

COMPOUNDS AND METHODS FOR MODULATING PLP1

Sequence Listing

5 The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0382WOSEQ_ST25.txt, created on June 22, 2021, which is 456 Kb in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field

10 Provided are compounds, methods, and pharmaceutical compositions for reducing the amount or activity of proteolipid protein 1 (PLP1) RNA in a cell or subject, and in certain instances reducing the amount of proteolipid protein 1 in a cell or subject. Such compounds, methods, and pharmaceutical compositions are useful to ameliorate at least one symptom or hallmark of a leukodystrophy. Such symptoms and hallmarks include hypotonia, nystagmus, optic atrophy, respiratory distress, motor delays, cognitive dysfunction, speech dysfunction, spasticity, ataxia, seizures, choreiform
15 movements, and death. Such leukodystrophies include Pelizaeus-Merzbacher disease.

Background

 Pelizaeus-Merzbacher disease (PMD) is a severe and fatal childhood X-linked leukodystrophy, associated with an extensive loss or lack of myelination of the central nervous system, and is caused by duplications or sequence
20 variations in the gene encoding proteolipid protein 1 (PLP1). Hundreds of mutations in *PLP1* have been identified, and lead to a toxic gain-of-function due to PLP1 misfolding and dysmyelination (Hobson, G., 2012, Semin. Neurol. 32, 62-67; Nevin, Z.S., 2017, American J. Hum. Genetics 100, 617-634; Sima, A.A.F., et al., 2009, Acta Neuropathologica 118, 431-439). The majority of PMD cases are due to overexpression of otherwise normal PLP1 protein, as a result of duplications or triplications of *PLP1* (Inoue, K., 2005, Neurogenetics 6, 1-16; Karim, S.A., 2010, Glia 58, 1727-1738).
25 PLP1 is expressed in myelinating oligodendrocytes and oligodendrocyte progenitor cells (OPCs) in the central nervous system (CNS), where it is responsible for about 50% of the total protein content of myelin and in Schwann cells in the peripheral nervous system (PNS) (Klugman, W., et al., 1997, Neuron 18, 59-70; Harlow, D.E., et al., 2014, J. Neurosci. 34, 1333-1343; Baumann, N., et al., 2001, Physiol. Rev. 81, 871-927).

 Because of the genetic heterogeneity associated with PMD, symptoms and hallmarks vary and have been
30 grouped into two main categories: connatal and classic. The connatal form (severe/early onset) of PMD is caused by mutations in *PLP1*, leading to dysmyelination. This most severe form of PMD leads to mortality in early childhood, typically within the first few years of life, and presents symptoms such as nystagmus and respiratory distress, extrapyramidal signs, laryngeal stridor, feeding difficulties, optic atrophy, seizures, and extreme neonatal hypotonia. The classic form, associated with PLP1 overexpression due to *PLP1* duplication or triplication, presents before the first
35 year of age with a constellation of motor delays, hypotonia, nystagmus, and/or motor delay in early childhood, with the development of progressive spasticity, ataxia, and/or choreiform movements through adolescence and early adulthood. Other PMD phenotypes include the transitional form of PMD, associated with PLP1 overexpression or with *PLP1* mutations, which combines clinical features of both the classic and connatal forms. A less severe phenotype, Spastic paraplegia type 2 (SPG2), has a later onset than classic PMD, and is associated with a mild, late-onset spasticity in the
40 legs or assorted mild peripheral neuropathies with minimal CNS deficits. Patients with *PLP1* deletions ("null" patients)

have significantly milder symptoms than patients with *PLP1* mutations or duplications, and can live until 40-60 years old. There are no approved therapies for PMD, with current therapy mainly being limited to palliative symptom management (Nevin, 2017; Inoue, 2005; Madry, J., et al., 2010, *Neurol. Neurochir. Pol.* 44, 511-515; Osorio, M.J., et al., 2017, *Stem Cells* 35, 311-315; Wang, P-J, et al., 2001, *J. Clin. Neurophys.* 18, 25-32).

5 Currently there is a lack of acceptable options for treating leukodystrophies such as PMD. It is therefore an object herein to provide compounds, methods, and pharmaceutical compositions for the treatment of such diseases.

Summary of the Invention

10 Provided herein are compounds, methods and pharmaceutical compositions for reducing the amount or activity of *PLP1* RNA, and in certain embodiments reducing the expression of proteolipid protein 1 in a cell or animal. In certain embodiments, the subject has a disease or disorder associated with overexpression of PLP1 or a mutation in PLP1. In certain embodiments, the subject has a leukodystrophy. In certain embodiments, the subject has Pelizaeus-Merzbacher disease. In certain embodiments, compounds useful for reducing the amount or activity of PLP1 RNA are oligomeric compounds. In certain embodiments, compounds useful for reducing the amount or activity of PLP1 RNA are modified oligonucleotides. In certain embodiments, compounds useful for decreasing expression of proteolipid protein 1 are oligomeric compounds. In certain embodiments, compounds useful for decreasing expression of proteolipid protein 1 are modified oligonucleotides.

15 Also provided are methods useful for ameliorating at least one symptom or hallmark of a leukodystrophy. In certain embodiments, the leukodystrophy is Pelizaeus-Merzbacher disease. In certain embodiments, the symptom or 20 hallmark includes hypotonia, nystagmus, optic atrophy, respiratory distress, motor delays, cognitive dysfunction, speech dysfunction, spasticity, ataxia, seizures, or choreiform movements.

Detailed Description of the Invention

25 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.

30 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.

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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 in the disclosure are incorporated by reference herein in their entirety.

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

5 **DEFINITIONS**

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

As used herein, “2′-MOE” means a 2′-OCH₂CH₂OCH₃ group in place of the 2′-OH group of a furanosyl sugar moiety. A “2′-MOE sugar moiety” means a sugar moiety with a 2′-OCH₂CH₂OCH₃ 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-ribose 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′-OCH₃ 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′-OCH₃ 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-ribose configuration.

As used herein, “2′-OMe nucleoside” means a nucleoside comprising a 2′-OMe sugar moiety.

As used herein, “2′-substituted nucleoside” means a nucleoside comprising a 2′-substituted 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, “5-methyl cytosine” means a cytosine modified with a methyl group attached to the 5 position. A 5-methyl cytosine is a modified nucleobase.

As used herein, “administering” means providing a pharmaceutical agent to a subject.

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.

As used herein, “antisense compound” means an oligomeric compound capable of achieving at least one antisense activity.

As used herein, “ameliorate” in reference to a treatment means improvement in at least one symptom or hallmark relative to the same symptom or hallmark in the absence of the treatment. In certain embodiments, amelioration is the reduction in the severity or frequency of a symptom or hallmark or the delayed onset or slowing of progression in the severity or frequency of a symptom or hallmark. In certain embodiments, the symptom or hallmark is one or more of hypotonia, nystagmus, optic atrophy, respiratory distress, motor delays, cognitive dysfunction, speech dysfunction, spasticity, ataxia, seizures, choreiform movements, and death.

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 moiety. In certain embodiments, the furanosyl sugar moiety is a ribosyl moiety. In certain embodiments, the bicyclic sugar moiety does not comprise a furanosyl moiety.

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-methyl cytosine (^mC) and guanine (G). Complementary oligonucleotides and/or target 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 target 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, “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, “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(CH₃)-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(CH₃)-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, "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.

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, "leukodystrophy" means a disorder due to abnormalities in the myelin sheath of neurons.

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.

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.

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

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

10 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-methyl cytosine” 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
15 contiguous nucleobases in a 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
20 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, “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
25 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,
30 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.

As used herein, “pharmaceutically acceptable carrier or diluent” means any substance suitable for use in
35 administering to a subject. 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 a subject. 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 a subject. 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, “prodrug” means a therapeutic agent in a form outside the body that is converted to a different form within a subject or cells thereof. Typically, conversion of a prodrug within the subject is facilitated by the action of an enzymes (e.g., endogenous or viral enzyme) or chemicals present in cells or tissues and/or by physiologic conditions.

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 compound” means an antisense compound 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 compounds include, but are not limited to double-stranded siRNA, single-stranded RNA (ssRNA), and microRNA, including microRNA mimics. In certain embodiments, an RNAi compound modulates the amount, activity, and/or splicing of a target nucleic acid. The term RNAi compound excludes antisense compounds that act through RNase H.

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

As used herein, “standard *in vitro* assay” means the assay described in Example 1 and reasonable variations thereof.

As used herein, “standard *in vivo* assay” means the assay described in Example 5 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” and “individual” are used interchangeably.

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-ribose sugar moiety, as found in RNA (an “unmodified RNA sugar moiety”), or a 2'-H(H) β-D-deoxyribose 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. In certain embodiments, a hallmark is apparent on a brain MRI scan.

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, "therapeutically effective amount" means an amount of a pharmaceutical agent that provides a therapeutic benefit to a subject. For example, a therapeutically effective amount improves a symptom or hallmark of a disease or disorder.

As used herein, "treating" means improving a subject's disease or disorder 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.

