGAUGGUAGAUGUGGUUAGCACU	609
1688974	7679	7701	4221	4243	UGGCUGUUGAAAGAGUGAUGGUA	610
1688980	7709	7731	4251	4273	UUGAUAAUCAGGUCAGGCUGCUG	611
1688986	N/A	N/A	4281	4303	UAGUUUUCAGUCUCAGGCAGAGG	612
1688989	59573	59595	4296	4318	UUGGAGUCAAAAGAAUAGUUUUC	613
1688995	59602	59624	4325	4347	UGAUUAAAUGGGCUCGGCUAUUC	614
1689001	68200	68222	4353	4375	UCUAAGUCCUUGAAGGUGGAGCU	615
1689007	68227	68249	4380	4402	UGUCCACUAUCCUUCAGGCUGUU	616
1689016	68266	68288	4419	4441	UGGACAUCAUGCUCACUGUCAGU	617
1689028	68347	68369	4500	4522	UGAUCAGGCAUCUGAGAUCCCAU	618
1689034	113404	113426	4530	4552	UCCCGGCAAUGAAAUCCUUCAUU	619
1689043	113515	113537	4641	4663	UCAAUAGACAGCGCGAUGAUGUU	620
1689046	113530	113552	4656	4678	UCAGCAGCAGUAGCUUCAAUAGA	621
1689061	113602	113624	4728	4750	UGGUCGCUGACAUCUUUCCCAAA	622
1689076	113824	113846	4950	4972	UUGACAUACUGCUCCAGAUCACG	623
1689085	113892	113914	5018	5040	UGACUUUCUCGCUAUCAGCUCCA	624
1689091	113931	113953	5057	5079	UGUUGCGACCUUCCUUCAGAAUG	625
1689097	113950	113972	5076	5098	UUCACACCAGGGGACUCUUUGUU	626
1689106	113995	114017	5121	5143	UCUUCUUCCUGGAGACUGGUUUA	627
1689118	114054	114076	5180	5202	UUGGUGAGCAAUUAAAACAAGAA	628
1689124	114084	114106	5210	5232	UCUGAAAUAUAGCCACUCAAGAA	629
1689130	114114	114136	5240	5262	UCACCUAUAAACAAUACAUUUAG	630
1689136	114144	114166	5270	5292	UUGAAACAAGGGACUGUCACAGA	631
1689139	114150	114172	5276	5298	UGCCUGUUGAAACAAGGGACUGU	632
1689154	114228	114250	5354	5376	UUGUCUCUGUUUCCCCAACAUCA	633
1689157	114243	114265	5369	5391	UUUUCACAACUGAAUUUGUCUCU	634
1689166	114288	114310	5414	5436	UUGACAUAGAAAAAUAUAUAAAU	635
1689169	114302	114324	5428	5450	UUUAUAUUAUAAUUUUGACAUAG	636
1689175	114332	114354	5458	5480	UUAAAUGUAAUCCUCCACAAACA	637
1689178	114347	114369	5473	5495	UCACUUUUUGCUUUUUUAAAUGU	638
1689199	114452	114474	5578	5600	UCACAUCACUGAAUCAAUGAAUA	639
1689202	114467	114489	5593	5615	UUUGGGGGCUCAAUUUCACAUCA	640
1689208	114497	114519	5623	5645	UGGGAAGUACUCGAGCUUCAGAA	641
1689214	114534	114556	5660	5682	UUUUAAAGCAGGGGUGUCCACAG	642
1689235	114639	114661	5765	5787	UUUUUAAGAAAAAGAAAACACCA	643
1689238	114654	114676	5780	5802	UGUAGUUUUAUUAUUUUUUUAAG	644
1689244	114684	114706	5810	5832	UGUCUCAGUUGUUUGCACUUUGU	645
1689247	114699	114721	5825	5847	UGCUCAUUCAUUUGCUGUCUCAG	646
1689259	114759	114781	5885	5907	UCACUACAUGAGUUAAAAAACGU	647
1689280	114856	114878	5982	6004	UAGCAGCCUAUCCAAAAAUGACU	648
1689304	114970	114992	6096	6118	UUCUAAGCCUGGAAACAUAACUU	649

1689307	114985	115007	6111	6133	UUGGAGAGAGGGAAUUUCUAAGC	650
1689310	115000	115022	6126	6148	UUCAAUUUUAGAUGAUUGGAGAG	651
1689328	115090	115112	6216	6238	UCUAAUUCUAAUCAUGAUUGGGA	652
1689331	115105	115127	6231	6253	UGACGUGCUUUGCAGUCUAAUUC	653
1689346	115176	115198	6302	6324	UACUGCUUACUCUAUCCCUACGU	654
1689352	115206	115228	6332	6354	UUACCUGUCUUUUCCAAAAUAUA	655
1689361	115251	115273	6377	6399	UCCGUUUAGAAGGCACAGUAAUU	656
1689367	115281	115303	6407	6429	UAAAAAGAUGAGUUCAAGUGUCU	657
1689373	115311	115333	6437	6459	UCACAUUUUUAAUCAAAAAACUA	658
1689376	115326	115348	6452	6474	UUAGUAUUUUCUUGUUCACAUUU	659
1689385	115371	115393	6497	6519	UAGCCUACAGCAAAAAGAGUUGG	660
1689403	115461	115483	6587	6609	UAAUAGACAAAAGAUAAAUGGGG	661
1689406	115476	115498	6602	6624	UUGGCUAGUGAAUAUUAAUAGAC	662
1689409	115491	115513	6617	6639	UGCAAAAAUACUAUGUUGGCUAG	663
1689427	115581	115603	6707	6729	UUGUUUCUCUAGAAACAACUCUC	664
1689439	115641	115663	6767	6789	UUCUCUCUGUGUAUUCCUGAAUU	665
1689442	115656	115678	6782	6804	UCUAACCUCUAGGCCUUCUCUCU	666
1689445	115671	115693	6797	6819	UUUGCAUUCUAGUGCUCUAACCU	667
1689451	115701	115723	6827	6849	UCUACCUAAACUUAAGAAAAUAA	668
1689463	115761	115783	6887	6909	UAAUGCGUAAAGCUAGGAACUCA	669
1689469	115791	115813	6917	6939	UCUCCCUCCUGUAAAAGAAAAUA	670
1689472	115801	115823	6927	6949	UCAAAACCCUUCUCCCUCCUGUA	671
1689478	115868	115890	6994	7016	UAAGUUCUUUUUCAGAAAUGUUC	672
1689481	115883	115905	7009	7031	UUUGUAGCUUCAUUAUAAGUUCU	673
1689490	115928	115950	7054	7076	UUUGCAUGAGGUAGUAUUCAGCA	674
1689496	115958	115980	7084	7106	UCAGAGGGAAAUUUGCAGCCACA	675
1689499	115973	115995	7099	7121	UUAAUUGUGUCAGCUUCAGAGGG	676
1689502	115988	116010	7114	7136	UAUGGUAAUUCAUCCUUAAUUGU	677
1689517	116063	116085	7189	7211	UCCACUACCAAAAUGAAAUAAAU	678
1689523	116093	116115	7219	7241	UGCAAAGAGAAAUAAAUACUUAA	679
1689544	116198	116220	7324	7346	UCAGGAUGGAUCAGGGUGAGAAA	680
1689562	116288	116310	7414	7436	UUCCCACUGAGCAUAGCAAGAAA	681
1689607	116523	116545	7649	7671	UGACUGCCCACUGAGAACAAAGU	682
1689619	116582	116604	7708	7730	UUCCUUAAUGAGAGGAAUUCUCU	683
1689622	116597	116619	7723	7745	UGUGGGGAAAAAUAUUUCCUUAA	684
1689640	116678	116700	7804	7826	UACAGCCUGCCUACAAAACCAGU	685
1689691	116947	116969	8073	8095	UCAUUAAAGCAUGUCACACUUCA	686
1689694	116962	116984	8088	8110	UUGCCAAAGCAGUUAUCAUUAAA	687
1689697	116977	116999	8103	8125	UACCUGUCUGGGGAAUUGCCAAA	688
1689700	116992	117014	8118	8140	UUGGAUGAAGAAGUAUACCUGUC	689
1689706	117022	117044	8148	8170	UUUGUCUAAAUGAACACCUUAGG	690
1689712	117052	117074	8178	8200	UAGAGAUCAGUGGAUCACUAAGC	691
1689718	117077	117099	8203	8225	UGUAUUUUUUAAAAAUAUUUCUG	692
1689721	117092	117114	8218	8240	UUCAGAGAUCUAAAUUGUAUUUU	693
1689724	117107	117129	8233	8255	UGAGUGGUUCCAAUUUUCAGAGA	694
1689727	117122	117144	8248	8270	UCAAGAUGAUACUCUUGAGUGGU	695
1689742	117197	117219	8323	8345	UAUGAUAGGGCUACAGGGAAAAG	696
1689748	117227	117249	8353	8375	UGCUUCAAGUGGACCACUUUUUG	697

1689754	117252	117274	8378	8400	UCCCUAAACUGCCCUUUGUCCUU	698
1689757	117299	117321	8425	8447	UUUUCCACUCUGGAUGCCCAAUC	699
1689781	117419	117441	8545	8567	UAAAGAGCCAAGUGGACCAAACU	700
1689784	117434	117456	8560	8582	UCUUAUUACCCGGGGUAAAGAGC	701
1689790	117464	117486	8590	8612	UUUAUGCCAGUUUUUCAAAGUCA	702
1689808	117554	117576	8680	8702	UACAAUUUGACUCAUGAAAUGAC	703
1689811	117569	117591	8695	8717	UUCAGUGUCAGCAGAUACAAUUU	704
1689820	117614	117636	8740	8762	UUACUUUGUUACAUACUUAAACU	705
1689853	117778	117800	8904	8926	UCACUUUUGCACAACAAGUGACC	706
1689862	117823	117845	8949	8971	UUUCUUUGUUUCACAAAAGCAAU	707
1689871	117868	117890	8994	9016	UACCAAGAGCGCCUUCCAAUCUA	708
1689874	117883	117905	9009	9031	UUGUGGGUUAUUCUUUACCAAGA	709
1689889	117951	117973	9077	9099	UGGAGCAACAGUCAGCAUCAUCA	710
1689901	118011	118033	9137	9159	UGCUAAGGUUGACAGCAACUUUC	711
1689916	118096	118118	9222	9244	UAUCCUAGCCUUCCUCAGCUGAA	712
1689925	118141	118163	9267	9289	UGAUUUCUAGCUCGAGCUAGUCU	713
1689949	118272	118294	9398	9420	UUUCCACCCUGGUUUGACAGGUA	714
1689952	118287	118309	9413	9435	UUGCAUCCCUCUAAAUUUCCACC	715
1689955	118302	118324	9428	9450	UGAGACAUACUGUACUUGCAUCC	716
1689961	118332	118354	9458	9480	UUCAUAUAAUCAGCAACAGAGAC	717
1689964	118347	118369	9473	9495	UACAACAAUUUUAUCUUCAUAUA	718
1689973	118392	118414	9518	9540	UGAUUCAAUCACUGUGAAAAUGU	719
1689976	118407	118429	9533	9555	UUUUUCUUUUUACAAUGAUUCAA	720
1690009	118567	118589	9693	9715	UUUUUGAAGCAGAGAAAACACAU	721
1690015	118597	118619	9723	9745	UAAUAGCCUUUAAUACUAAAAUG	722

"Start site" indicates the 5'-most nucleoside to which the antisense RNAi oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the antisense RNAi oligonucleotide is complementary in the target nucleic acid sequence. Each antisense RNAi oligonucleoside listed in the Table 8 below is complementary to SEQ ID NO: 1 (ENSEMBL Accession No. ENSG00000165194.15 from version 104: May 2021), to SEQ ID NO: 2 (ENSEMBL Accession No. ENST00000373034.8 from version 104: May 2021), or to both with the exception of a single mismatch at position 1 (from 5' to 3') of the antisense RNAi oligonucleotide. "N/A" indicates that the antisense RNAi oligonucleotide has two or more mismatches to that particular target nucleic acid sequence in Table 8 below.