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 30 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 85% complementary to an equal length portion of a PLP1 nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

Embodiment 2. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 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 any of the nucleobase sequences of SEQ ID NOs: 20-2155, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

Embodiment 3. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising 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, or at least 20 contiguous nucleobases complementary to:

- 5 an equal length portion of nucleobases 9198-9222 of SEQ ID NO: 2;
- an equal length portion of nucleobases 13702-13766 of SEQ ID NO: 2;
- an equal length portion of nucleobases 14037-14062 of SEQ ID NO: 2;
- an equal length portion of nucleobases 16761-16800 of SEQ ID NO: 2;
- an equal length portion of nucleobases 17558-17602 of SEQ ID NO: 2;
- 10 an equal length portion of nucleobases 17615-17667 of SEQ ID NO: 2;
- an equal length portion of nucleobases 17853-17883 of SEQ ID NO: 2;
- an equal length portion of nucleobases 18097-18160 of SEQ ID NO: 2;
- an equal length portion of nucleobases 18206-18237 of SEQ ID NO: 2;
- an equal length portion of nucleobases 18237-18340 of SEQ ID NO: 2;
- 15 an equal length portion of nucleobases 18350-18387 of SEQ ID NO: 2;
- an equal length portion of nucleobases 18412-18469 of SEQ ID NO: 2;
- an equal length portion of nucleobases 18461-18506 of SEQ ID NO: 2;
- an equal length portion of nucleobases 18539-18579 of SEQ ID NO: 2;
- an equal length portion of nucleobases 18697-18727 of SEQ ID NO: 2;
- 20 an equal length portion of nucleobases 18755-18793 of SEQ ID NO: 2;
- an equal length portion of nucleobases 18797-18819 of SEQ ID NO: 2;
- an equal length portion of nucleobases 18839-18862 of SEQ ID NO: 2;
- an equal length portion of nucleobases 18974-19021 of SEQ ID NO: 2;
- an equal length portion of nucleobases 19028-19080 of SEQ ID NO: 2;
- 25 an equal length portion of nucleobases 19146-19173 of SEQ ID NO: 2;
- an equal length portion of nucleobases 19228-19253 of SEQ ID NO: 2;
- an equal length portion of nucleobases 19347-19393 of SEQ ID NO: 2;
- an equal length portion of nucleobases 19500-19523 of SEQ ID NO: 2; or
- an equal length portion of nucleobases 19512-19534 of SEQ ID NO: 2,
- 30 wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

Embodiment 4. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising 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, or at least 18 contiguous nucleobases of a sequence selected from:

- 35 SEQ ID NOs: 1050, 1124, 2145, 2151, 2152, 2153;
- SEQ ID NOs: 36, 86, 114, 164, 191, 242, 269, 426, 523, 602, 691, 780;
- SEQ ID NOs: 89, 167, 245, 322, 323;
- SEQ ID NOs: 720, 808, 904, 937, 1058, 1097, 1184, 1278, 1340;

- SEQ ID NOs: 40, 41, 117, 118, 195, 196, 273, 274, 588, 690;
 SEQ ID NOs: 42, 43, 119, 120, 197, 198, 275, 276, 373, 460, 1431, 1542, 1645, 1850, 1965, 2109;
 SEQ ID NOs: 1451, 1499, 1543, 1654, 1733, 2154, 2155,
 SEQ ID NOs: 200, 420, 504, 620, 646, 709, 823, 980, 1029, 1149, 1196, 1253, 1323, 1423, 1476, 1605, 1613,
 5 1728, 1832;
 SEQ ID NOs: 45, 46, 123, 124, 201, 202, 279, 280, 538, 562, 2091;
 SEQ ID NOs: 48, 49, 50, 51, 52, 53, 125, 126, 127, 128, 129, 130, 131, 203, 204, 205, 206, 207, 208, 281, 282,
 283, 284, 285, 286, 414, 459, 485, 503, 579, 580, 693, 724, 840, 873, 911, 1034, 1081, 1125, 1159, 1318, 1413,
 1513, 1548, 1672, 1701, 1794, 1868, 1958, 2002;
 10 SEQ ID NOs: 209, 287, 335, 439, 506, 606, 659, 1922, 2033, 2104;
 SEQ ID NOs: 784, 842, 869, 978, 1082, 1131, 1218, 1250, 1320, 1453, 1529, 1538, 1616, 1712, 1821;
 SEQ ID NOs: 54, 55, 132, 133, 210, 288, 419, 499, 564, 665, 764, 800, 881, 993, 1059, 1200, 1295, 1354, 1422,
 1465, 1544, 1705, 1802, 2149;
 SEQ ID NOs: 338, 438, 525, 604, 658, 758, 813, 887, 977, 1043, 1108, 1199, 1258, 1336, 1395, 1514, 1557,
 15 1668, 1697, 2089;
 SEQ ID NOs: 875, 934, 1047, 1110, 1229, 1243, 1373, 1438, 2146, 2147;
 SEQ ID NOs: 761, 798, 890, 946, 1022, 1120, 1198, 1293, 1358, 1398, 1463;
 SEQ ID NOs: 56, 134, 683, 718;
 SEQ ID NOs: 1610, 1663, 1702, 1786;
 20 SEQ ID NOs: 212, 1060, 1090, 1181, 1277, 1446, 1510, 1589, 1646, 1693, 1772, 2148;
 SEQ ID NOs: 57, 586, 666, 714, 812, 914, 951, 1052, 1138, 1162, 1248, 1363, 1455;
 SEQ ID NOs: 385, 416, 545, 621, 682, 1968, 2055, 2101, 2150;
 SEQ ID NOs: 363, 467, 541, 2008, 2111;
 SEQ ID NOs: 58, 59, 136, 213, 214, 291, 292, 383, 417, 519, 612, 671, 730, 900, 986, 1019, 1136, 1353, 1457,
 25 1504, 1546, 2093;
 SEQ ID NOs: 398, 435, 2095, 2010, 2144; or
 SEQ ID NOs: 1201, 1238, 1341, 1435,

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

- 30 Embodiment 5. The oligomeric compound of any of embodiments 1-4, wherein the modified oligonucleotide has a nucleobase sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to the nucleobase sequence of SEQ ID NO: 1 or SEQ ID NO: 2 when measured across the entire nucleobase sequence of the modified oligonucleotide.

- Embodiment 6. The oligomeric compound of any of embodiments 1-5, wherein the modified oligonucleotide
 35 comprises at least one modified nucleoside comprising a modified sugar moiety.

Embodiment 7. The oligomeric compound of embodiment 6, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.

Embodiment 8. The oligomeric compound of embodiment 7, wherein the bicyclic sugar moiety comprises a 4'-2' bridge, wherein the 4'-2' bridge is selected from -CH₂-O-; and -CH(CH₃)-O-.

Embodiment 9. The oligomeric compound of any of embodiments 6-8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.

5 Embodiment 10. The oligomeric compound of embodiment 9, wherein the non-bicyclic modified sugar moiety is a 2'-MOE sugar moiety or a 2'-OMe sugar moiety.

Embodiment 11. The oligomeric compound of any of embodiments 6-10, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.

10 Embodiment 12. The oligomeric compound of embodiment 11, wherein the sugar surrogate is any of morpholino, modified morpholino, PNA, THP, and F-HNA.

Embodiment 13. The oligomeric compound of any of embodiments 1-6 or 9-12, wherein the modified oligonucleotide does not comprise a bicyclic sugar moiety.

Embodiment 14. The oligomeric compound of any of embodiments 1-13, wherein the modified oligonucleotide is a gapmer.

15 Embodiment 15. The oligomeric compound of any of embodiments 1-14, wherein the modified oligonucleotide comprises:

a 5'-region consisting of 1-7 linked 5'-region nucleosides;
a central region consisting of 6-10 linked central region nucleosides; and
a 3'-region consisting of 1-7 linked 3'-region nucleosides; wherein
20 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'-deoxyfuranosyl sugar moiety.

Embodiment 16. The oligomeric compound of embodiment 15, wherein the modified oligonucleotide comprises:

a 5'-region consisting of 5 linked 5'-region nucleosides;
a central region consisting of 10 linked central region nucleosides; and
25 a 3'-region consisting of 5 linked 3'-region nucleosides; wherein
each of the 5'-region nucleosides and each of the 3'-region nucleosides is a 2'-MOE nucleoside, and each of the central region nucleosides is a 2'-β-D-deoxynucleoside.

Embodiment 17. The oligomeric compound of embodiment 15, wherein the modified oligonucleotide comprises:

a 5'-region consisting of 6 linked 5'-region nucleosides;
30 a central region consisting of 10 linked central region nucleosides; and
a 3'-region consisting of 4 linked 3'-region nucleosides; wherein
each of the 5'-region nucleosides and each of the 3'-region nucleosides is a 2'-MOE nucleoside, and each of the central region nucleosides is a 2'-β-D-deoxynucleoside.

Embodiment 18. The oligomeric compound of any of embodiments 1-17, wherein the modified oligonucleotide
35 comprises at least one modified internucleoside linkage.