Table 8

Design of antisense strand modified oligonucleotides targeted to human PCDH19

Antisense Strand Compound No.	SEQ ID NO: 1 Antisense Strand Start Site	SEQ ID NO: 1 Antisense Strand Stop Site	SEQ ID NO: 2 Antisense Strand Start Site	SEQ ID NO: 2 Antisense Strand Stop Site	Antisense Strand Sequence (5' to 3')	SEQ ID NO
1688312	190	211	190	211	UUUUCGGAUGAAAUCGCUCAGCC	723
1688315	205	226	205	226	UGUAGGAGGUUUAGGAUUUCGGA	724
1688318	216	237	216	237	UAUGGGUUUGGGGUAGGAGGUUU	725
1688330	423	444	423	444	UCUUGCAGGAGCGUCUUGAUUUC	726
1688333	430	451	430	451	UAAGUUUACUUGCAGGAGCGUCU	727

1688336	445	466	445	466	UAUUUUGUCGCCGCCGAAGUUUA	728
1688342	712	733	712	733	UUUUGUCCAAGAAAAUCAAAGCC	729
1688345	723	744	723	744	UGGAGAUGGCAAUUUGUCCAAGA	730
1688348	738	759	738	759	UAGUUUGUGGAAACGGGGAGAUG	731
1688351	748	769	748	769	UCUCCACGUCAAGUUUGUGGAAA	732
1688354	770	791	770	791	UAAGUUAACAACGCAGUCCGACC	733
1688360	792	813	792	813	UGGCGUUUUCGUCUAGGAAAUCA	734
1688366	1259	1280	1259	1280	UACAGUACUUGAGGCGAAGGUAA	735
1688372	1370	1391	1370	1391	UGCUACUCAGUUUUACCCCUUCA	736
1688375	1733	1754	1733	1754	UCUUGAGAUUAAUGAGGGCGGCA	737
1688378	1748	1769	1748	1769	UCUCUUCUACCGAGUACUUGAGA	738
1688384	1879	1900	1879	1900	UUUGAUGUCCACUAGGUGUGGAG	739
1688387	1888	1909	1888	1909	UGAGCUGGGAUUGAUGUCCACUA	740
1688390	1915	1936	1915	1936	UAUCUUCUGCUUGGUGACCAGCA	741
1688393	1930	1951	1930	1951	UAGCAGAUCACGGUCAAUCUUCU	742
1688396	1932	1953	1932	1953	UACAGCAGAUCACGGUCAAUCUU	743
1688402	2002	2023	2002	2023	UUUUAUCACGCAGAUUUCCAUUG	744
1688405	2017	2038	2017	2038	UUCCUUGAUCUCCACCUUUAUCA	745
1688408	2031	2052	2031	2052	UCAUUGUCGUUCAGGUCCUUGAU	746
1688411	2135	2156	2135	2156	UGCUUCCUGAGUCUGGAUCGUAA	747
1688414	2137	2158	2137	2158	UAAGCUUCCUGAGUCUGGAUCGU	748
1688420	2337	2358	2337	2358	UCCUUGAUACUAAGGCCAACGGU	749
1688426	2367	2388	2367	2388	UACACCGGGUUGUUGUCAUUGGA	750
1688429	2371	2392	2371	2392	UCUAAACACCGGGUUGUUGUCAU	751
1688453	2851	2872	2851	2872	UUAUUCCUGCAGUCGAAAGGGCA	752
1688456	2866	2887	2866	2887	UGUGGAGAAGCUCUCAUAUUCCU	753
1688465	2931	2952	2931	2952	UGUGCCUGAAUUGUGAGGUUGUA	754
1688474	3014	3035	3014	3035	UAAAGUGCGGGUGGUUGUCAUUU	755
1688477	3015	3036	3015	3036	UAAAAGUGCGGGUGGUUGUCAUU	756
1688486	3055	3076	3055	3076	UGUGUUGUUCUCCUGCACAAUGA	757
1688489	3171	3192	3171	3192	UCAUAGGUGAAGACAGGCAUGUC	758
1688516	3423	3444	3423	3444	UCAACAGUCACCAGGUAGCCUAU	759
1688525	3455	3476	3455	3476	UAUUUUCGCCCUCAUCGUAGUCU	760
1688534	3525	3546	3525	3546	UCUUCGCCAUUGACCUGGUCUAU	761
1688543	3638	3659	3638	3659	UGUAGAUUAGGACGAGAGCAGAG	762
1688546	3652	3673	3652	3673	UAGAGCAGGGGACAAGUAGAUUA	763
1688552	3696	3717	3696	3717	UAAAUCAAGGACAAGUUCACAGA	764
1688555	3711	3732	3711	3732	UCCAGGGCAAUAAUGAAAAUCAA	765
1688558	3718	3739	3718	3739	UAUGGAGCCCAGGGCAAUAAUGA	766
1688564	3752	3773	3752	3773	UCACGAAGAUCAUAGUUACAAAG	767
1688567	3766	3787	3766	3787	UUUGCACUUGAUUGCCACGAAGA	768
1688570	3781	3802	3781	3802	UUCUUUGUUGUCUCGCUUGCACU	769
1688573	3796	3817	3796	3817	UUUGUAGGUCCGGAUCUCUUUGU	770
1688579	6612	6633	3826	3847	UAGACAAGUGAUGGUUAAACAAU	771
1688585	6642	6663	3856	3877	UCUGUUUUGUCCUUUUAUAAAAC	772
1688588	6657	6678	3871	3892	UCAAUGCAGACACUUGCUGUUUU	773
1688591	6670	6691	3884	3905	UAGAAACCGAGAUGCAAUGCAGA	774
1688600	6710	6731	3924	3945	UCUUUCUCCUCUGUCUUUUUGUC	775

1688609	7425	7446	3967	3988	UUGCCCAUAGGAGUACUCAGCAA	776
1688612	7440	7461	3982	4003	UCUUGAUUUCUUUUGAUGCCCAU	777
1688615	7455	7476	3997	4018	UAUUUUUUUCUUCUUGCUUGAUU	778
1688618	7470	7491	4012	4033	UAUGUCAUUCUUACUGAUUUUUU	779
1688621	7480	7501	4022	4043	UUACCAGGCGGAUGUCAUUCUUA	780
1688624	7508	7529	4050	4071	UUCUUGUCUGUCUCCUCCACAUC	781
1688944	7523	7544	4065	4086	UAACUGACAACGUUCAUCUUGUC	782
1688947	7532	7553	4074	4095	UGGGAAGAGCAACUGACAACGUU	783
1688950	7553	7574	4095	4116	UAAUAGUUGAGGGAGGAGGUCAG	784
1688956	7572	7593	4114	4135	UGUCUGCUGGUGGUAGUCAAAAU	785
1688959	7614	7635	4156	4177	UUUCAGGAAAGUGCUCUCAGAGC	786
1688962	7629	7650	4171	4192	UUUCUGGUUCUCCACAUUCAGGA	787
1688965	7634	7655	4176	4197	UGGGUAUUCUGGUUCUCCACAUU	788
1688977	7680	7701	4222	4243	UUGGCUGUUGAAAGAGUGAUGGU	789
1688983	7722	7743	4264	4285	UAGAGGCACACCGUUGAUAAUCA	790
1688992	59587	59608	4310	4331	UGCUAUUCACGUAGUUGGAGUCA	791
1688998	N/A	N/A	4340	4361	UGGUGGAGCUGCUCUUGAUUAAA	792
1689004	68209	68230	4362	4383	UUGUUGCCCUCUAAGUCCUUGAA	793
1689010	68240	68261	4393	4414	UUCACUCUCCUCAUGUCCACUAU	794
1689013	68255	68276	4408	4429	UUCACUGUCAGUUUGGUCACUCU	795
1689019	68288	68309	4441	4462	UGUAUCACAAUACAGGCUCCGCU	796
1689022	68303	68324	4456	4477	UACAUCGUUGACAGCAGUAUCAC	797
1689025	68317	68338	4470	4491	UCACUGGUGUUCAGCACAUCGUU	798
1689031	N/A	N/A	4515	4536	UCUUCAUUCUGAUCAUGAUCAGG	799
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1689040	113500	113521	4626	4647	UUGAUGUUCCUCACAUGCUCAGG	801
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1689052	113550	113571	4676	4697	UGUCGUCAUAAGCCUCGACAUCA	803
1689055	113581	113602	4707	4728	UAGGUUGCGAAAGUCCGUUUGGU	804
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1689079	113839	113860	4965	4986	UCAUUGUUGACAUUGUUGACAUA	810
1689082	113849	113870	4975	4996	UCGAGUAGGGCCAUUGUUGACAU	811
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1689094	113938	113959	5064	5085	UACUCUUUGUUGCGACCUUCCUU	813
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1689103	113980	114001	5106	5127	UUGGUUUAGAGAACGAUAUCCUU	815
1689109	114010	114031	5136	5157	UGUGUGGUUUCUUUCUCUUCUUC	816
1689112	114024	114045	5150	5171	UUUCUUCACUAGCCAGUGUGGUU	817
1689115	114039	114060	5165	5186	UACAAGAAGCUCCUGCUUCUUCA	818
1689121	114069	114090	5195	5216	UUCAAGAACCAACCAUUGGUGAG	819
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1689133	114129	114150	5255	5276	UUCACAGAAUGAUAAUCACCUAU	821
1689142	114175	114196	5301	5322	UUUUGCUCCAACUGAACACCCCU	822
1689145	114190	114211	5316	5337	UUCAAGCCAAAGCUAAUUUGCUC	823

1689148	114202	114223	5328	5349	UCCCAUGAACAACUCAAGCCAAA	824
1689151	114213	114234	5339	5360	UAACAUCAAGGCCCCAUGAACAA	825
1689160	114258	114279	5384	5405	UUUAAUACAUAAUACUUUUCACA	826
1689163	114273	114294	5399	5420	UUAUAAAUUCAAACACUUAAUAC	827
1689172	114317	114338	5443	5464	UACAAACAAUGGUAAUUUAUAUU	828
1689181	114362	114383	5488	5509	UAGAGCUUUUUUUUUUCACUUUU	829
1689184	114377	114398	5503	5524	UUUAUUAAAGGUGUCCAGAGCUU	830
1689187	114392	114413	5518	5539	UAAAACAGUGGCGAGCUUAUUAA	831
1689190	114407	114428	5533	5554	UUUGUCUACACUACAAAAAACAG	832
1689193	114422	114443	5548	5569	UUAAAUGACCAUUAACUUGUCUA	833
1689196	114437	114458	5563	5584	UAUGAAUAGUACACAAUAAAUGA	834
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1689211	114511	114532	5637	5658	UAAAGUAGCGGCAUUGGGAAGUA	836
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1689223	114579	114600	5705	5726	UAUUUGCAAUAUCAAAUACAACA	839
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1689229	114609	114630	5735	5756	UAAGCCUUUUGCCAUCACCACAC	841
1689232	114624	114645	5750	5771	UAACACCAACUUUUAAAAGCCUU	842
1689241	114669	114690	5795	5816	UACUUUGUUUUUGUCUGUAGUUU	843
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1689253	114729	114750	5855	5876	UUCCAAGUACUCAAUCUAUAUGC	845
1689256	114744	114765	5870	5891	UAAAACGUGAGUAUUCUCCAAGU	846
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1689271	114805	114826	5931	5952	UAGACCACUGAAAGGCAGGAAAA	850
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1689286	114886	114907	6012	6033	UCACAGUAUUUCUGACAACUGCA	854
1689289	114901	114922	6027	6048	UUCAUAAAACUUUCAGCACAGUA	855
1689292	114916	114937	6042	6063	UUUUAAAAGAUGGAUGUCAUAAA	856
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1689313	115015	115036	6141	6162	UUAGAUUCAGUCAUCUUCAAUUU	860
1689316	115030	115051	6156	6177	UAUUUAGAUCUUAAAAUAGAUUC	861
1689319	115045	115066	6171	6192	UUCUGAAGAGAUGCUAAUUUAGA	862
1689322	115060	115081	6186	6207	UAUCAGGAAGUGUGUGUCUGAAG	863
1689325	115075	115096	6201	6222	UAUUGGGAAACACUGAAUCAGGA	864
1689334	115108	115129	6234	6255	UCAUGACGUGCUUUGCAGUCUAA	865
1689337	115131	115152	6257	6278	UACAUGGAGUUCUCAAUCCCAGC	866
1689340	115146	115167	6272	6293	UCUAAGAUACAGAGCAACAUGGA	867
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1689355	115221	115242	6347	6368	UGAUGCUGUUACCUGUUACCUGU	870
1689358	115236	115257	6362	6383	UAGUAAUUGGAUUAGCGAUGCUG	871

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1689475	115853	115874	6979	7000	UAAUGUUCUCCCCUACCUAACCC	894
1689484	115898	115919	7024	7045	UGAAAUAAGGAUGGAUUUGUAGC	895
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1689559	116273	116294	7399	7420	UCAAGAAAUACACCUGUAGAAAA	913
1689565	116289	116310	7415	7436	UUUCCCACUGAGCAUAGCAAGAA	914
1689568	116307	116328	7433	7454	UAUCUUUUCUGCUCCCUGGUUCC	915
1689571	116322	116343	7448	7469	UUUCCCACUUUCCACAAUCUUUU	916
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1689670	116842	116863	7968	7989	UUUUAUGUGUGCAACAUGUUUAG	945
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1689946	118257	118278	9383	9404	UACAGGUAAACAGUAAUAGUGUC	1009
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1689967	118362	118383	9488	9509	UUACAGAUCAGCAUAUACAACAA	1011
1689970	118377	118398	9503	9524	UAAAAUGUACAUAACAUACAGAU	1012
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1690000	118527	118548	9653	9674	UAACCACCAGAUAAAAGGAAACA	1020
1690003	118537	118558	9663	9684	UGGAAACAGAGAACCACCAGAUA	1021
1690006	118552	118573	9678	9699	UAACACAUUUAAAGGGGGAAACA	1022
1690012	118582	118603	9708	9729	UUAAAAUGCAUUAAAUUUUUGAA	1023
1690018	114806	114827	5932	5953	UCAGACCACUGAAAGGCAGGAAA	1024
1690021	115835	115856	6961	6982	UACCCCAUCCCUACUGCCUUACC	1025
1690024	116763	116784	7889	7910	UCAAAAAGGAGAAGGUGGGGUGG	1026
1690027	117647	117668	8773	8794	UCCAGCCCCACCCCCAAACAUCC	1027
1690030	118230	118251	9356	9377	UGCUCAUUCCCCUCACUAGAGGA	1028

The sense RNAi oligonucleotide in each case is 21 nucleosides in length; has a sugar motif (from 5' to 3') of: yyyyyyfyfffyyyyyyyyyy; wherein "y" represents a 2'-O-methylribosyl sugar and the "f" represents a 2'-fluororibosyl sugar; and an internucleoside linkage motif (from 5' to 3') of: ssooooooooooooooooss; wherein 'o' represents a phosphodiester internucleoside linkage and 's' represents a phosphorothioate internucleoside linkage. The sense RNAi oligonucleotides are listed below in Table 9.