Embodiment 19. The oligomeric compound of embodiment 18, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

Embodiment 20. The oligomeric compound of embodiment 18 or embodiment 19, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.

5 Embodiment 21. The oligomeric compound of embodiment 18 or embodiment 20 wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

Embodiment 22. The oligomeric compound of any of embodiments 18, 20, or 21, wherein each internucleoside linkage is either a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.

10 Embodiment 23. The oligomeric compound of embodiment 19, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 24. The oligomeric compound of any of embodiments 1-18 or 20-22, wherein the modified oligonucleotide has an internucleoside linkage motif of sooooooooooooo or sooooooooooooo; wherein,
s = a phosphorothioate internucleoside linkage and o = a phosphodiester internucleoside linkage.

15 Embodiment 25. The oligomeric compound of any of embodiments 1-24, wherein the modified oligonucleotide comprises at least one modified nucleobase.

Embodiment 26. The oligomeric compound of embodiment 25, wherein the modified nucleobase is a 5-methyl cytosine.

Embodiment 27. The oligomeric compound of any of embodiments 1-26, wherein the modified oligonucleotide consists of 12-30, 12-22, 12-20, 14-18, 14-20, 15-17, 15-25, 16-18, 16-20, 17-20, 18-20 or 18-22 linked nucleosides.

20 Embodiment 28. The oligomeric compound of any of embodiments 1-26, wherein the modified oligonucleotide consists of 16, 17, 18, 19, or 20 linked nucleosides.

Embodiment 29. The oligomeric compound of embodiment 28, wherein the modified oligonucleotide consists of 20 linked nucleosides.

Embodiment 30. The oligomeric compound of embodiment 28, wherein the modified oligonucleotide consists of 18 linked nucleosides.

25 Embodiment 31. An oligomeric compound comprising a modified oligonucleotide according to any of the following chemical notations:

30 ${}^m\text{C}_{\text{es}}{}^m\text{C}_{\text{eo}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{eo}}\text{A}_{\text{eo}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{A}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{eo}}\text{A}_{\text{eo}}\text{G}_{\text{es}}{}^m\text{C}_{\text{es}}{}^m\text{C}_{\text{e}}$ (SEQ ID NO: 134);
 $\text{A}_{\text{es}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{eo}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{eo}}\text{A}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{A}_{\text{eo}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{es}}\text{A}_{\text{es}}\text{A}_{\text{e}}$ (SEQ ID NO: 411);
 $\text{T}_{\text{es}}{}^m\text{C}_{\text{eo}}\text{T}_{\text{eo}}{}^m\text{C}_{\text{eo}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{eo}}\text{A}_{\text{eo}}\text{T}_{\text{es}}\text{G}_{\text{es}}{}^m\text{C}_{\text{e}}$ (SEQ ID NO: 934);
35 $\text{G}_{\text{es}}\text{T}_{\text{eo}}\text{G}_{\text{eo}}\text{T}_{\text{eo}}\text{G}_{\text{eo}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}\text{A}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{eo}}\text{A}_{\text{eo}}\text{T}_{\text{es}}\text{T}_{\text{es}}{}^m\text{C}_{\text{e}}$ (SEQ ID NO: 1238);
 $\text{A}_{\text{es}}\text{T}_{\text{eo}}\text{T}_{\text{eo}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{eo}}\text{G}_{\text{es}}\text{A}_{\text{es}}\text{A}_{\text{e}}$ (SEQ ID NO: 2010);
 $\text{A}_{\text{es}}\text{T}_{\text{eo}}\text{G}_{\text{eo}}\text{T}_{\text{eo}}\text{G}_{\text{eo}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{G}_{\text{eo}}\text{G}_{\text{eo}}\text{A}_{\text{es}}\text{G}_{\text{es}}\text{A}_{\text{e}}$ (SEQ ID NO: 1772); or
 $\text{A}_{\text{es}}{}^m\text{C}_{\text{eo}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{eo}}\text{G}_{\text{eo}}\text{A}_{\text{ds}}\text{G}_{\text{ds}}\text{G}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{eo}}\text{G}_{\text{es}}\text{G}_{\text{es}}\text{T}_{\text{e}}$ (SEQ ID NO: 881)
 $\text{T}_{\text{es}}\text{G}_{\text{eo}}\text{T}_{\text{eo}}\text{A}_{\text{eo}}\text{G}_{\text{eo}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{eo}}{}^m\text{C}_{\text{eo}}{}^m\text{C}_{\text{es}}\text{T}_{\text{es}}\text{T}_{\text{e}}$ (SEQ ID NO: 2101);
35 $\text{G}_{\text{es}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{eo}}\text{T}_{\text{eo}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{eo}}\text{T}_{\text{eo}}{}^m\text{C}_{\text{es}}\text{T}_{\text{es}}\text{T}_{\text{e}}$ (SEQ ID NO: 1050);

${}^m\text{C}_{\text{es}}{}^m\text{C}_{\text{eo}}\text{T}_{\text{eo}}{}^m\text{C}_{\text{eo}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{eo}}\text{A}_{\text{eo}}{}^m\text{C}_{\text{es}}\text{T}_{\text{es}}\text{T}_{\text{e}}$ (SEQ ID NO: 1449),

wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

5 G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

10 o = a phosphodiester internucleoside linkage.

Embodiment 32. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

$\text{T}_{\text{es}}\text{G}_{\text{eo}}\text{T}_{\text{eo}}\text{A}_{\text{eo}}\text{G}_{\text{eo}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{eo}}{}^m\text{C}_{\text{eo}}{}^m\text{C}_{\text{es}}\text{T}_{\text{es}}\text{T}_{\text{e}}$ (SEQ ID NO: 2101), wherein:

A = an adenine nucleobase,

15 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

20 s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 33. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

$\text{A}_{\text{es}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{eo}}\text{A}_{\text{eo}}\text{A}_{\text{eo}}\text{T}_{\text{eo}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{A}_{\text{eo}}\text{T}_{\text{es}}\text{T}_{\text{es}}\text{A}_{\text{e}}$ (SEQ ID NO: 682), wherein:

25 A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

30 d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 34. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

35 ${}^m\text{C}_{\text{es}}\text{A}_{\text{eo}}\text{G}_{\text{eo}}\text{A}_{\text{eo}}\text{T}_{\text{eo}}\text{G}_{\text{eo}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{es}}{}^m\text{C}_{\text{es}}\text{A}_{\text{e}}$ (SEQ ID NO: 1124), wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 5 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

Embodiment 35. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

${}^m\text{C}_{\text{es}}\text{A}_{\text{eo}}\text{T}_{\text{eo}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{eo}}\text{G}_{\text{eo}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{eo}}\text{T}_{\text{es}}{}^m\text{C}_{\text{e}}$ (SEQ ID NO: 2145), wherein:

10 A = an adenine nucleobase,
 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 15 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

Embodiment 36. The oligomeric compound of any of embodiments 1-35 wherein the oligomeric compound is a singled-stranded oligomeric compound.

20 Embodiment 37. The oligomeric compound of any of embodiments 1-36, consisting of the modified oligonucleotide.

Embodiment 38. The oligomeric compound of any of embodiments 1-36, further comprising a conjugate group.

Embodiment 39. The oligomeric compound of embodiment 38, wherein the conjugate group comprises a conjugate moiety and a conjugate linker.

Embodiment 40. The oligomeric compound of embodiment 38, wherein the conjugate group comprises a GalNAc
 25 cluster comprising 1-3 GalNAc ligands.

Embodiment 41. The oligomeric compound of embodiment 38 or embodiment 39, wherein the conjugate linker consists of a single bond.

Embodiment 42. The oligomeric compound of and of embodiments 39 or embodiment 41, wherein the conjugate linker is cleavable.

30 Embodiment 43. The oligomeric compound of embodiment 39 or embodiment 42, wherein the conjugate linker comprises 1-3 linker-nucleosides.

Embodiment 44. The oligomeric compound of any of embodiments 38-43, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.

Embodiment 45. The oligomeric compound of any of embodiments 38-43, wherein the conjugate group is attached to
 35 the modified oligonucleotide at the 3'-end of the modified oligonucleotide.

Embodiment 46. The oligomeric compound of any of embodiments 1-36 or 38-45 further comprising a terminal group.

Embodiment 47. The oligomeric compound of any of embodiments 1-42 or 44-46, wherein the oligomeric compound does not comprise linker-nucleosides.