Each antisense RNAi oligonucleotide is complementary to the target nucleic acid (PCDH19), and each sense RNAi oligonucleotides is complementary to the first of the 21 nucleosides of the antisense RNAi oligonucleotide (from 5' to 3') wherein the last two 3'-nucleosides of the antisense RNAi oligonucleotides are not paired with the sense RNAi oligonucleotide (are overhanging nucleosides). The sense RNAi oligonucleotides and siRNAs are listed in Table 9 below.

Table 9

Design of sense strand modified oligonucleotides of siRNAs targeted to human PCDH19

Duplex Compound Number	Antisense Strand Compound No.	Sense Strand Compound No.	Sense Strand Sequence (5' to 3')	SEQ ID NO
1688314	1688312	1688313	CUGAGCGAUUUCAUCCGAAAA	1029
1688317	1688315	1688316	CGAAAUCCUAAACCUCCUACA	1030
1688320	1688318	1688319	ACCUCCUACCCCAAACCCAUA	1031
1688323	1688321	1688322	ACAGACAGAGAAAGCGAGACA	1032
1688326	1688324	1688325	AGACAGAGAAAGCGAGACAGA	1033
1688329	1688327	1688328	UCUCCGGGAAGAUGAAAUCAA	1034
1688332	1688330	1688331	AAUCAAGACGCUCCUGCAAGA	1035
1688335	1688333	1688334	ACGCUCCUGCAAGUAAACUUA	1036
1688338	1688336	1688337	AACUUCGGCGGCGACAAAAUA	1037
1688341	1688339	1688340	UUAGAAAGACCGGGGCUUUGA	1038
1688344	1688342	1688343	CUUUGAUUUUCUUGGACAAAA	1039
1688347	1688345	1688346	UUGGACAAAUUGCCAUCUCCA	1040
1688350	1688348	1688349	UCUCCCCGUUUCCACAAACUA	1041
1688353	1688351	1688352	UCCACAAACUUGACGUGGAGA	1042

1688356	1688354	1688355	UCGGACUGCGUUGUUAACUUA	1043
1688359	1688357	1688358	AACUUUGAUUUCCUAGACGAA	1044
1688362	1688360	1688361	AUUUCCUAGACGAAAACGCCA	1045
1688365	1688363	1688364	UCUUUACCUUCGCCUCAAGUA	1046
1688368	1688366	1688367	ACCUUCGCCUCAAGUACUGUA	1047
1688371	1688369	1688370	GGCUAACUUUGAAGGGGUAAA	1048
1688374	1688372	1688373	AAGGGGUAAAACUGAGUAGCA	1049
1688377	1688375	1688376	CCGCCCUCAUUAAUCUCAAGA	1050
1688380	1688378	1688379	UCAAGUACUCGGUAGAAGAGA	1051
1688383	1688381	1688382	GUACUCGGUAGAAGAGGAGCA	1052
1688386	1688384	1688385	CCACACCUAGUGGACAUCAAA	1053
1688389	1688387	1688388	GUGGACAUCAAUCCCAGCUCA	1054
1688392	1688390	1688391	CUGGUCACCAAGCAGAAGAUA	1055
1688395	1688393	1688394	AAGAUUGACCGUGAUCUGCUA	1056
1688398	1688396	1688397	GAUUGACCGUGAUCUGCUGUA	1057
1688401	1688399	1688400	GUCAUGUCCAGCUCAAUGGAA	1058
1688404	1688402	1688403	AUGGAAAUCUGCGUGAUAAAA	1059
1688407	1688405	1688406	AUAAAGGUGGAGAUCAAGGAA	1060
1688410	1688408	1688409	CAAGGACCUGAACGACAAUGA	1061
1688413	1688411	1688412	ACGAUCCAGACUCAGGAAGCA	1062
1688416	1688414	1688415	GAUCCAGACUCAGGAAGCUUA	1063
1688419	1688417	1688418	UGCCGAACUCGUGGUGGAAAA	1064
1688422	1688420	1688421	CGUUGGCCUUAGUAUCAAGGA	1065
1688425	1688423	1688424	CAAGGUGACCGACUCCAAUGA	1066
1688428	1688426	1688427	CAAUGACAACAACCCGGUGUA	1067
1688431	1688429	1688430	GACAACAACCCGGUGUUUAGA	1068
1688434	1688432	1688433	GGUCUACUCCUUCUAUGGCUA	1069
1688437	1688435	1688436	CUUCUAUGGCUACGUCAACGA	1070
1688440	1688438	1688439	UGUCACUGGCGCUUUAGACUA	1071
1688443	1688441	1688442	UGGCGCUUUAGACUACGAAGA	1072
1688446	1688444	1688445	UGACAAUCCGCCGGUCAUCAA	1073
1688449	1688447	1688448	CAUCAACCUGCUGUCAGUCAA	1074
1688452	1688450	1688451	AGUCAACAGUGAGCUUGUGGA	1075
1688455	1688453	1688454	CCCUUUCGACUGCAGGAAUAA	1076
1688458	1688456	1688457	GAAUAUGAGAGCUUCUCCACA	1077
1688461	1688459	1688460	CUUCUCCACUAUUCUGGUGGA	1078
1688464	1688462	1688463	CACGACCAAUACAACCUCACA	1079
1688467	1688465	1688466	CAACCUCACAAUUCAGGCACA	1080
1688470	1688468	1688469	AGUCCUUUACCGUGCUCAUCA	1081
1688473	1688471	1688472	UCAUCACUGACGAAAAUGACA	1082
1688476	1688474	1688475	AUGACAACCACCCGCACUUUA	1083
1688479	1688477	1688478	UGACAACCACCCGCACUUUUA	1084
1688482	1688480	1688481	CUUUUCCAAGCCCUACUACCA	1085
1688485	1688483	1688484	CUACCAGGUCAUUGUGCAGGA	1086
1688488	1688486	1688487	AUUGUGCAGGAGAACAACACA	1087

1688491	1688489	1688490	CAUGCCUGUCUUCACCUAUGA	1088
1688494	1688492	1688493	CUAUGUCUCCAUCAAUCCCAA	1089
1688497	1688495	1688496	UCCCAACUCAGGCGACAUCUA	1090
1688500	1688498	1688499	CUACGCGCUGCGAUCCUUUAA	1091
1688503	1688501	1688502	CUUUAACCACGAGCAGACCAA	1092
1688506	1688504	1688505	GACCAAGGCGUUCGAAUUCAA	1093
1688509	1688507	1688508	CGAAUUCAAGGUGCUGGCCAA	1094
1688512	1688510	1688511	CAUCCUCGACGUCAACGACAA	1095
1688515	1688513	1688514	CACAGCCCCACCUCUGAUUAA	1096
1688518	1688516	1688517	AGGCUACCUGGUGACUGUUGA	1097
1688521	1688519	1688520	UGUUGUCAAGGCAGAAGACUA	1098
1688524	1688522	1688523	AGACUACGAUGAGGGCGAAAA	1099
1688527	1688525	1688526	ACUACGAUGAGGGCGAAAAUA	1100
1688530	1688528	1688529	CCGCGGCUUCUUUGAAAUAGA	1101
1688533	1688531	1688532	AAUAGACCAGGUCAAUGGCGA	1102
1688536	1688534	1688535	AGACCAGGUCAAUGGCGAAGA	1103
1688539	1688537	1688538	CCAAGUCCUCCUAUGAGCUUA	1104
1688542	1688540	1688541	UGAGCUUAUCGUGGUGGCUCA	1105
1688545	1688543	1688544	CUGCUCUCGUCCUAAUCUACA	1106
1688548	1688546	1688547	AUCUACUUGUCCCCUGCUCUA	1107
1688551	1688549	1688550	AGAGUCAAUGGGCUCUGUGAA	1108
1688554	1688552	1688553	UGUGAACUUGUCCUUGAUUUA	1109
1688557	1688555	1688556	GAUUUUCAUUAUUGCCCUGGA	1110
1688560	1688558	1688559	AUUAUUGCCCUGGGCUCCAUA	1111
1688563	1688561	1688562	UUGCGGGCAUCCUCUUUGUAA	1112
1688566	1688564	1688565	UUGUAACUAUGAUCUUCGUGA	1113
1688569	1688567	1688568	UUCGUGGCAAUCAAGUGCAAA	1114
1688572	1688570	1688571	UGCAAGCGAGACAACAAAGAA	1115
1688575	1688573	1688574	AAAGAGAUCCGGACCUACAAA	1116
1688578	1688576	1688577	UACAACUGCAGUAAUUGUUUA	1117
1688581	1688579	1688580	UGUUUAACCAUCACUUGUCUA	1118
1688584	1688582	1688583	UGUCUCCUCGGCUGUUUUAUA	1119
1688587	1688585	1688586	UUUAUAAAAGGACAAAACAGA	1120
1688590	1688588	1688589	AACAGCAAGUGUCUGCAUUGA	1121
1688593	1688591	1688592	UGCAUUGCAUCUCGGUUUCUA	1122
1688596	1688594	1688595	CUCGGUUUCUCCCAUUAGCGA	1123
1688599	1688597	1688598	UAGCGAGGAGCAAGACAAAAA	1124
1688602	1688600	1688601	CAAAAAGACAGAGGAGAAAGA	1125
1688605	1688603	1688604	GAAAGUGAGCCUAAGGGGAAA	1126
1688608	1688606	1688607	GGGAAAGAGAAUUGCUGAGUA	1127
1688611	1688609	1688610	GCUGAGUACUCCUAUGGGCAA	1128
1688614	1688612	1688613	GGGCAUCAAAAGAAAUCAAGA	1129
1688617	1688615	1688616	UCAAGCAAGAAGAAAAAAAUA	1130
1688620	1688618	1688619	AAAAUCAGUAAGAAUGACAUA	1131
1688623	1688621	1688622	AGAAUGACAUCCGCCUGGUAA	1132