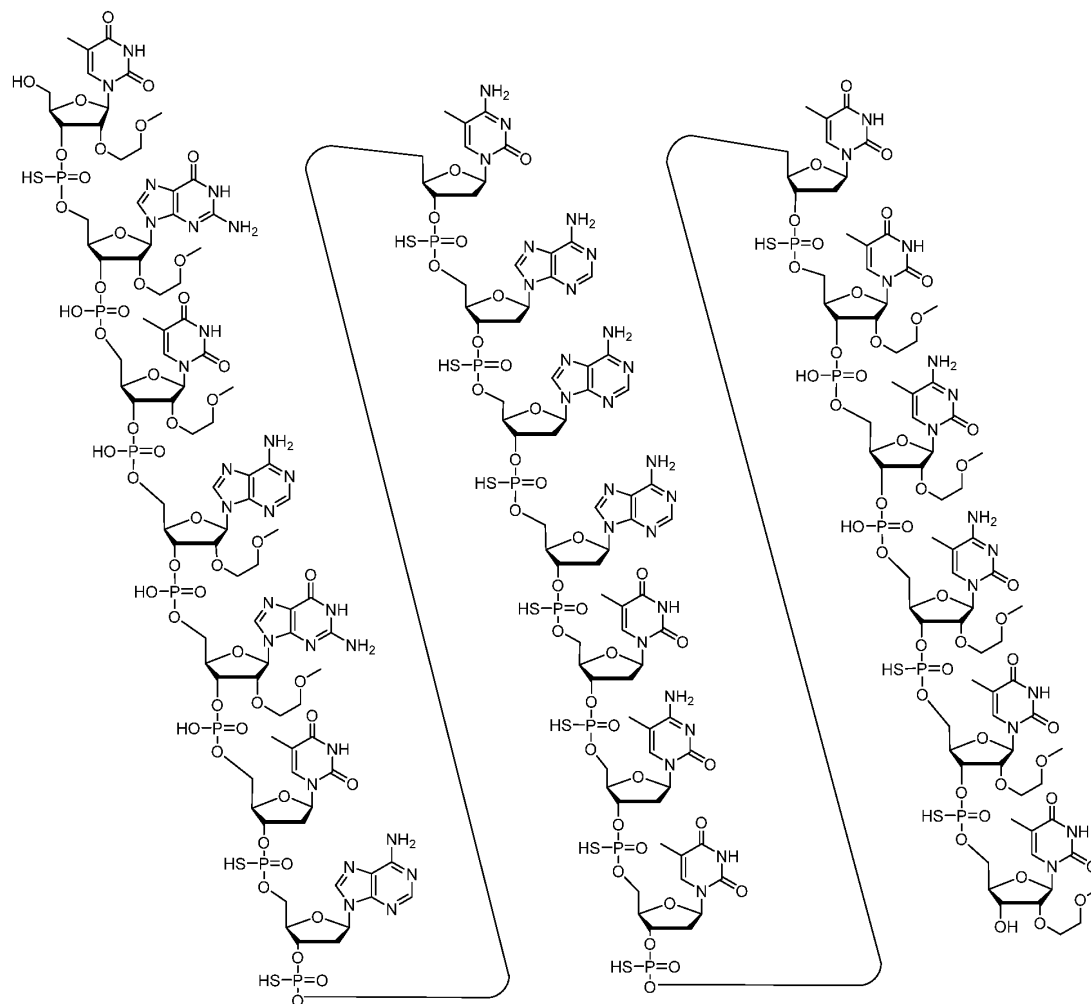
5 Embodiment 48. The oligomeric compound of any of embodiments 1-47, wherein the modified oligonucleotide of the oligomeric compound is a salt, and wherein the salt is a sodium salt or a potassium salt.

Embodiment 49. The oligomeric compound of any of embodiments 1-48, wherein the modified oligonucleotide is an RNAi compound.

Embodiment 50. An oligomeric duplex comprising an oligomeric compound of any of embodiments 1-35 or 37-49.

10 Embodiment 51. An antisense compound comprising or consisting of an oligomeric compound of any of embodiments 1-49 or an oligomeric duplex of embodiment 50.

Embodiment 52. A modified oligonucleotide according to the following chemical structure:

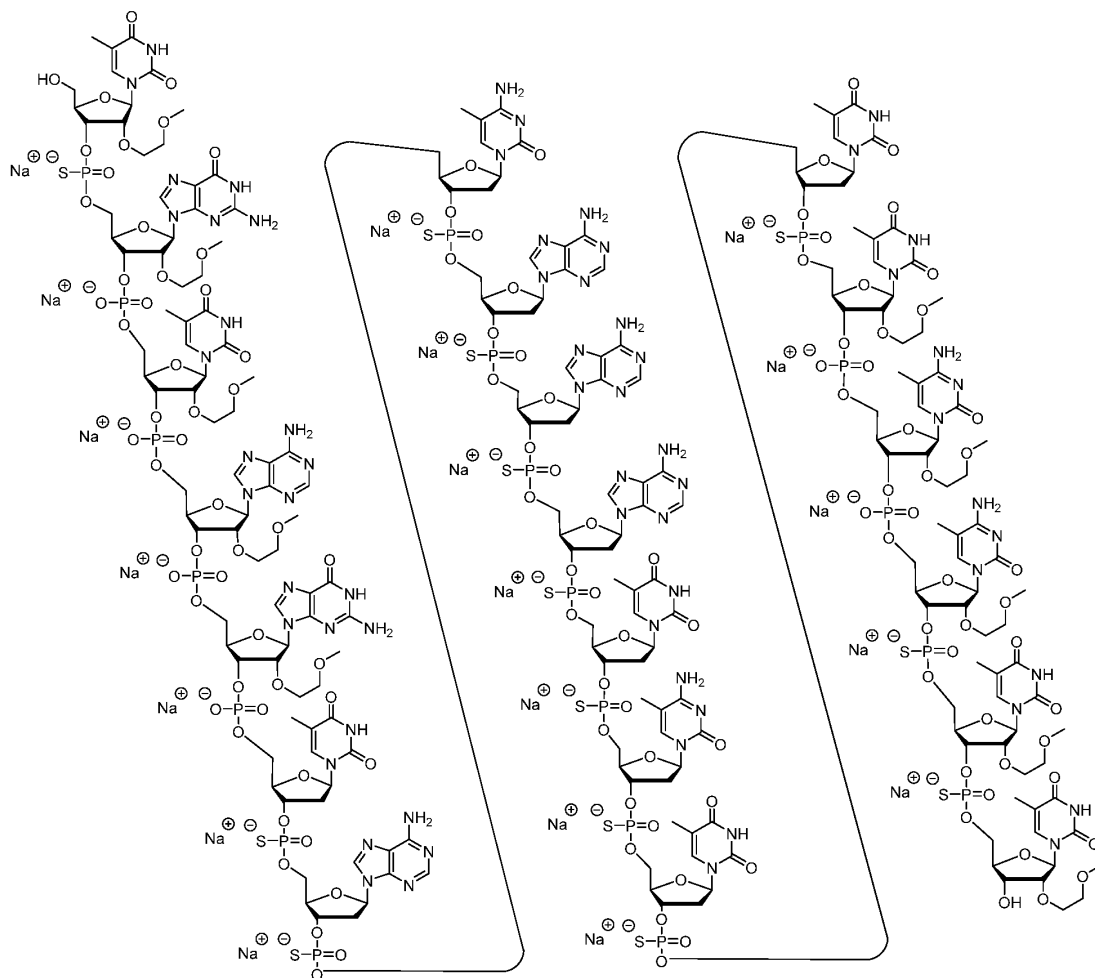


(SEQ ID NO: 2101)

5 or a salt thereof.

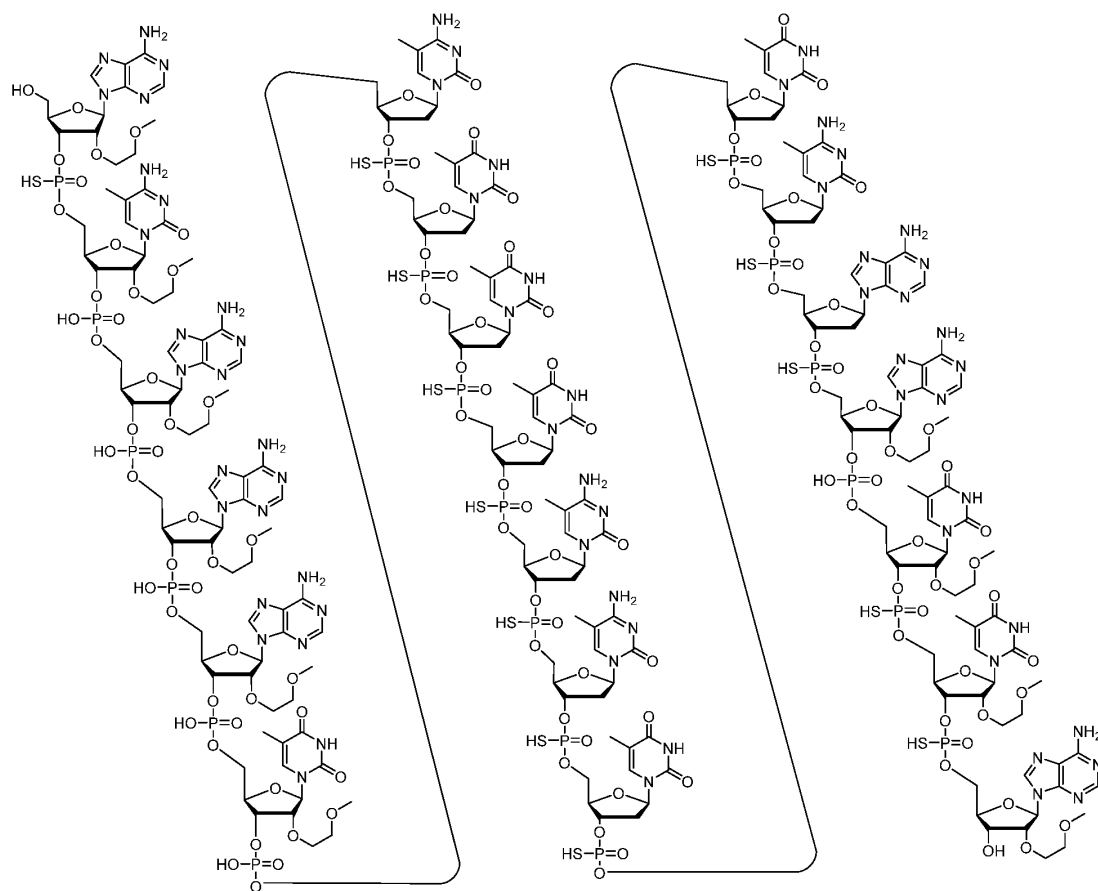
Embodiment 53. The modified oligonucleotide of embodiment 52, which is the sodium salt or the potassium salt.

Embodiment 54. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2101).

Embodiment 55. A modified oligonucleotide according to the following chemical structure:

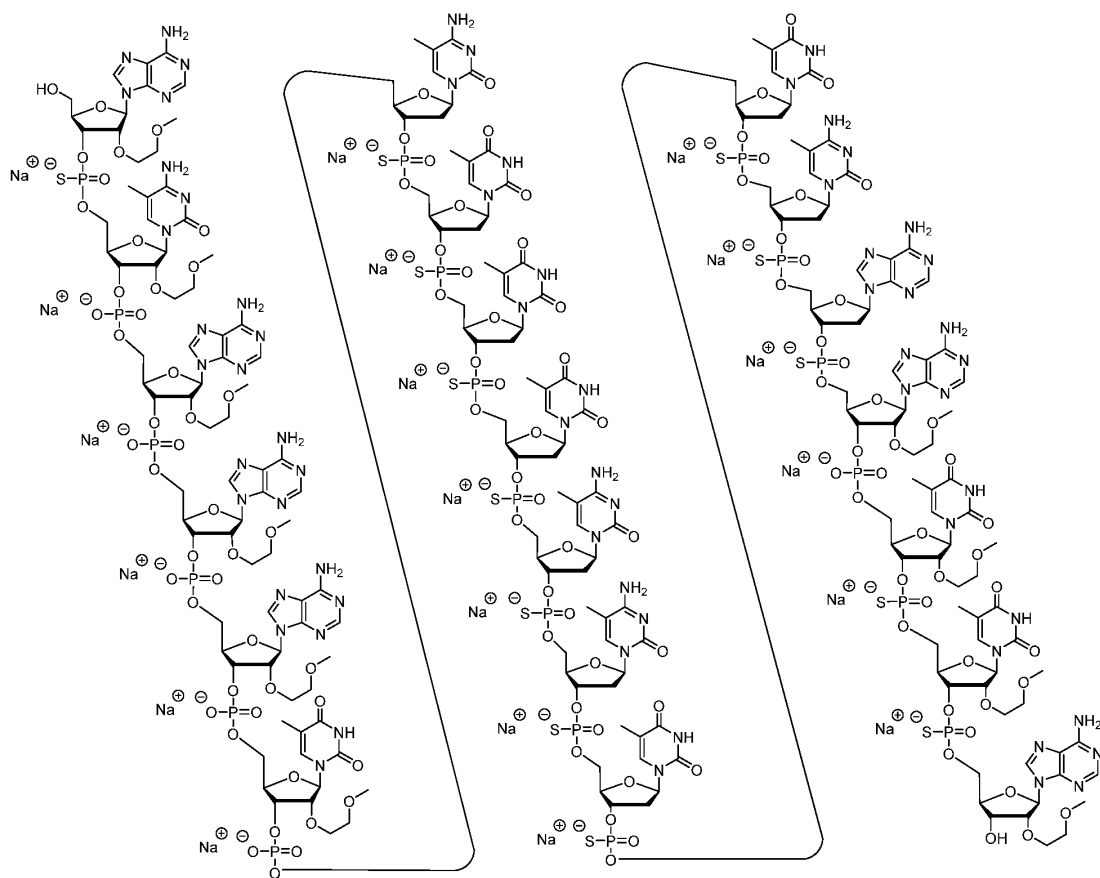


(SEQ ID NO: 682)

or a salt thereof.

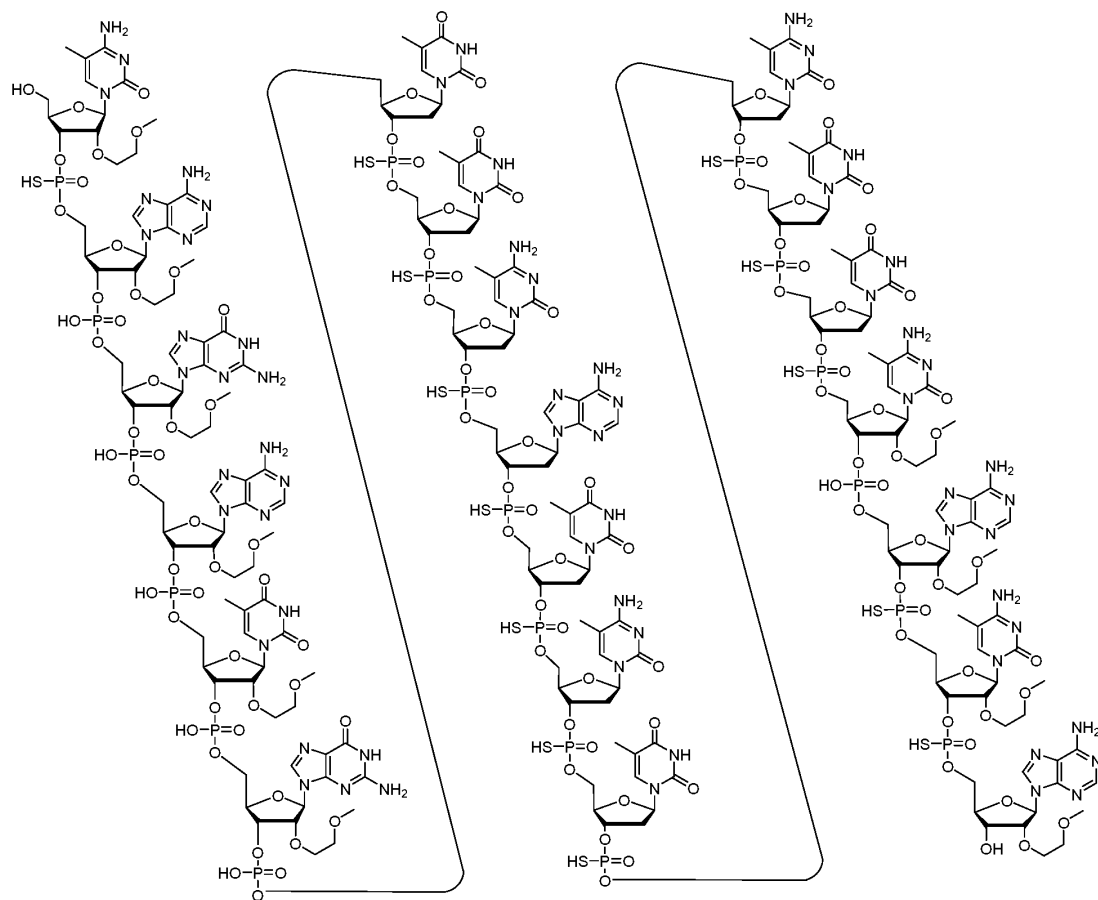
- 5 Embodiment 56. The modified oligonucleotide of embodiment 55, which is the sodium salt or the potassium salt.

Embodiment 57. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 682).