1688626	1688624	1688625	UGUGGAGGAGACAGACAAGAA	1133
1688946	1688944	1688945	CAAGAUGAACGUUGUCAGUUA	1134
1688949	1688947	1688948	CGUUGUCAGUUGCUCUUCCCA	1135
1688952	1688950	1688951	GACCUCCUCCCUCAACUAUUA	1136
1688955	1688953	1688954	CUAUUUUGACUACCACCAGCA	1137
1688958	1688956	1688957	UUUGACUACCACCAGCAGACA	1138
1688961	1688959	1688960	UCUGAGAGCACUUUCCUGAAA	1139
1688964	1688962	1688963	CUGAAUGUGGAGAACCAGAAA	1140
1688967	1688965	1688966	UGUGGAGAACCAGAAUACCCA	1141
1688970	1688968	1688969	UACCCGCAACACCAGUGCUAA	1142
1688973	1688971	1688972	UGCUAACCACAUCUACCAUCA	1143
1688976	1688974	1688975	CCAUCACUCUUUCAACAGCCA	1144
1688979	1688977	1688978	CAUCACUCUUUCAACAGCCAA	1145
1688982	1688980	1688981	GCAGCCUGACCUGAUUAUCAA	1146
1688985	1688983	1688984	AUUAUCAACGGUGUGCCUCUA	1147
1688988	1688986	1688987	UCUGCCUGAGACUGAAAACUA	1148
1688991	1688989	1688990	AAACUAUUCUUUUGACUCCAA	1149
1688994	1688992	1688993	ACUCCAACUACGUGAAUAGCA	1150
1688997	1688995	1688996	AUAGCCGAGCCCAUUUAAUCA	1151
1689000	1688998	1688999	UAAUCAAGAGCAGCUCCACCA	1152
1689003	1689001	1689002	CUCCACCUUCAAGGACUUAGA	1153
1689006	1689004	1689005	CAAGGACUUAGAGGGCAACAA	1154
1689009	1689007	1689008	CAGCCUGAAGGAUAGUGGACA	1155
1689012	1689010	1689011	AGUGGACAUGAGGAGAGUGAA	1156
1689015	1689013	1689014	AGUGACCAAACUGACAGUGAA	1157
1689018	1689016	1689017	UGACAGUGAGCAUGAUGUCCA	1158
1689021	1689019	1689020	CGGAGCCUGUAUUGUGAUACA	1159
1689024	1689022	1689023	GAUACUGCUGUCAACGAUGUA	1160
1689027	1689025	1689026	CGAUGUGCUGAACACCAGUGA	1161
1689030	1689028	1689029	GGGAUCUCAGAUGCCUGAUCA	1162
1689033	1689031	1689032	UGAUCAUGAUCAGAAUGAAGA	1163
1689036	1689034	1689035	UGAAGGAUUUCAUUGCCGGGA	1164
1689039	1689037	1689038	UUCAUUGCCGGGAAGAAUGCA	1165
1689042	1689040	1689041	UGAGCAUGUGAGGAACAUCAA	1166
1689045	1689043	1689044	CAUCAUCGCGCUGUCUAUUGA	1167
1689048	1689046	1689047	UAUUGAAGCUACUGCUGCUGA	1168
1689051	1689049	1689050	GAAGCUACUGCUGCUGAUGUA	1169
1689054	1689052	1689053	AUGUCGAGGCUUAUGACGACA	1170
1689057	1689055	1689056	CAAACGGACUUUCGCAACCUA	1171
1689060	1689058	1689059	AACCUUUGGGAAAGAUGUCAA	1172
1689063	1689061	1689062	UGGGAAAGAUGUCAGCGACCA	1173
1689066	1689064	1689065	AAAGGCAAGAGGACUGUCGAA	1174
1689069	1689067	1689068	GAGGACUGUCGAUGUGACCAA	1175
1689072	1689070	1689071	GCCUUCCGUGUCUUACACCAA	1176
1689075	1689073	1689074	CCUUCCGUGUCUUACACCAUA	1177

1689078	1689076	1689077	UGAUCUGGAGCAGUAUGUCAA	1178
1689081	1689079	1689080	UGUCAACAAUGUCAACAAUGA	1179
1689084	1689082	1689083	GUCAACAAUGGCCCUACUCGA	1180
1689087	1689085	1689086	GAGCUGAUAGCGAGAAAGUCA	1181
1689090	1689088	1689089	AAAGUCAUGCAUGAGGUCAGA	1182
1689093	1689091	1689092	UUCUGAAGGAAGGUCGCAACA	1183
1689096	1689094	1689095	GGAAGGUCGCAACAAAGAGUA	1184
1689099	1689097	1689098	CAAAGAGUCCCCUGGUGUGAA	1185
1689102	1689100	1689101	UGUGAAGCGUCUGAAGGAUAA	1186
1689105	1689103	1689104	GGAUAUCGUUCUCUAAACCAA	1187
1689108	1689106	1689107	AACCAGUCUCCAGGAAGAAGA	1188
1689111	1689109	1689110	AGAAGAGAAAGAAACCACACA	1189
1689114	1689112	1689113	CCACACUGGCUAGUGAAGAAA	1190
1689117	1689115	1689116	AAGAAGCAGGAGCUUCUUGUA	1191
1689120	1689118	1689119	CUUGUUUUAAUUGCUCACCAA	1192
1689123	1689121	1689122	CACCAAUGGUUGGUUCUUGAA	1193
1689126	1689124	1689125	CUUGAGUGGCUAUAUUUCAGA	1194
1689129	1689127	1689128	UUCAGAGCUUUUCCUAAAUGA	1195
1689132	1689130	1689131	AAAUGUAUUGUUUAUAGGUGA	1196
1689135	1689133	1689134	AGGUGAUUAUCAUUCUGUGAA	1197
1689138	1689136	1689137	UGUGACAGUCCCUUGUUUCAA	1198
1689141	1689139	1689140	AGUCCCUUGUUUCAACAGGCA	1199
1689144	1689142	1689143	GGGUGUUCAGUUGGAGCAAAA	1200
1689147	1689145	1689146	GCAAAUUAGCUUUGGCUUGAA	1201
1689150	1689148	1689149	UGGCUUGAGUUGUUCAUGGGA	1202
1689153	1689151	1689152	GUUCAUGGGGCCUUGAUGUUA	1203
1689156	1689154	1689155	AUGUUGGGGAAACAGAGACAA	1204
1689159	1689157	1689158	AGACAAAUUCAGUUGUGAAAA	1205
1689162	1689160	1689161	UGAAAAGUAUUAUGUAUUAAA	1206
1689165	1689163	1689164	AUUAAGUGUUUGAAUUUAUAA	1207
1689168	1689166	1689167	UUAUAUAUUUUUCUAUGUCAA	1208
1689171	1689169	1689170	AUGUCAAAAUUAUAAUAUAAA	1209
1689174	1689172	1689173	UAUAAAUUACCAUUGUUUGUA	1210
1689177	1689175	1689176	UUUGUGGAGGAUUACAUUUAA	1211
1689180	1689178	1689179	AUUUAAAAAAGCAAAAAGUGA	1212
1689183	1689181	1689182	AAGUGAAAAAAAAAAGCUCUA	1213
1689186	1689184	1689185	GCUCUGGACACCUUUAAUAAA	1214
1689189	1689187	1689188	AAUAAGCUCGCCACUGUUUUA	1215
1689192	1689190	1689191	GUUUUUUGUAGUGUAGACAAA	1216
1689195	1689193	1689194	GACAAGUUAAUGGUCAUUUAA	1217
1689198	1689196	1689197	AUUUAUUGUGUACUAUUCAUA	1218
1689201	1689199	1689200	UUCAUUGAUUCAGUGAUGUGA	1219
1689204	1689202	1689203	AUGUGAAAUUGAGCCCCCAAA	1220
1689207	1689205	1689206	CCCAAAAGGUUGUUUCUGAAA	1221
1689210	1689208	1689209	CUGAAGCUCGAGUACUUCCCA	1222

1689213	1689211	1689212	CUUCCCAAUGCCGCUACUUUA	1223
1689216	1689214	1689215	GUGGACACCCCUGCUUUAAAA	1224
1689219	1689217	1689218	UUAAAAACCCUUUUGCUAGCA	1225
1689222	1689220	1689221	CUAGCUGUGCUAUUGUUGUAA	1226
1689225	1689223	1689224	UUGUAUUUGAUAUUGCAAAUA	1227
1689228	1689226	1689227	CAAAUUGCUAUGUGUGUGGUA	1228
1689231	1689229	1689230	GUGGUGAUGGCAAAAGGCUUA	1229
1689234	1689232	1689233	GGCUUUUAAAAGUUGGUGUUA	1230
1689237	1689235	1689236	GUGUUUUCUUUUUCUUAAAAA	1231
1689240	1689238	1689239	UAAAAAAAUAAUAAAACUACA	1232
1689243	1689241	1689242	ACUACAGACAAAAACAAAGUA	1233
1689246	1689244	1689245	AAAGUGCAAACAACUGAGACA	1234
1689249	1689247	1689248	GAGACAGCAAAUGAAUGAGCA	1235
1689252	1689250	1689251	UGAGCAACACCAUGCAUAUAA	1236
1689255	1689253	1689254	AUAUAGAUUGAGUACUUGGAA	1237
1689258	1689256	1689257	UUGGAGAAUACUCACGUUUUA	1238
1689261	1689259	1689260	GUUUUUUAACUCAUGUAGUGA	1239
1689264	1689262	1689263	UAGUGAUUGCUCACCACUUUA	1240
1689267	1689265	1689266	ACUUUGCAAAGUAUUUUUCCA	1241
1689270	1689268	1689269	UUUCCUGCCUUUCAGUGGUCA	1242
1689273	1689271	1689272	UUCCUGCCUUUCAGUGGUCUA	1243
1689276	1689274	1689275	CCCAGGUCCAUGAUAGAUCAA	1244
1689279	1689277	1689278	GAUCAUUGCAGAAAGUCAUUA	1245
1689282	1689280	1689281	UCAUUUUUGGAUAGGCUGCUA	1246
1689285	1689283	1689284	CUGCUAUCUAAUUUGCAGUUA	1247
1689288	1689286	1689287	CAGUUGUCAGAAAUACUGUGA	1248
1689291	1689289	1689290	CUGUGCUGAAAGUUUUAUGAA	1249
1689294	1689292	1689293	UAUGACAUCCAUCUUUUAAAA	1250
1689297	1689295	1689296	UUAAAUUUUCAGGCCCUGAAA	1251
1689300	1689298	1689299	CAGGCCCUGAACAGGAAAGUA	1252
1689303	1689301	1689302	AAAGUUGCUCCUGAAGUUAUA	1253
1689306	1689304	1689305	GUUAUGUUUCCAGGCUUAGAA	1254
1689309	1689307	1689308	UUAGAAAUUCCCUCUCUCCAA	1255
1689312	1689310	1689311	CUCCAAUCAUCUAAAAUUGAA	1256
1689315	1689313	1689314	AUUGAAGAUGACUGAAUCUAA	1257
1689318	1689316	1689317	AUCUAUUUUAAGAUCUAAAUA	1258
1689321	1689319	1689320	UAAAUUAGCAUCUCUUCAGAA	1259
1689324	1689322	1689323	UCAGACACACACUUCCUGAUA	1260
1689327	1689325	1689326	CUGAUUCAGUGUUUCCCAAUA	1261
1689330	1689328	1689329	CCAAUCAUGAUUAGAAUUAGA	1262
1689333	1689331	1689332	AUUAGACUGCAAAGCACGUCA	1263
1689336	1689334	1689335	AGACUGCAAAGCACGUCAUGA	1264
1689339	1689337	1689338	UGGGAUUGAGAACUCCAUGUA	1265
1689342	1689340	1689341	CAUGUUGCUCUGUAUCUUAGA	1266
1689345	1689343	1689344	CUUAGGCUUAUAUACGUAGGA	1267

1689348	1689346	1689347	GUAGGGAUAGAGUAAGCAGUA	1268
1689351	1689349	1689350	GCAGUACAAAGUGUAUAUUUA	1269
1689354	1689352	1689353	UAUUUUGGAAAAGACAGGUAA	1270
1689357	1689355	1689356	AGGUAACAGGUAACAGCAUCA	1271
1689360	1689358	1689359	GCAUCGCUAAUCCAAUUACUA	1272
1689363	1689361	1689362	UUACUGUGCCUUCUAAACGGA	1273
1689366	1689364	1689365	AACGGAGACACUCAGACACUA	1274
1689369	1689367	1689368	ACACUUGAACUCAUCUUUUUA	1275
1689372	1689370	1689371	UUUUUAUGACUAAUAGUUUUA	1276
1689375	1689373	1689374	GUUUUUUGAUUAAAAAUGUGA	1277
1689378	1689376	1689377	AUGUGAACAAGAAAAUACUAA	1278
1689381	1689379	1689380	UACUAAAAUAAAAAUCCUUUA	1279
1689384	1689382	1689383	CCUUUCGAUUUAGCCAACUCA	1280
1689387	1689385	1689386	AACUCUUUUUGCUGUAGGCUA	1281
1689390	1689388	1689389	AGGCUAGGAAUACACCCUUUA	1282
1689393	1689391	1689392	CCUUUUUAAAUUAACACACUA	1283
1689396	1689394	1689395	ACACUGUAGAUCCUUUUUUUA	1284
1689399	1689397	1689398	UUUUUCUGUUUUAACAUUCCA	1285
1689402	1689400	1689401	AUUCCUCUAACUCCCCCAUUA	1286
1689405	1689403	1689404	CCAUUUAUCUUUUGUCUAUUA	1287
1689408	1689406	1689407	CUAUUAAUAUUCACUAGCCAA	1288
1689411	1689409	1689410	AGCCAACAUAGUAUUUUUGCA	1289
1689414	1689412	1689413	UUUGCAGCCUAAGAGUUCAUA	1290
1689417	1689415	1689416	UUCAUUAUUUAAAAAUAAACA	1291
1689420	1689418	1689419	UAAACUAAAGAAAUAUGUCAA	1292
1689423	1689421	1689422	UGUCACCUUUGUUCUGCCUUA	1293
1689426	1689424	1689425	GCCUUGGUCUUAAGAGAGUUA	1294
1689429	1689427	1689428	GAGUUGUUUCUAGAGAAACAA	1295
1689432	1689430	1689431	AAACAAGUUUUAUGGUUCUGA	1296
1689435	1689433	1689434	UUCUGUUUUCAUUUGUUUCAA	1297
1689438	1689436	1689437	UUUCAUUUUUUGAAAUUCAGA	1298
1689441	1689439	1689440	UUCAGGAAUACACAGAGAGAA	1299
1689444	1689442	1689443	AGAGAAGGCCUAGAGGUUAGA	1300
1689447	1689445	1689446	GUUAGAGCACUAGAAUGCAAA	1301
1689450	1689448	1689449	UGCAAAAGAGGAUUUAUUUUA	1302
1689453	1689451	1689452	AUUUUCUUAAGUUUAGGUAGA	1303
1689456	1689454	1689455	GGUAGAUAAGUCAGCUCUUUA	1304
1689459	1689457	1689458	UCUUUUGAAUGUUUUACUUAA	1305
1689462	1689460	1689461	ACUUAUUUUUGCCUGAGUUCA	1306
1689465	1689463	1689464	AGUUCCUAGCUUUACGCAUUA	1307
1689468	1689466	1689467	GCAUUACUAGGAAUAUUUUCA	1308
1689471	1689469	1689470	UUUUCUUUUACAGGAGGGAGA	1309
1689474	1689472	1689473	CAGGAGGGAGAAGGGUUUUGA	1310
1689477	1689475	1689476	GUUAGGUAGGGGAGAACAUUA	1311
1689480	1689478	1689479	ACAUUUCUGAAAAAGAACUUA	1312

1689483	1689481	1689482	AACUUAUAAUGAAGCUACAAA	1313
1689486	1689484	1689485	UACAAAUCCAUCCUUAUUUCA	1314
1689489	1689487	1689488	AUUUCUUAUUCAGUGCUGAAA	1315
1689492	1689490	1689491	CUGAAUACUACCUCAUGCAAA	1316
1689495	1689493	1689494	UGCAAAAUAUUGGUGUGGCUA	1317
1689498	1689496	1689497	UGGCUGCAAAUUUCCCUCUGA	1318
1689501	1689499	1689500	CUCUGAAGCUGACACAAUUAA	1319
1689504	1689502	1689503	AAUUAAGGAUGAAUUACCAUA	1320
1689507	1689505	1689506	ACCAUAACAUCUUCAUUUUUA	1321
1689510	1689508	1689509	UUUUUCCUCAUUUCAUUGCCA	1322
1689513	1689511	1689512	UUGCCUCUCAUACAGUUUUCA	1323
1689516	1689514	1689515	UUUUCUCCCUCUGAUUUAUUA	1324
1689519	1689517	1689518	UUAUUUCAUUUUGGUAGUGGA	1325
1689522	1689520	1689521	AGUGGAUUUUGAAUUAAGUAA	1326
1689525	1689523	1689524	AAGUAUUUAUUUCUCUUUGCA	1327
1689528	1689526	1689527	UUUGCAAGUGACUAUUUGAUA	1328
1689531	1689529	1689530	UUGAUUAACACAUUAAAAAUA	1329
1689534	1689532	1689533	AAAAUUUUUUAAAAAUUUCCA	1330
1689537	1689535	1689536	UUUCCCCUUUAAGUUAUGAUA	1331
1689540	1689538	1689539	AUGAUGGCUGCCUAUAGAAUA	1332
1689543	1689541	1689542	AGAAUUUAGACUGUUUCUCAA	1333
1689546	1689544	1689545	UCUCACCCUGAUCCAUCCUGA	1334
1689549	1689547	1689548	UCCUGAUAUUAUGUUAUUAGA	1335
1689552	1689550	1689551	AUUAGCUACGAUUUCAAGGUA	1336
1689555	1689553	1689554	AAGGUCACUUUGAAGUCAGAA	1337
1689558	1689556	1689557	UCAGACUUCACAGUUUUCUAA	1338
1689561	1689559	1689560	UUCUACAGGUGUAUUUCUUGA	1339
1689564	1689562	1689563	UCUUGCUAUGCUCAGUGGGAA	1340
1689567	1689565	1689566	CUUGCUAUGCUCAGUGGGAAA	1341
1689570	1689568	1689569	AACCAGGGAGCAGAAAAGAUA	1342
1689573	1689571	1689572	AAGAUUGUGGAAAGUGGGAAA	1343
1689576	1689574	1689575	GGGAACAUUAAUUGUCACGUA	1344
1689579	1689577	1689578	AUUGUCACGUGGCUGUUGAGA	1345
1689582	1689580	1689581	UGCCUCUUACCAGCCAAGUUA	1346
1689585	1689583	1689584	AAGUUUUAAAUGGUUAGAGUA	1347
1689588	1689586	1689587	AGAGUGGCAUUGGCAUUGAUA	1348
1689591	1689589	1689590	UUGAUUUUGCUUUUCUCUUGA	1349
1689594	1689592	1689593	UCUUGGGUUUUCUUCAUUUCA	1350
1689597	1689595	1689596	AUUUCUUUUCAUAAUUCAUCA	1351
1689600	1689598	1689599	UCAUCUUCAAGCUAUAGAUCA	1352
1689603	1689601	1689602	AGAUCCAUCCUUCUUCCCUAA	1353
1689606	1689604	1689605	CCCUAUCCAAAUACUUUGUUA	1354
1689609	1689607	1689608	UUUGUUCUCAGUGGGCAGUCA	1355
1689612	1689610	1689611	CAGUCAGAUUUUUUUGGCUUA	1356
1689615	1689613	1689614	UGGCUUCCAAACCUCACUGAA	1357

1689618	1689616	1689617	ACUGAGCAUGUUCAGAGAAUA	1358
1689621	1689619	1689620	AGAAUUCCUCUCAUUAAGGAA	1359
1689624	1689622	1689623	AAGGAAAUAUUUUUCCCCACA	1360
1689627	1689625	1689626	CCCACAAUUGUCUGAUGUAUA	1361
1689630	1689628	1689629	UGUAUGAGUCCUCUCAGAAGA	1362
1689633	1689631	1689632	AGAAGCACAAGUGCAUACUAA	1363
1689636	1689634	1689635	UACUAGGAAGGCUUUGUAAAA	1364
1689639	1689637	1689638	GUAAACUGGUUUUGUAGGCAA	1365
1689642	1689640	1689641	UGGUUUUGUAGGCAGGCUGUA	1366
1689645	1689643	1689644	GCUGUACCUGCAAAUAGGCAA	1367
1689648	1689646	1689647	AGGCAUUCUGAGCAAGGAUCA	1368
1689651	1689649	1689650	GGAUCCUAAAUUUCCCUUUGA	1369
1689654	1689652	1689653	UUUCCCUUUGGCUCAUGUCCA	1370
1689657	1689655	1689656	ACCUUCUCCUUUUUGGCAUGA	1371
1689660	1689658	1689659	GCAUGUCUGGUGAAAAGCUAA	1372
1689663	1689661	1689662	AAGCUACAAGGUUCACAGGGA	1373
1689666	1689664	1689665	CAGGGCCAAAUAUUCUCCCUA	1374
1689669	1689667	1689668	UCCCUUUUGUUCUCUAAACAA	1375
1689672	1689670	1689671	AAACAUGUUGCACACAUAAAA	1376
1689675	1689673	1689674	AUAAACUCAAGGGAGUGAUUA	1377
1689678	1689676	1689677	UGAUUUCGGUUCCUAAGUCCA	1378
1689681	1689679	1689680	AGUCCUAGGGAGUUCUAUUCA	1379
1689684	1689682	1689683	UAUUCCAUUUAUUCUGAUGUA	1380
1689687	1689685	1689686	GAUGUCCCUUUUAAGGAGGAA	1381
1689690	1689688	1689689	GAGGAGUUGGUGUUGAAGUGA	1382
1689693	1689691	1689692	AAGUGUGACAUGCUUUAAUGA	1383
1689696	1689694	1689695	UAAUGAUAACUGCUUUGGCAA	1384
1689699	1689697	1689698	UGGCAAUUCCCCAGACAGGUA	1385
1689702	1689700	1689701	CAGGUAUACUUCUUCAUCCAA	1386
1689705	1689703	1689704	AUCCAAAAUUGCACCUAAGGA	1387
1689708	1689706	1689707	UAAGGUGUUCAUUUAGACAAA	1388
1689711	1689709	1689710	GACAAAAUUGUUCGCUUAGUA	1389
1689714	1689712	1689713	UUAGUGAUCCACUGAUCUCUA	1390
1689717	1689715	1689716	UCUCUAAUCAGAAAUAUUUUA	1391
1689720	1689718	1689719	GAAAUAUUUUUAAAAAAUACA	1392
1689723	1689721	1689722	AAUACAAUUUAGAUCUCUGAA	1393
1689726	1689724	1689725	UCUGAAAAUUGGAACCACUCA	1394
1689729	1689727	1689728	CACUCAAGAGUAUCAUCUUGA	1395
1689732	1689730	1689731	UCUUGAUAGUGUUACUUCAGA	1396
1689735	1689733	1689734	UUCAGCAUAUGACUGACUGAA	1397
1689738	1689736	1689737	ACUGAUUUUAUGAAGGGAGUA	1398
1689741	1689739	1689740	GGAGUUUAGCUGACUUUUCCA	1399
1689744	1689742	1689743	UUUCCCUGUAGCCCUAUCAUA	1400
1689747	1689745	1689746	AUCAUAUUAAAAACAAAAAGA	1401
1689750	1689748	1689749	AAAAGUGGUCCACUUGAAGCA	1402

1689753	1689751	1689752	UUGAAGCAGCAAGGACAAAGA	1403
1689756	1689754	1689755	GGACAAAGGGCAGUUUAGGGA	1404
1689759	1689757	1689758	UUGGGCAUCCAGAGUGGAAAA	1405
1689762	1689760	1689761	GGAAAAGGAUUAUUAUUGUAA	1406
1689765	1689763	1689764	UUGUACAUAAUAGCAGUUCUA	1407
1689768	1689766	1689767	GUUCUGGCUGGAAUUCCAAUA	1408
1689771	1689769	1689770	CCAAUCCACUUUCUGGGGAUA	1409
1689774	1689772	1689773	GGGAUCAUUUUGAUGUUGAAA	1410
1689777	1689775	1689776	UUGAAUGUUCCCCCAAAGCAA	1411
1689780	1689778	1689779	AAGCAUUCUGACAAGUUUGGA	1412
1689783	1689781	1689782	UUUGGUCCACUUGGCUCUUUA	1413
1689786	1689784	1689785	UCUUUACCCCGGGUAAUAAGA	1414
1689789	1689787	1689788	AUAAGACCCUUAUUGACUUUA	1415
1689792	1689790	1689791	ACUUUGAAAAACUGGCAUAAA	1416
1689795	1689793	1689794	CAUAAAUGAGCUUAAGAAAUA	1417
1689798	1689796	1689797	GAAAUCCAUUGUAUACAGUCA	1418
1689801	1689799	1689800	CAGUCCUAGUGUUUGCCUUCA	1419
1689804	1689802	1689803	CCUUCUUGGUAAAAUUACAUA	1420
1689807	1689805	1689806	UACAUUUAAGGAUGUCAUUUA	1421
1689810	1689808	1689809	CAUUUCAUGAGUCAAAUUGUA	1422
1689813	1689811	1689812	AUUGUAUCUGCUGACACUGAA	1423
1689816	1689814	1689815	ACUGAAGUGUAUUGAGAUGUA	1424
1689819	1689817	1689818	GAUGUUGUUCUUUAGUUUAAA	1425
1689822	1689820	1689821	UUUAAGUAUGUAACAAAGUAA	1426
1689825	1689823	1689824	AAGUAAUAUUCAAAGGGGAUA	1427
1689828	1689826	1689827	UCAAAGGGGAUGUUUGGGGGA	1428
1689831	1689829	1689830	ACCGGGUGGCUUUAUAUUGAA	1429
1689834	1689832	1689833	AUUGAUAAUGAAAUAUUCCAA	1430
1689837	1689835	1689836	UUCCAGAGCAAAACACAUUGA	1431
1689840	1689838	1689839	CAUUGUCCUAAUGAAGUUGUA	1432
1689843	1689841	1689842	GUUGUUGCAGCUCUCUUCGUA	1433
1689846	1689844	1689845	UCUUCGUUUUCUUGUGCCGCA	1434
1689849	1689847	1689848	UUCUUGUGCCGCUGGAAUUGA	1435
1689852	1689850	1689851	GAAUUGGCUUGUGGGUCACUA	1436
1689855	1689853	1689854	UCACUUGUUGUGCAAAAGUGA	1437
1689858	1689856	1689857	AAGUGAAUUAAUUUCAAAUAA	1438
1689861	1689859	1689860	AAAUAGGAAUCAUAUUGCUUA	1439
1689864	1689862	1689863	UGCUUUUGUGAAACAAAGAAA	1440
1689867	1689865	1689866	AAGAAAAUUUACCACCUUGUA	1441
1689870	1689868	1689869	CUUGUCUGAUACAUAGAUUGA	1442
1689873	1689871	1689872	GAUUGGAAGGCGCUCUUGGUA	1443
1689876	1689874	1689875	UUGGUAAAGAAUAACCCACAA	1444
1689879	1689877	1689878	CCACAAACACCUGAUCUUGAA	1445
1689882	1689880	1689881	CUUGAUUGGAAAGCAUUGUAA	1446
1689885	1689883	1689884	UUGUAGGUCAUUAGGGAAAAA	1447