Embodiment 58. A modified oligonucleotide according to the following chemical structure:

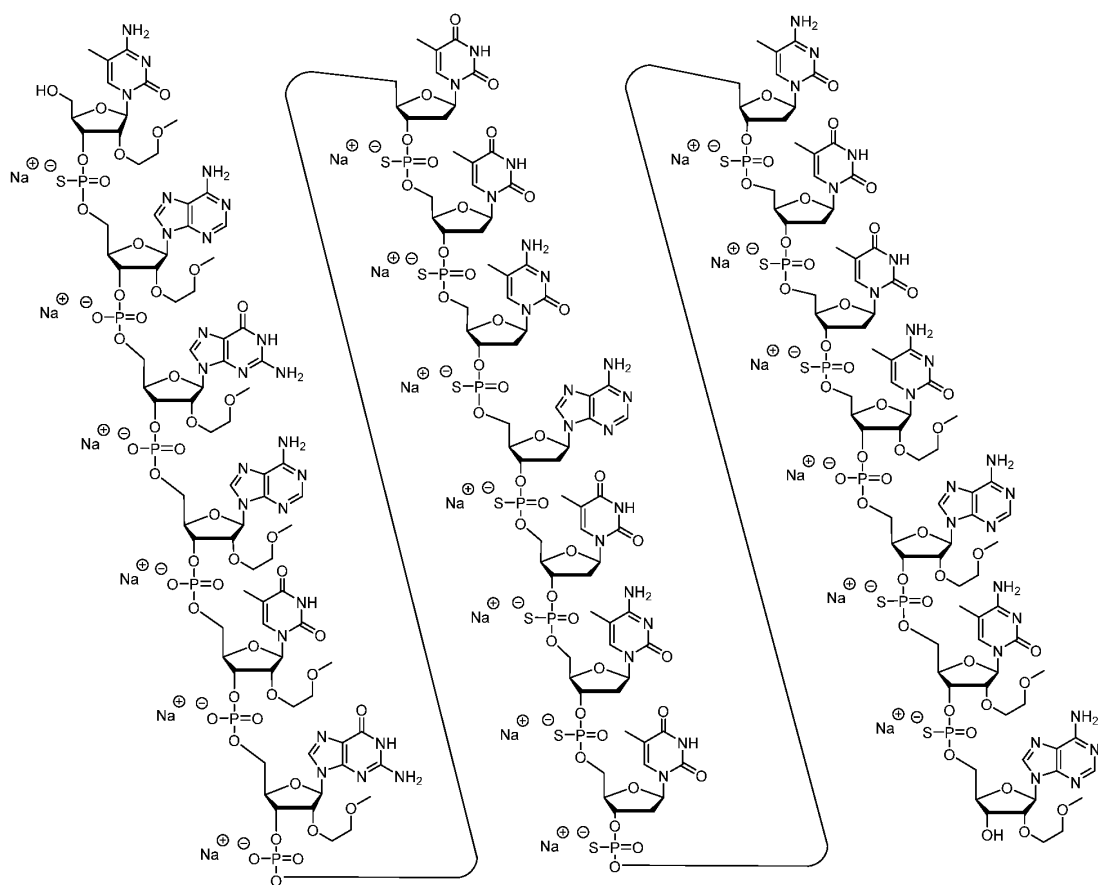


(SEQ ID NO: 1124)

or a salt thereof.

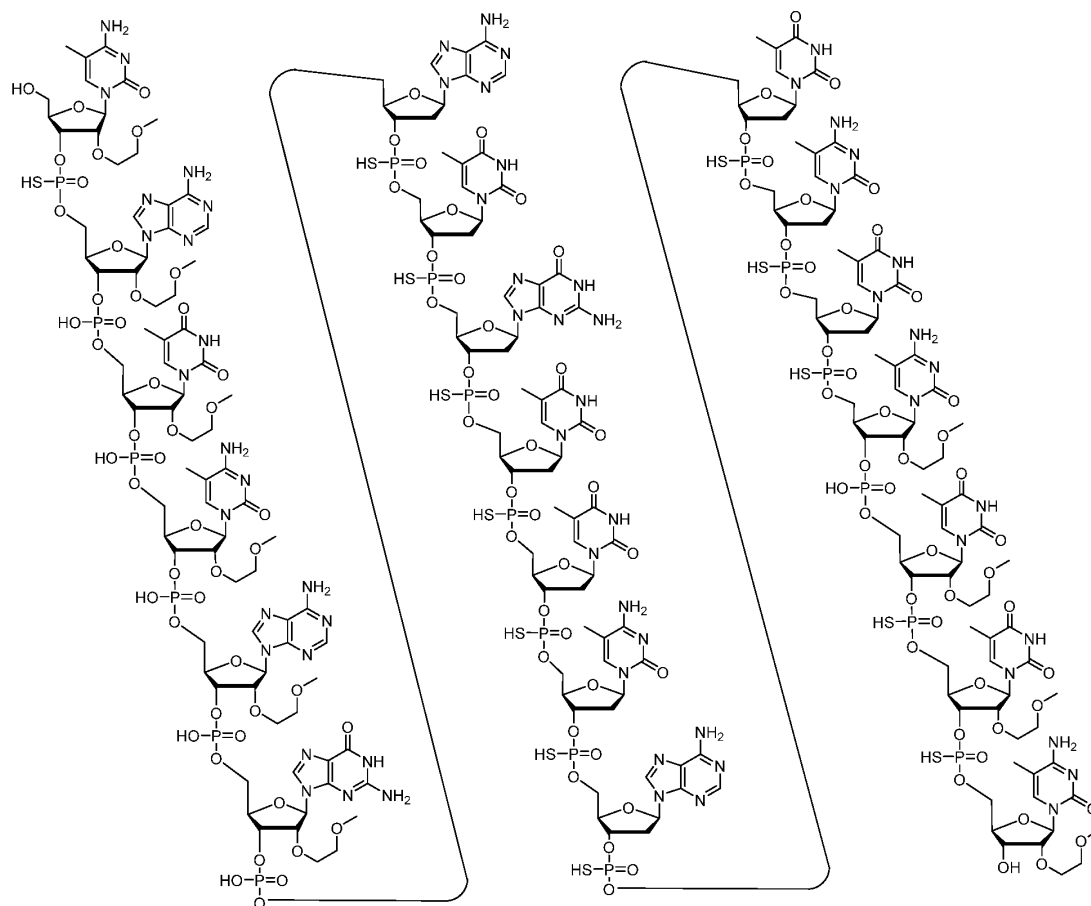
- 5 Embodiment 59. The modified oligonucleotide of embodiment 58, which is the sodium salt or the potassium salt.

Embodiment 60. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 1124).

Embodiment 61. A modified oligonucleotide according to the following chemical structure:

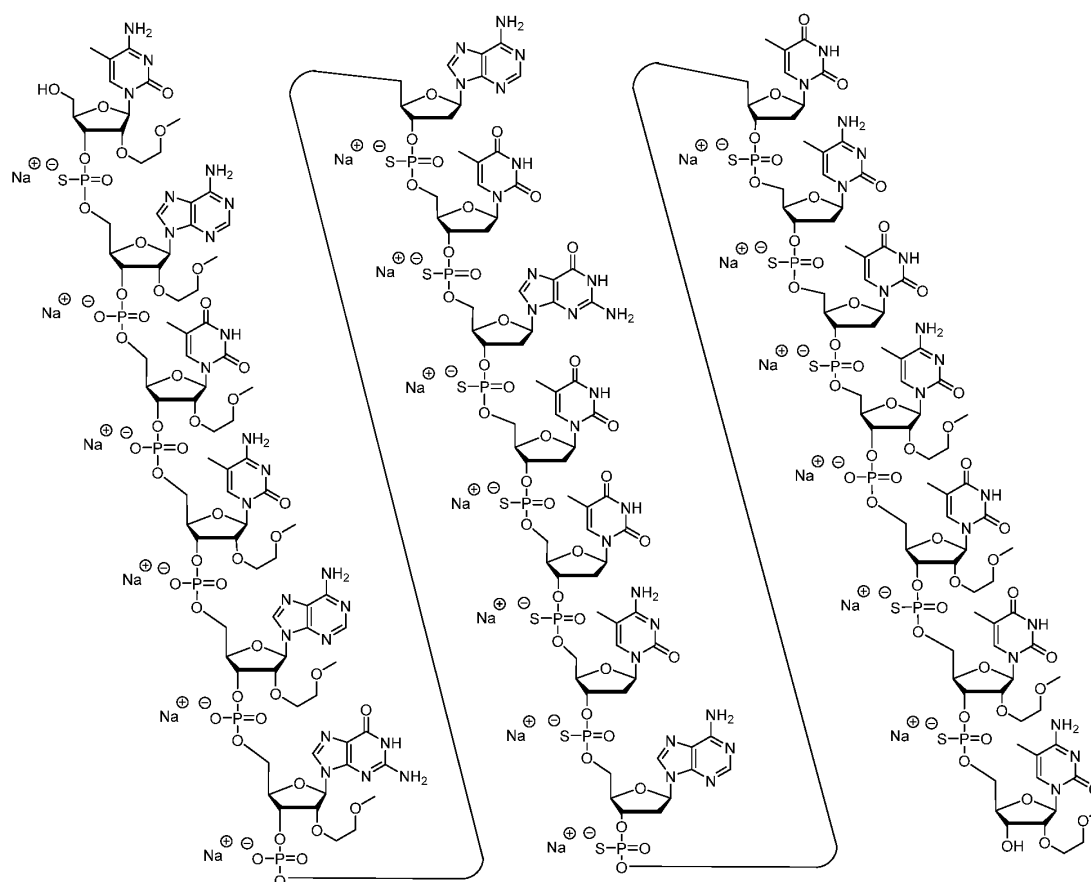


(SEQ ID NO: 2145)

or a salt thereof.

- 5 Embodiment 62. The modified oligonucleotide of embodiment 61, which is the sodium salt or the potassium salt.