1689888	1689886	1689887	GAAAACUGAUGAUGCUGACUA	1448
1689891	1689889	1689890	AUGAUGCUGACUGUUGCUCCA	1449
1689894	1689892	1689893	GCUCCAGCUGUGUUGGCAAUA	1450
1689897	1689895	1689896	GCAAUUCAAGAUGACCUUGUA	1451
1689900	1689898	1689899	CUUGUUACUAACUGAAAGUUA	1452
1689903	1689901	1689902	AAGUUGCUGUCAACCUUAGCA	1453
1689906	1689904	1689905	UUAGCAAACAAACCAGCUAAA	1454
1689909	1689907	1689908	GCUAACACCAUUACAGCACUA	1455
1689912	1689910	1689911	GCACUGGUUAAGUAGAUUUUA	1456
1689915	1689913	1689914	AUUUUUACUGGCACUGGCUGA	1457
1689918	1689916	1689917	CAGCUGAGGAAGGCUAGGAUA	1458
1689921	1689919	1689920	AGGAUACAGACUUUAAUGACA	1459
1689924	1689922	1689923	AUGACCAAGAGCCAGACUAGA	1460
1689927	1689925	1689926	ACUAGCUCGAGCUAGAAAUCA	1461
1689930	1689928	1689929	AAAUCAGCAACAAAUACCUCA	1462
1689933	1689931	1689932	ACCUCCUUGUGCUAUUUGAAA	1463
1689936	1689934	1689935	UUGAAUGCUAAGGUAUUAGUA	1464
1689939	1689937	1689938	UUAGUUGCAAUAGGCUUACGA	1465
1689942	1689940	1689941	UUGCAAUAGGCUUACGCCUUA	1466
1689945	1689943	1689944	GAAUGAGCCUGAUGACACUAA	1467
1689948	1689946	1689947	CACUAUUACUGUUUACCUGUA	1468
1689951	1689949	1689950	CCUGUCAAACCAGGGUGGAAA	1469
1689954	1689952	1689953	UGGAAAUUUAGAGGGAUGCAA	1470
1689957	1689955	1689956	AUGCAAGUACAGUAUGUCUCA	1471
1689960	1689958	1689959	GUCUCAUUAAGCAGUCUCUGA	1472
1689963	1689961	1689962	CUCUGUUGCUGAUUAUAUGAA	1473
1689966	1689964	1689965	UAUGAAGAUAAAAUUGUUGUA	1474
1689969	1689967	1689968	GUUGUAUAUGCUGAUCUGUAA	1475
1689972	1689970	1689971	CUGUAUGUUAUGUACAUUUUA	1476
1689975	1689973	1689974	AUUUUCACAGUGAUUGAAUCA	1477
1689978	1689976	1689977	GAAUCAUUGUAAAAAGAAAAA	1478
1689981	1689979	1689980	GAAAAAAGACAAAAAAGAAUA	1479
1689984	1689982	1689983	AGAAUCACCACUGUCUAUUUA	1480
1689987	1689985	1689986	UAUUUUAUGAAGAUGAUAAAA	1481
1689990	1689988	1689989	AUAAAGCAGCUUUAUUAAAUA	1482
1689993	1689991	1689992	UAAAUUAUUACAGUUAUGUUA	1483
1689996	1689994	1689995	AUGUUUCAAAUGGUGUUAUCA	1484
1689999	1689997	1689998	UUAUCUGCCACAUUGUUUCCA	1485
1690002	1690000	1690001	UUUCCUUUUAUCUGGUGGUUA	1486
1690005	1690003	1690004	UCUGGUGGUUCUCUGUUUCCA	1487
1690008	1690006	1690007	UUUCCCCCUUUAAAUGUGUUA	1488
1690011	1690009	1690010	GUGUUUUCUCUGCUUCAAAAA	1489
1690014	1690012	1690013	CAAAAAUUUAAUGCAUUUUAA	1490
1690017	1690015	1690016	UUUUAGUAUUAAAGGCUAUUA	1491
1690020	1690018	1690019	UCCUGCCUUUCAGUGGUCUGA	1492

1690023	1690021	1690022	UAAGGCAGUAGGGAUGGGGUA	1493
1690026	1690024	1690025	ACCCCACCUUCUCCUUUUUGA	1494
1690029	1690027	1690028	AUGUUUGGGGGUGGGGCUGGA	1495
1690032	1690030	1690031	CUCUAGUGAGGGGAAUGAGCA	1496

Example 7: Effect of RNAi compounds on human PCDH19 *in vitro*, single dose

Double-stranded RNAi compounds described above are tested in a series of experiments for their single dose effects on PCDH19 RNA *in vitro* in cultured cells that express PCDH19.

Cultured cells are treated with double-stranded RNAi. RNA is isolated from the cells and PCDH19 RNA levels are measured by quantitative real-time RTPCR. A human PCDH19 primer-probe set is used to measure RNA levels. PCDH19 RNA levels are normalized to total RNA content, as measured by RIBOGREEN®.

Example 8: Effect of modified oligonucleotides on human PCDH19 RNA levels in neurons differentiated from IPS cells, multiple dose

Modified oligonucleotides selected from the examples above were tested at various doses in neurons differentiated from IPSCs (Gibco, Cat. # A18945). The IPSCs were differentiated into neurons using the Elixirgen Scientific Quick Neuron™ Excitatory kit (Cat.# EX-SeV-L) . The neurons were aged for 2 weeks, and were treated by free uptake with various concentrations of modified oligonucleotide as specified in the tables below.

Seven days post treatment total RNA was isolated from the cells, and PCDH19 RNA levels were measured by quantitative real-time RT-PCR. Human PCDH19 primer-probe set RTS53390 (described herein above) was used to measure RNA levels as described above. PCDH19 RNA levels were normalized to total RNA content, as measured by human GAPDH. Human GAPDH was amplified using human primer probe set RTS104 (described herein above). Reduction of PCDH19 RNA is presented in the tables below as percent PCDH19 RNA, relative to the amount of PCDH19 in untreated control cells (% UTC).

The half maximal inhibitory concentration (IC_{50}) of each modified oligonucleotide was calculated using GraphPad Prism and is also presented in the tables below.

Table 10

Effect of modified oligonucleotides on human PCDH19 RNA levels in neurons differentiated from IPS cells

Compound No.	PCDH19 RNA (% UTC)				IC_{50} (µM)
	40 nM	200 nM	1000 nM	5000 nM	
1626339	82	63	33	16	0.28
1626361	96	57	34	20	0.18

Table 11

Effect of modified oligonucleotides on human PCDH19 RNA levels in neurons differentiated from IPS cells

Compound No.	PCDH19 RNA (% UTC)					IC_{50} (µM)
	32 nM	160 nM	800 nM	4000 nM	20000 nM	
1653817	101	96	89	93	52	18.36
1653823	102	84	78	50	26	2.47
1653827	84	87	79	59	28	4.37

Example 9: Effect of modified oligonucleotides on human PCDH19 protein levels in neurons differentiated from IPS cells, multiple dose

Modified oligonucleotides selected from the examples above were tested at various doses in neurons differentiated from IPSCs (neurons derived as described herein above). The neurons were aged for 2 weeks, and were treated by free uptake with various concentrations of modified oligonucleotide as specified in the table below.

Seven days post treatment, human PCDH19 protein levels in the treated neurons were determined using western blot analysis, detecting PCDH19 using a PCDH19 polyclonal antibody from Bethyl Laboratories (cat. # A304-468A). Reduction of PCDH19 protein is presented in the table below as percent PCDH19 protein relative to the amount of PCDH19 in untreated control cells (% UTC).

Table 12

Effect of modified oligonucleotides on human PCDH19 protein levels in neurons differentiated from IPS cells

Compound No.	Dose (nM)	PCDH19 Protein (% UTC)
1626339	5000	19
1626361	5000	28
1653817	20000	85
1653823	20000	52
1653827	20000	48

Example 10: Effect of RNAi compounds that target a human PCDH19 nucleic acid, *in vitro*, single dose

RNAi compounds described in the example above were tested for their single dose effects on PCDH19 RNA *in vitro*. The RNAi compounds were tested in a series of experiments that had the same culture conditions.

Cultured HEK293 cells were treated with RNAi compounds at a concentration of 200 nM by Lipofectamine RNAiMAX at a density of 10,000 cells per well. After a treatment period of 72 hours, total RNA was isolated from the cells and PCDH19 RNA levels were measured by quantitative real-time RT-PCR using human primer-probe set RTS53390 (described herein above). PCDH19 RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of PCDH19 RNA is presented in the table below as percent PCDH19 RNA relative to the amount in untreated control cells (% UTC). The values marked with a "†" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of the modified oligonucleotides complementary to the amplicon region. Each table below represents a separate experiment.

Table 13

Reduction of PCDH19 RNA by RNAi compounds at a concentration of 200 nM in HEK293 cells

Compound No.	PCDH19 RNA (% UTC)
1688359	26
1688389	61
1688404	71
1688431	45

1688440	43
1688443	46
1688464	25
1688467	35
1688494	34
1688521	17
1688524	132
1688542	66
1688581	54
1688599	66
1688946	24
1688949	29
1688961	17
1688973	2†
1688985	9†
1689000	59
1689015	26
1689024	79
1689063	14
1689069	76
1689096	48
1689129	11
1689132	26
1689153	37
1689168	26
1689183	36
1689195	44
1689204	27
1689213	22
1689231	35
1689243	21
1689258	34
1689270	19
1689276	32
1689282	33
1689285	52
1689297	29
1689306	24
1689333	39
1689351	36
1689381	24
1689411	26
1689414	44
1689453	34
1689459	21
1689465	27
1689489	33
1689501	36

1689504	20
1689531	51
1689546	38
1689552	31
1689555	24
1689576	17
1689603	109
1689633	29
1689684	47
1689726	52
1689744	97
1689783	47
1689801	37
1689804	34
1689819	21
1689825	69
1689837	39
1689858	59
1689861	88
1689870	46
1689915	69
1689939	45
1690002	25
1690005	40
1690008	64
1690032	79

Table 14

Reduction of PCDH19 RNA by RNAi compounds at a concentration of 200 nM in HEK293 cells

Compound No.	PCDH19 RNA (% UTC)
1688317	70
1688320	37
1688335	41
1688338	59
1688347	44
1688353	72
1688392	48
1688395	26
1688407	31
1688425	18
1688434	32
1688446	77
1688476	65
1688485	22
1688509	33
1688578	65
1688584	78

1688596	62
1688614	12
1688620	45
1688958	95
1688967	15
1688979	10†
1688991	7†
1689033	50
1689042	69
1689057	21
1689087	13
1689105	10
1689123	41
1689138	20
1689159	23
1689174	31
1689273	32
1689288	24
1689309	32
1689312	36
1689315	18
1689321	39
1689327	92
1689339	45
1689354	31
1689363	47
1689366	36
1689378	31
1689432	24
1689468	25
1689480	19
1689528	24
1689534	111
1689564	36
1689600	41
1689624	45
1689627	29
1689645	62
1689648	247
1689660	37
1689663	43
1689705	86
1689711	38
1689723	31
1689732	33
1689765	29

1689777	45
1689789	54
1689798	23
1689822	16
1689834	28
1689843	70
1689927	32
1689957	37
1689972	27
1689975	16
1689981	39
1689990	73
1690011	34
1690017	33
1690023	170

Table 15

Reduction of PCDH19 RNA by RNAi compounds at a concentration of 200 nM in HEK293 cells

Compound No.	**PCDH19 RNA (% UTC)**
1688344	37
1688380	107
1688386	47
1688437	91
1688461	76
1688470	39
1688479	51
1688488	97
1688491	19
1688500	32
1688515	52
1688518	51
1688539	46
1688554	32
1688569	43
1688587	74
1688605	47
1688611	22
1688623	82
1688970	53†
1688994	17†
1689036	38
1689075	32
1689144	43
1689165	21
1689192	24
1689210	19