Embodiment 63. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2145).

Embodiment 64. A pharmaceutical composition comprising the oligomeric compound of any of embodiments 1-49, the oligomeric duplex of embodiment 50, the antisense compound of embodiment 51, or the modified oligonucleotide of any of embodiments 52-63 and a pharmaceutically acceptable diluent or carrier.

Embodiment 65. The pharmaceutical composition of embodiment 64, comprising a pharmaceutically acceptable diluent and wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or phosphate-buffered saline (PBS).

Embodiment 66. The pharmaceutical composition of embodiment 65, wherein the pharmaceutical composition consists essentially of the oligomeric compound or the modified oligonucleotide and aCSF.

Embodiment 67. The pharmaceutical composition of embodiment 65, wherein the pharmaceutical composition consists essentially of the oligomeric compound or the modified oligonucleotide and PBS.

Embodiment 68. A pharmaceutical composition comprising a modified oligonucleotide of any of embodiments 52-63 and a pharmaceutically acceptable diluent.

Embodiment 69. The pharmaceutical composition of embodiment 68, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or phosphate-buffered saline (PBS).

Embodiment 70. The pharmaceutical composition of embodiment 69, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and aCSF.

- 5 Embodiment 71. The pharmaceutical composition of embodiment 69, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.

Embodiment 72. A pharmaceutical composition comprising an oligomeric compound of any of embodiments 32-35 and a pharmaceutically acceptable diluent.

- 10 Embodiment 73. The pharmaceutical composition of embodiment 72, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or phosphate-buffered saline (PBS).

Embodiment 74. The pharmaceutical composition of embodiment 73, wherein the pharmaceutical composition consists essentially of the oligomeric compound and aCSF.

Embodiment 75. The pharmaceutical composition of embodiment 73, wherein the pharmaceutical composition consists essentially of the oligomeric compound and PBS.

- 15 Embodiment 76. A chirally enriched population of modified oligonucleotides of any of embodiments 52-63, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

- Embodiment 77. The chirally enriched population of embodiment 76, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Sp)
20 configuration.

Embodiment 78. The chirally enriched population of embodiment 76, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Rp) configuration.

- Embodiment 79. The chirally enriched population of embodiment 76, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.
25

Embodiment 80. The chirally enriched population of embodiment 79, wherein the population is enriched for modified oligonucleotides having the (Sp) configuration at each phosphorothioate internucleoside linkage or for modified oligonucleotides having the (Rp) configuration at each phosphorothioate internucleoside linkage.

- 30 Embodiment 81. The chirally enriched population of embodiment 79, 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 82. The chirally enriched population of embodiment 79, wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the Sp, Sp, and Rp
35 configurations, in the 5' to 3' direction.

Embodiment 83. A population of modified oligonucleotides of any of embodiments 52-63, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

Embodiment 84. A chirally enriched population of oligomeric compounds of any of embodiments 32-35, wherein the population is enriched for oligomeric compounds comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

Embodiment 85. The chirally enriched population of embodiment 84, wherein the population is enriched for oligomeric compounds comprising at least one particular phosphorothioate internucleoside linkage having the (Sp) configuration.

Embodiment 86. The chirally enriched population of embodiment 84, wherein the population is enriched for oligomeric compounds comprising at least one particular phosphorothioate internucleoside linkage having the (Rp) configuration.

Embodiment 87. The chirally enriched population of embodiment 84, wherein the population is enriched for oligomeric compounds having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

Embodiment 88. The chirally enriched population of embodiment 87, wherein the population is enriched for oligomeric compounds having the (Sp) configuration at each phosphorothioate internucleoside linkage or for modified oligonucleotides having the (Rp) configuration at each phosphorothioate internucleoside linkage.

Embodiment 89. The chirally enriched population of embodiment 87, wherein the population is enriched for oligomeric compounds having the (Rp) configuration at one particular phosphorothioate internucleoside linkage and the (Sp) configuration at each of the remaining phosphorothioate internucleoside linkages.

Embodiment 90. The chirally enriched population of embodiment 87, wherein the population is enriched for oligomeric compounds having at least 3 contiguous phosphorothioate internucleoside linkages in the Sp, Sp, and Rp configurations, in the 5' to 3' direction.

Embodiment 91. A population of oligomeric compounds of any of embodiments 32-35, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

Embodiment 92. A pharmaceutical composition comprising the chirally enriched population of any of embodiments 76-82 or 84-90, the population of claim 83, or the population of claim 91 and a pharmaceutically acceptable diluent.

Embodiment 93. The pharmaceutical composition of claim 92, wherein the pharmaceutically acceptable diluent is artificial CSF (aCSF) or phosphate-buffered saline (PBS).

Embodiment 94. The pharmaceutical composition of claim 93, wherein the pharmaceutical composition consists essentially of the oligomeric compounds or the modified oligonucleotides and artificial CSF (aCSF).

Embodiment 95. The pharmaceutical composition of embodiment 93, wherein the pharmaceutical composition consists essentially of the oligomeric compounds or the modified oligonucleotides and PBS.

Embodiment 96. A method comprising administering to an animal the pharmaceutical composition of any of embodiments 64-75 or 92-95.

Embodiment 97. A method of treating a disease or disorder associated with PLP1, comprising administering to a subject having or at risk for developing a disease or disorder associated with PLP1 a therapeutically effective amount of a pharmaceutical composition according to any of embodiments 64-75 or 92-95, and thereby treating the disease or disorder associated with PLP1.

- 5 Embodiment 98. A method of reducing PLP1 protein in the CSF of a subject having or at risk for developing a disease or disorder associated with PLP1 a therapeutically effective amount of a pharmaceutical composition according any of embodiments 64-75 or 92-95, and thereby reducing PLP1 protein in the CSF.

Embodiment 99. The method of embodiment 97 or embodiment 98, wherein the disease or disorder associated with PLP1 is a neurodegenerative disease.

- 10 Embodiment 100. The method of any of embodiments 97-99, wherein the disease or disorder associated with PLP1 is a leukodystrophy.

Embodiment 101. The method of embodiment 100, wherein the leukodystrophy is PMD.

Embodiment 102. The method of embodiment 101, wherein the PMD is any of connatal PMD, classic PMD, transitional PMD.

- 15 Embodiment 103. The method of embodiment 101, wherein the PMD is caused by overexpression of PLP1 protein.

Embodiment 104. The method of embodiment 101, wherein the PMD is caused by multiple copies of the PLP1 gene.

Embodiment 105. The method of embodiment 101, wherein the PMD is caused by the expression of duplicate copies of the PLP1 gene.

- 20 Embodiment 106. The method of any of embodiments 100-105, wherein at least one symptom or hallmark of the leukodystrophy is ameliorated.

Embodiment 107. The method of embodiment 97 or embodiment 98, wherein the disease or disorder associated with PLP1 is SPG2.

Embodiment 108. The method of embodiment 107, wherein at least one symptom or hallmark of SPG2 is ameliorated.

- 25 Embodiment 109. The method of embodiment 106 or embodiment 108, wherein the symptom or hallmark is any of hypotonia, nystagmus, optic atrophy, respiratory distress, motor delays, cognitive dysfunction, speech dysfunction, spasticity, ataxia, seizures, choreiform movements, and death.

Embodiment 110. The method of any of embodiments 96-109 wherein administering the modified oligonucleotide reduces hypotonia, nystagmus, optic atrophy, respiratory distress, motor delays, cognitive dysfunction, speech dysfunction, spasticity, ataxia, seizures, or choreiform movements, or delays death in the subject.

- 30 Embodiment 111. The method of any of embodiments 96-110, wherein the pharmaceutical composition is administered to the central nervous system or systemically.

Embodiment 112. The method of embodiment 111, wherein the pharmaceutical composition is administered to the central nervous system and systemically.

Embodiment 113. The method of any of embodiments 96-110, wherein the pharmaceutical composition is administered any of intrathecally, systemically, subcutaneously, or intramuscularly.

Embodiment 114. A method of reducing PLP1 RNA in a cell comprising contacting the cell with an oligomeric compound of any of embodiments 1-49, an oligomeric duplex according to embodiment 50, an antisense compound according to embodiment 51, or a modified oligonucleotide of any of embodiments 52-63, and thereby reducing PLP1 RNA in the cell.

Embodiment 115. A method of reducing PLP1 protein in a cell comprising contacting the cell with an oligomeric compound of any of embodiments 1-49, an oligomeric duplex according to embodiment 50, an antisense compound according to embodiment 51, or a modified oligonucleotide of any of embodiments 52-63, and thereby reducing PLP1 protein in the cell.

Embodiment 116. The method of embodiment 114 or embodiment 115, wherein the cell is an oligodendrocyte or an oligodendrocyte progenitor cell.

Embodiment 117. The method of embodiment 114 or embodiment 115, wherein the cell is a Schwann cell or a Schwann cell progenitor.

Embodiment 118. The method of any of embodiments 114-117, wherein the cell is in an animal.