1689222	15
1689249	32
1689252	75
1689291	24
1689294	23
1689303	27
1689324	36
1689342	20
1689360	34
1689369	17
1689375	25
1689393	26
1689408	40
1689423	30
1689438	36
1689441	45
1689456	33
1689462	37
1689486	51
1689498	22
1689543	30
1689561	26
1689579	95
1689597	51
1689609	51
1689618	20
1689630	42
1689636	45
1689675	42
1689714	44
1689720	90
1689735	41
1689762	59
1689768	26
1689771	128
1689816	38
1689831	31
1689852	51
1689891	41
1689894	147
1689897	54
1689909	44
1689912	49
1689936	53
1689951	47
1689960	32

1689966	24
1689993	47
1689996	38
1689999	37
1690029	85

Table 16

Reduction of PCDH19 RNA by RNAi compounds at a concentration of 200 nM in HEK293 cells

Compound No.	PCDH19 RNA (% UTC)
1688314	38
1688323	54
1688329	44
1688350	60
1688356	30
1688365	26
1688368	43
1688383	35
1688401	15
1688410	24
1688413	45
1688416	38
1688428	81
1688449	26
1688473	18
1688503	53
1688545	18
1688548	26
1688560	51
1689003	31
1689018	75
1689021	22
1689027	52
1689030	45
1689048	37
1689054	24
1689078	17
1689081	17
1689099	30
1689108	33
1689111	20
1689114	50
1689147	18
1689162	21
1689171	31
1689177	21
1689180	23

1689216	39
1689237	18
1689264	53
1689279	40
1689300	55
1689318	46
1689336	42
1689348	31
1689357	33
1689387	29
1689390	36
1689426	47
1689444	39
1689447	27
1689483	30
1689549	30
1689570	42
1689582	74
1689612	39
1689615	39
1689639	42
1689654	79
1689699	57
1689702	23
1689747	80
1689753	35
1689774	39
1689810	23
1689828	50
1689849	54
1689855	57
1689864	35
1689867	94
1689888	87
1689900	25
1689918	36
1689924	50
1689948	22
1689963	36
1689978	35
1689984	30

Table 17

Reduction of PCDH19 RNA by RNAi compounds at a concentration of 200 nM in HEK293 cells

Compound No.	PCDH19 RNA (% UTC)
1688326	36

1688332	45
1688341	118
1688371	85
1688377	58
1688419	45
1688422	61
1688452	72
1688455	51
1688497	25
1688512	25
1688530	38
1688551	65
1688566	14
1688572	18
1688602	32
1688608	28
1688617	5
1688626	25
1688955	34
1688964	49
1688988	1†
1688997	11†
1689006	76
1689012	51
1689039	26
1689060	18
1689072	13
1689090	14
1689093	54
1689117	54
1689120	24
1689126	21
1689141	21
1689186	35
1689198	32
1689201	29
1689228	16
1689234	26
1689255	43
1689267	14
1689345	25
1689396	41
1689399	24
1689402	33
1689405	54
1689435	13

1689450	30
1689471	42
1689477	46
1689492	56
1689495	33
1689507	45
1689510	11
1689513	45
1689558	30
1689585	61
1689606	27
1689621	54
1689657	82
1689678	25
1689693	38
1689696	32
1689717	47
1689756	65
1689759	37
1689780	53
1689840	32
1689873	59
1689876	33
1689882	39
1689885	68
1689903	25
1689906	36
1689933	52
1689942	50
1689954	46
1689987	60

Table 18

Reduction of PCDH19 RNA by RNAi compounds at a concentration of 200 nM in HEK293 cells

Compound No.	PCDH19 RNA (% UTC)
1688362	27
1688374	47
1688398	80
1688458	44
1688482	44
1688506	37
1688527	129
1688533	40
1688536	44
1688557	31
1688563	26

1688575	114
1688590	86
1688593	126
1688952	22
1688976	3†
1688982	0†
1689009	38
1689045	12
1689051	51
1689066	77
1689084	21
1689102	32
1689135	18
1689150	21
1689156	25
1689189	16
1689207	13
1689219	15
1689225	45
1689240	21
1689246	32
1689261	15
1689330	33
1689372	28
1689384	42
1689417	45
1689420	26
1689429	57
1689474	63
1689516	33
1689519	21
1689522	22
1689525	29
1689537	61
1689540	33
1689567	26
1689573	32
1689588	35
1689591	27
1689594	27
1689642	50
1689651	48
1689666	69
1689669	31
1689672	47
1689681	34

1689687	37
1689690	81
1689708	29
1689729	65
1689738	43
1689741	34
1689750	15
1689786	48
1689792	74
1689795	38
1689807	19
1689813	27
1689846	19
1689879	34
1689921	38
1689930	36
1689945	33
1689969	24
1690014	105
1690020	31
1690026	67

CLAIMS:

1. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion of an PCDH19 nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar and a modified internucleoside linkage.

2. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of SEQ ID NOs: 15-482, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar and a modified internucleoside linkage.

3. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, or 16 contiguous nucleobases of any of SEQ ID NOs: 15-560, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar and a modified internucleoside linkage.

4. The oligomeric compound of claim 2 or claim 3, wherein the modified oligonucleotide has a nucleobase sequence consisting of the nucleobase sequence of any of SEQ ID NOs: 15-560.

5. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 contiguous nucleobases of any of SEQ ID NOs: 561-1028, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar and a modified internucleoside linkage.

6. The oligomeric compound of claim 5, wherein the modified oligonucleotide has a nucleobase sequence consisting of the nucleobase sequence of any of SEQ ID NOs: 561-1028.

7. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases complementary to:

an equal length portion of nucleobases 4,743-4,767 of SEQ ID NO: 1;

an equal length portion of nucleobases 12,319-12,346 of SEQ ID NO: 1;

an equal length portion of nucleobases 34,364-34,389 of SEQ ID NO: 1; or

an equal length portion of nucleobases 84,408-84,431 of SEQ ID NO: 1;

wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar and a modified internucleoside linkage.

8. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of a sequence selected from:

SEQ ID NO: 132, 228, 284, 330, or 440;

SEQ ID NO: 416, 72, 129, or 204;

SEQ ID NO: 371, 425, 20, or 111; or

SEQ ID NO: 367, 407, 24, 93, or 218;

wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar and a modified internucleoside linkage.

9. The oligomeric compound of any of claims 1-8, wherein the nucleobase sequence of the modified oligonucleotide is at least 80%, 85%, 90%, 95%, or 100% complementary to any of the nucleobase sequences of SEQ ID NO: 1 or SEQ ID NO: 2 when measured across the entire nucleobase sequence of the modified oligonucleotide.

10. The oligomeric compound of any of claims 1-9, wherein the modified oligonucleotide consists of 12 to 20, 12 to 25, 12 to 30, 12 to 50, 13 to 20, 13 to 25, 13 to 30, 13 to 50, 14 to 20, 14 to 25, 14 to 30, 14 to 50, 15 to 20, 15 to 25, 15 to 30, 15 to 50, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 16 to 50, 17 to 20, 17 to 25, 17 to 30, 17 to 50, 18 to 20, 18 to 25, 18 to 30, 18 to 50, 19 to 20, 19 to 25, 19 to 30, 19 to 50, 20 to 25, 20 to 30, 20 to 50, 21 to 25, 21 to 30, 21 to 50, 22 to 25, 22 to 30, 22 to 50, 23 to 25, 23 to 30, or 23 to 50 linked nucleosides.

11. The oligomeric compound of any of claims 1-10, wherein the modified oligonucleotide comprises at least one modified nucleoside.

12. The oligomeric compound of claim 11, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.

13. The oligomeric compound of claim 12, wherein the modified sugar moiety comprises a bicyclic sugar moiety.

14. The oligomeric compound of claim 13, wherein the bicyclic sugar moiety comprises a 2'-4' bridge selected from –O-CH_2-; and –O-$CH(CH_3)$-.

15. The oligomeric compound of any of claims 11-14, wherein at least one modified nucleoside of the modified oligonucleotide comprises a non-bicyclic modified sugar moiety.

16. The oligomeric compound of claim 15, wherein at least one modified nucleoside of the modified oligonucleotide comprises a bicyclic sugar moiety having a 2'-4' bridge and at least one nucleoside comprising a non-bicyclic modified sugar moiety.

17. The oligomeric compound of claim 15 or claim 16, wherein the non-bicyclic modified sugar moiety is a 2'-O$(CH_2)_2$-OCH_3 ribosyl sugar moiety, a 2'-OMe sugar moiety, or a 2'-F sugar moiety.

18. The oligomeric compound of any of claims 1-17, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.

19. The oligomeric compound of claim 18, wherein at least one modified nucleoside of the modified oligonucleotide comprises a sugar surrogate selected from morpholino and PNA.

20. The oligomeric compound of any of claims 1-19, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

21. The oligomeric compound of claim 20, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

22. The oligomeric compound of claim 20 or claim 21, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.

23. The oligomeric compound of claim 20 or 22, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

24. The oligomeric compound of any of claims 20, 22, or 23, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.

25. The oligomeric compound of any of claims 20 or 22-24, wherein at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, or at least 19 internucleoside linkages of the modified oligonucleotide are phosphorothioate internucleoside linkages.

26. The oligomeric compound of any of claims 20-22, 24, or 25, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

27. The oligomeric compound of any of claims 20 or 22-26, wherein the internucleoside linkage motif of the modified oligonucleotide is selected from: 5'- sssssssssssssssss -3', 5'- sssssssssssssss -3', 5'- soooossssssssssooss-3', and ssooooooooooooooooooss; wherein each 'o' represents a phosphodiester internucleoside linkage and each 's' represents a phosphorothioate internucleoside linkage.

28. The oligomeric compound of any of claims 1-27, wherein the modified oligonucleotide comprises a modified nucleobase.

29. The oligomeric compound of claim 28, wherein the modified nucleobase is a 5-methylcytosine.

30. The oligomeric compound of any of claims 1-29, wherein the oligomeric compound comprises a modified oligonucleotide consisting of 12-22, 12-20, 14-18, 14-20, 15-17, 15-25, 16-20, 16-18, 18-22, 18-25, 18-20, 20-25, or 21-23 linked nucleosides, or a pharmaceutically acceptable salt thereof.

31. The oligomeric compound of claim 30, wherein the modified oligonucleotide is a pharmaceutically acceptable salt comprising one or more cations selected from sodium, potassium, calcium, and magnesium.

32. The oligomeric compound of any of claims 1-31, wherein the modified oligonucleotide consists of 16 linked nucleosides.

33. The oligomeric compound of any of claims 1-31, wherein the modified oligonucleotide consists of 18 linked nucleosides.

34. The oligomeric compound of any of claims 1-31, wherein the modified oligonucleotide consists of 20 linked nucleosides.

35. The oligomeric compound of any of claims 1-31, wherein the modified oligonucleotide consists of 21 linked nucleosides.

36. The oligomeric compound of any of claims 1-31, wherein the modified oligonucleotide consists of 23 linked nucleosides.

37. The oligomeric compound of any of claims 1-35, wherein the oligomeric compound activates RNase H.

38. The oligomeric compound of claim 37, wherein the modified oligonucleotide is a gapmer.

39. The oligomeric compound of any of claims 1-34, wherein the modified oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 1-6 linked 5'-region nucleosides;

a central region consisting of 6-10 linked central region nucleosides; and

a 3'-region consisting of 1-6 linked 3'-region nucleosides;

wherein the 3'-most nucleoside of the 5'-region and the 5'-most nucleoside of the 3'-region comprise modified sugar moieties, and

each of the central region nucleosides is selected from a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety and a nucleoside comprising a 2'-substituted sugar moiety, wherein the central region comprises at least six nucleosides comprising a 2'-β-D-deoxyribosyl sugar moiety and no more than two nucleosides comprising a 2'-substituted sugar moiety.

40. The oligomeric compound of any of claims 1-39, wherein the modified oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 1-6 linked 5'-region nucleosides;

a central region consisting of 6-10 linked central region nucleosides; and

a 3'-region consisting of 1-6 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a modified sugar moiety and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

41. The oligomeric compound of claim 40, wherein the modified oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 5 linked 5'-region nucleosides;

a central region consisting of 10 linked central region nucleosides; and

a 3'-region consisting of 5 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-$O(CH_2)_2$-OCH_3 ribosyl modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

42. The oligomeric compound of claim 40, wherein the modified oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 3 linked 5'-region nucleosides;

a central region consisting of 10 linked central region nucleosides; and

a 3'-region consisting of 3 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a cEt sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

43. A chirally enriched population of oligomeric compounds of any of claims 1-42, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

44. The chirally enriched population of claim 43, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the *(Sp)* or *(Rp)* configuration.

45. The chirally enriched population of claim 43, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

46. The chirally enriched population of claim 43, wherein the population is enriched for modified oligonucleotides having the *(Rp)* configuration at one particular phosphorothioate internucleoside linkage and the *(Sp)* configuration at each of the remaining phosphorothioate internucleoside linkages.

47. The chirally enriched population of claim 43, wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the *Sp*, *Sp*, and *Rp* configurations, in the 5' to 3' direction.

48. A population of oligomeric compounds of any of claims 1-42, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

49. An oligomeric duplex, comprising a first oligomeric compound and a second oligomeric compound comprising a second modified oligonucleotide, wherein the first oligomeric compound is an oligomeric compound of any of claims 1-42.

50. The oligomeric duplex of claim 49, wherein the second oligomeric compound comprises a second modified oligonucleotide consisting of 12 to 50 linked nucleosides, and wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 12 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

51. An oligomeric duplex comprising:

a first oligomeric compound comprising a first modified oligonucleotide consisting of 19 to 30 linked nucleosides wherein the nucleobase sequence of the first modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 contiguous nucleobases of the nucleobase sequence of any of SEQ ID NOs: 561-1028; and

a second oligomeric compound comprising a second modified oligonucleotide consisting of 15 to 30 linked nucleosides wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 12 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

52. An oligomeric duplex comprising:

a first oligomeric compound comprising a first modified oligonucleotide consisting of 19 to 30 linked nucleosides wherein the nucleobase sequence of the first modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 contiguous nucleobases of the nucleobase sequence of any of SEQ ID NOs: 561-1028; and

a second oligomeric compound comprising a second modified oligonucleotide consisting of 15 to 30 linked nucleosides wherein the nucleobase sequence of the second modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, or at least 21 contiguous nucleobases of the nucleobase sequence of any of SEQ ID NOs: 1029-1496, wherein the nucleobase sequence of the second modified oligonucleotide is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

53. An oligomeric duplex comprising:

a first oligomeric compound comprising a first modified oligonucleotide consisting of 23 linked nucleosides wherein the nucleobase sequence of the first modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 561-1028; and

a second oligomeric compound comprising a second modified oligonucleotide consisting of 21 linked nucleosides wherein the nucleobase sequence of the second modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 1029-1496, wherein the nucleobase sequence of the second modified oligonucleotide is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

54. The oligomeric duplex of any of claims 49-53, wherein the modified oligonucleotide of the first oligomeric compound comprises a 5'-stabilized phosphate group.

55. The oligomeric duplex of claim 54, wherein the 5'-stabilized phosphate group comprises a cyclopropyl phosphonate or a vinyl phosphonate.

56. The oligomeric duplex of any of claims 49-53, wherein the modified oligonucleotide of the first oligomeric compound comprises a glycol nucleic acid (GNA) sugar surrogate.

57. The oligomeric duplex of any of claims 49-55, wherein the modified oligonucleotide of the first oligomeric compound comprises a 2'-NMA sugar moiety.

58. The oligomeric duplex of any of claims 49-57, wherein at least one nucleoside of the second modified oligonucleotide comprises a modified sugar moiety.

59. The oligomeric duplex of claim 58, wherein the modified sugar moiety of the second modified oligonucleotide comprises a bicyclic sugar moiety.

60. The oligomeric duplex of claim 59, wherein the bicyclic sugar moiety of the second modified oligonucleotide comprises a 2'-4' bridge selected from $-O-CH_2-$; and $-O-CH(CH_3)-$.

61. The oligomeric duplex of claim 59 or claim 60, wherein the modified sugar moiety of the second modified oligonucleotide comprises a non-bicyclic modified sugar moiety.

62. The oligomeric duplex of claim 61, wherein the non-bicyclic modified sugar moiety of the second modified oligonucleotide is a 2'-MOE sugar moiety, a 2'-F sugar moiety, or 2'-OMe sugar moiety.

63. The oligomeric duplex of any of claims 49-62, wherein at least one nucleoside of the second modified oligonucleotide comprises a sugar surrogate.

64. The oligomeric duplex of any of claims 49-63, wherein the second modified oligonucleotide comprises at least one modified internucleoside linkage.

65. The oligomeric duplex of claim 64, wherein at least one modified internucleoside linkage of the second modified oligonucleotide is a phosphorothioate internucleoside linkage.

66. The oligomeric duplex of any of claims 49-65, wherein the second modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

67. The oligomeric duplex of any of claims 49-66, wherein each internucleoside linkage of the second modified oligonucleotide is independently selected from a phosphodiester or a phosphorothioate internucleoside linkage.

68. The oligomeric duplex of any of claims 49-67, wherein the internucleoside linkage motif of the first modified oligonucleotide is ssooooooooooooooooooss and the internucleoside linkage motif of the second modified oligonucleotide is ssooooooooooooooooss, wherein each "o" represents a phosphodiester internucleoside linkage and each "s" represents a phosphorothioate internucleoside linkage.

69. The oligomeric duplex of any of claims 49-68, wherein the second modified oligonucleotide comprises at least one modified nucleobase.

70. The oligomeric duplex of claim 69, wherein the modified nucleobase of the second modified oligonucleotide is 5-methylcytosine.

71. The oligomeric duplex of any of claims 49-70, wherein the second modified oligonucleotide comprises a conjugate group.

72. The oligomeric duplex of claim 71, wherein the conjugate group comprises a conjugate linker and a conjugate moiety.

73. The oligomeric duplex of claim 71 or claim 72, wherein the conjugate group is attached to the second modified oligonucleotide at the 5'-end of the second modified oligonucleotide.

74. The oligomeric duplex of claim 71 or claim 72, wherein the conjugate group is attached to the second modified oligonucleotide at the 3'-end of the modified oligonucleotide.

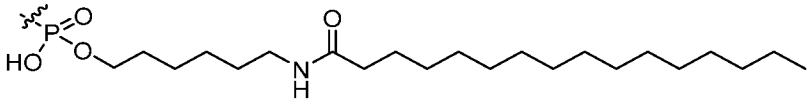
75. The oligomeric duplex of claim 71 or claim 72, wherein the conjugate group is attached to the second modified oligonucleotide through a modified internucleoside linkage.

76. The oligomeric duplex of any of claims 71-75, wherein the conjugate group comprises a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, C5 alkyl, C22 alkenyl, C20 alkenyl, C16 alkenyl, C10 alkenyl, C21 alkenyl,

C19 alkenyl, C18 alkenyl, C15 alkenyl, C14 alkenyl, C13 alkenyl, C12 alkenyl, C11 alkenyl, C9 alkenyl, C8 alkenyl, C7 alkenyl, C6 alkenyl, or C5 alkenyl.

77. The oligomeric duplex of any of claims 71-76, wherein the conjugate moiety is a 6-palmitamidohexyl conjugate moiety.

78. The oligomeric duplex of any of claims 71-74, wherein the conjugate group has the following structure:



79. The oligomeric duplex of any of claims 71-78, wherein the conjugate group comprises a cell-targeting moiety.

80. The oligomeric duplex of any of claims 49-79, wherein the second modified oligonucleotide comprises a terminal group.

81. The oligomeric duplex of claim 80, wherein the terminal group is an abasic sugar moiety.

82. The oligomeric duplex of any of claims 49-81, wherein the second modified oligonucleotide consists of 12 to 20, 12 to 25, 12 to 30, 12 to 50, 13 to 20, 13 to 25, 13 to 30, 13 to 50, 14 to 20, 14 to 25, 14 to 30, 14 to 50, 15 to 20, 15 to 25, 15 to 30, 15 to 50, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 16 to 50, 17 to 20, 17 to 25, 17 to 30, 17 to 50, 18 to 20, 18 to 25, 18 to 30, 18 to 50, 19 to 20, 19 to 25, 19 to 30, 19 to 50, 20 to 25, 20 to 30, 20 to 50, 21 to 25, 21 to 30, 21 to 50, 22 to 25, 22 to 30, 22 to 50, 23 to 25, 23 to 30, or 23 to 50 linked nucleosides.

83. The oligomeric duplex of any of claims 49-81, wherein the modified oligonucleotide of the first oligomeric compound consists of 23 linked nucleosides and the second modified oligonucleotide consists of 21 linked nucleosides.

84. The oligomeric duplex of claim 83, wherein the modified oligonucleotide of the first oligomeric compound has a sugar motif (from 5′ to 3′) of: yfyyyfyyyyyyyfyfyyyyyyy and the second modified oligonucleotide has a sugar motif (from 5′ to 3′) of: yyyyyyfyfffyyyyyyyyyy, wherein each “y” represents a 2’-OMe sugar moiety and each “f” represents a 2’-F sugar moiety.

85. An antisense agent comprising an antisense compound, wherein the antisense compound is the oligomeric compound of any of claims 1-42.

86. An antisense agent, wherein the antisense agent is the oligomeric duplex of any of claims 49-84.

87. The antisense agent of claim 85 or claim 86, wherein the antisense agent is:

iii. an RNase H agent capable of reducing the amount of PCDH19 nucleic acid through the activation of RNase H; or

iv. an RNAi agent capable of reducing the amount of PCDH19 nucleic acid through the activation of RISC/Ago2.

88. The antisense agent of any of claims 85-87, wherein the conjugate group is a cell-targeting moiety.

89. A pharmaceutical composition comprising an oligomeric compound of any of claims 1-42, a population of any of claims 43-48, an oligomeric duplex of any of claims 49-84, or an antisense agent of any of claims 85-88, and a pharmaceutically acceptable diluent.

90. The pharmaceutical composition of claim 89, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or PBS.

91. The pharmaceutical composition of claim 90, wherein the pharmaceutical composition consists essentially of the oligomeric compound, the population, the oligomeric duplex, or the antisense agent, and aCSF.

92. The pharmaceutical composition of claim 90, wherein the pharmaceutical composition consists essentially of the oligomeric compound, the population, the oligomeric duplex, or the antisense agent, and PBS.

93. A method comprising administering to a subject an oligomeric compound of any of claims 1-42, a population of any of claims 43-48, an oligomeric duplex of any of claims 49-84, an antisense agent of any of claims 85-88, or a pharmaceutical composition of any of claims 89-92.

94. The method of claim 93, wherein the subject has a disease associated with PCDH19.

95. The method of claim 93, wherein the subject has PCDH19 Epilepsy.

96. A method of treating a disease associated with PCDH19 comprising administering to a subject having or at risk for developing a disease associated with PCDH19 a therapeutically effective amount of an oligomeric compound of any of claims 1-42, a population of any of claims 43-48, an oligomeric duplex of any of claims 49-84, an antisense agent of any of claims 85-88, or a pharmaceutical composition of any of claims 89-92; and thereby treating the disease associated with PCDH19.

97. The method of claim 96, wherein the disease associated with PCDH19 is a neurodevelopmental disease.

98. The method of claim 96 or claim 97, wherein the disease associated with PCDH19 is PCDH19 Epilepsy.

99. The method of any of claims 96-98, wherein at least one symptom or hallmark of the disease associated with PCDH19 is ameliorated.

100. The method of claim 99, wherein the symptom or hallmark is seizures, cognitive impairment, intellectual disabilities, autism spectrum disorder, behavioral problems, aggression, anxiety, obsessive-compulsive disorder, hyperactivity, attention deficit disorder (ADD), or attention deficit hyperactivity disorder (ADHD).

101. The method of claim 100, wherein the seizures are any of clusters of seizures, generalized tonic-clonic seiaures, focal seizures, or bilateral seizures.

102. The method of any of claims 96-101, wherein administering an oligomeric compound of any of claims 1-42, a population of any of claims 43-48, an oligomeric duplex of any of claims 49-84, an antisense agent of any of claims 85-88, or a pharmaceutical composition of any of claims 89-92 reduces seizures, reduces or delays cognitive impairment, reduces or delays intellectual disabilities, reduces or delays symptoms of autism spectrum disorder, reduces behavioral problems, reduces aggression, reduces anxiety, reduces obsessive-compulsive behavior, reduces hyperactivity, reduces symptoms of attention deficit disorder (ADD), or reduces symptoms of attention deficit hyperactivity disorder (ADHD) in the subject.

103. The method of any of claims 93-102, wherein the subject is human.

104. A method of reducing expression of PCDH19 in a cell comprising contacting the cell with an oligomeric compound of any of claims 1-42, a population of any of claims 43-48, an oligomeric duplex of any of claims 49-84, an antisense agent of any of claims 85-88, or a pharmaceutical composition of any of claims 89-92.

105. The method of claim 104, wherein the cell is a neuron.

106. The method of claim 104 or claim 105, wherein the cell is a human cell.

107. Use of an oligomeric compound of any of claims 1-42, a population of any of claims 43-48, an oligomeric duplex of any of claims 49-84, an antisense agent of any of claims 85-88, or a pharmaceutical composition of any of claims 89-92 for treating a disease associated with PCDH19.

108. Use of an oligomeric compound of any of claims 1-42, a population of any of claims 43-48, an oligomeric duplex of any of claims 49-84, or an antisense agent of any of claims 85-88in the manufacture of a medicament for treating a disease associated with PCDH19.

109. The use of claim 107 or claim 108, wherein the disease associated with PCDH19 is PCDH19 Epilepsy.