Embodiment 119. The method of embodiment 96 or embodiment 118, wherein the animal is human.

Embodiment 120. A method comprising administering to a subject a pharmaceutical composition of any of embodiments 68-71.

Embodiment 121. A method of treating a disease or disorder associated with PLP1, comprising administering to an subject having or at risk for developing a disease or disorder associated with PLP1 a therapeutically effective amount of a pharmaceutical composition according to any of embodiments 68-71 and thereby treating the disease or disorder associated with PLP1.

Embodiment 122. The method of embodiment 121, wherein the disease associated with PLP1 is a neurodegenerative disease.

Embodiment 123. The method of embodiment 122, wherein the neurodegenerative disease is a leukodystrophy.

Embodiment 124. The method of embodiment 123, wherein the leukodystrophy is PMD.

Embodiment 125. The method of embodiment 124, wherein the PMD is any of connatal PMD, classic PMD, transitional PMD.

Embodiment 126. The method of embodiment 124, wherein the PMD is caused by overexpression of PLP1 protein.

Embodiment 127. The method of embodiment 124, wherein the PMD is caused by multiple copies of the PLP1 gene.

Embodiment 128. The method of embodiment 124, wherein the PMD is caused by the expression of duplicate copies of the PLP1 gene.

Embodiment 129. The method of any of embodiments 122-128, wherein at least one symptom or hallmark of the neurodegenerative disease is ameliorated.

Embodiment 130. The method of embodiment 129, wherein the symptom or hallmark is any of hypotonia, nystagmus, optic atrophy, respiratory distress, motor delays, cognitive dysfunction, speech dysfunction, spasticity, ataxia, seizures, choreiform movements, and death.

5 Embodiment 131. The method of any of embodiments 121-130 wherein administering the pharmaceutical composition reduces hypotonia, nystagmus, optic atrophy, respiratory distress, motor delays, cognitive dysfunction, speech dysfunction, spasticity, ataxia, seizures, or choreiform movements, or delays death in the subject.

Embodiment 132. The method of any of embodiments 120-131, wherein the subject is human.

Embodiment 133. A method of reducing expression of PLP1 in a cell comprising contacting the cell with a modified oligonucleotide of any of embodiments 52-63.

10 Embodiment 134. The method of embodiment 133, wherein the cell is a human cell.

Embodiment 135. Use of an oligomeric compound any of embodiments 1-49, an oligomeric duplex according to embodiment 50, an antisense compound according to embodiment 51, or a modified oligonucleotide of any of embodiments 52-63 for reducing PLP1 expression in a cell.

Embodiment 136. The use of embodiment 135, wherein the level of PLP1 RNA in the cell is reduced.

15 Embodiment 137. The use of embodiment 135, wherein the level of PLP1 protein in the cell is reduced.

Embodiment 138. The use of any of embodiments 133-137, wherein the cell is an oligodendrocyte or an oligodendrocyte progenitor cell.

Embodiment 139. The use of any of embodiments 133-137, wherein the cell is a Schwann cell or a Schwann cell progenitor.

20 **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.

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.

1. Certain Sugar Moieties

30 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', 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'-OCH₃ ("OMe" or "O-methyl"), and 2'-O(CH₂)₂OCH₃ ("MOE" or "O-methoxyethyl"). In certain embodiments, 2'-substituent groups are selected from among: halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, O-C₁-C₁₀ alkyl, O-C₁-C₁₀ 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-alkenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n) or OCH₂C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ alkyl, 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 (NO₂), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl, alkenyl and alkynyl. 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, 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, NH₂, N₃, OCF₃, OCH₃, O(CH₂)₃NH₂, CH₂CH=CH₂, OCH₂CH=CH₂, OCH₂CH₂OCH₃, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n), O(CH₂)₂O(CH₂)₂N(CH₃)₂, and N-substituted acetamide (OCH₂C(=O)-N(R_m)(R_n)), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ alkyl.

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCF₃, OCH₃, OCH₂CH₂OCH₃, O(CH₂)₂SCH₃, O(CH₂)₂ON(CH₃)₂, O(CH₂)₂O(CH₂)₂N(CH₃)₂, and OCH₂C(=O)-N(H)CH₃ ("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, OCH₃, and OCH₂CH₂OCH₃.

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-deoxyribose 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-ribose isomeric configuration unless otherwise specified.

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. In 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'-CH₂-2', 4'-(CH₂)₂-2', 4'-(CH₂)₃-2', 4'-CH₂-O-2' ("LNA"), 4'-CH₂-S-2', 4'-(CH₂)₂-O-2' ("ENA"), 4'-CH(CH₃)-O-2' (referred to as "constrained ethyl" or "cEt" when in the *S* configuration), 4'-CH₂-O-CH₂-2', 4'-CH₂-N(R)-2', 4'-CH(CH₂OCH₃)-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(CH₃)(CH₃)-O-2' and analogs thereof (*see, e.g.*, Seth et al., U.S. 8,278,283), 4'-CH₂-N(OCH₃)-2' and analogs thereof (*see, e.g.*, Prakash et al., U.S. 8,278,425), 4'-CH₂-O-N(CH₃)-2' (*see, e.g.*, Allerson et al., U.S. 7,696,345 and Allerson et al., U.S. 8,124,745), 4'-CH₂-C(H)(CH₃)-2' (*see, e.g.*, Zhou, *et al.*, *J. Org. Chem.*, 2009, 74, 118-134), 4'-CH₂-C(=CH₂)-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'-CH₂-O-N(R)-2', and 4'-CH₂-N(R)-O-2', wherein each R, R_a, and R_b is, independently, H, a protecting group, or C₁-C₁₂ 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(R_a)(R_b)]_n-, -[C(R_a)(R_b)]_n-O-, -C(R_a)=C(R_b)-, -C(R_a)=N-, -C(=NR_a)-, -C(=O)-, -C(=S)-, -O-, -Si(R_a)₂-, -S(=O)_x-, and -N(R_a)-;

wherein:

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

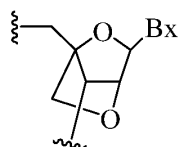
each R_a and R_b is, independently, H, a protecting group, hydroxyl, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₅-C₂₀ aryl, substituted C₅-C₂₀ aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, 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.

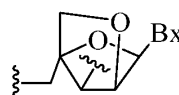
Additional bicyclic sugar moieties are known in the art, *see, for example*: Freier et al., *Nucleic Acids Research*, 1997, 25(22), 4429-4443, Alback et al., *J. Org. Chem.*, 2006, 71, 7731-7740, Singh et al., *Chem. Commun.*, 1998, 4, 455-456; Koshkin et al., *Tetrahedron*, 1998, 54, 3607-3630; Wahlestedt 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 Inven. 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'-CH₂-O-2'



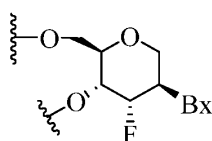
α -L-LNA (α -L-configuration)
bridge = 4'-CH₂-O-2'

α -L-methyleneoxy (4'-CH₂-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). 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).

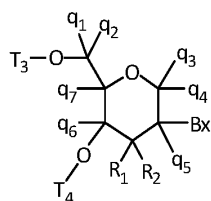
In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the sugar moiety is replaced, *e.g.*, with a sulfur, carbon or nitrogen atom. In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents 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 the modified THP nucleosides:

Bx is a nucleobase moiety;

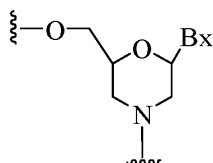
T₃ and T₄ are each, independently, an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide or one of T₃ and T₄ is an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide and the other of T₃ and T₄ is H, a hydroxyl protecting group, a linked conjugate group, or a 5' or 3'-terminal group;

q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each, independently, H, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₆ alkynyl, or substituted C₂-C₆ alkynyl; and

each of R₁ and R₂ is independently selected from among: hydrogen, halogen, substituted or unsubstituted alkoxy, NJ₁J₂, SJ₁, N₃, OC(=X)J₁, OC(=X)NJ₁J₂, NJ₃C(=X)NJ₁J₂, and CN, wherein X is O, S or NJ₁, and each J₁, J₂, and J₃ is, independently, H or C₁-C₆ alkyl.

In certain embodiments, modified THP nucleosides are provided wherein q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each H. In certain embodiments, at least one of q₁, q₂, q₃, q₄, q₅, q₆ and q₇ is other than H. In certain embodiments, at least one of q₁, q₂, q₃, q₄, q₅, q₆ and q₇ is methyl. In certain embodiments, modified THP nucleosides are provided wherein one of R₁ and R₂ is F. In certain embodiments, R₁ is F and R₂ is H, in certain embodiments, R₁ is methoxy and R₂ is H, and in certain embodiments, R₁ is methoxyethoxy and R₂ 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.

Many other bicyclic and tricyclic sugar and sugar surrogate ring systems 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 nucleoside comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside that does not comprise a nucleobase, referred to as an abasic nucleoside.

5 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-methyl cytosine, 2-aminopropyladenine, 5-hydroxymethyl
cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine, 2-
thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (-C≡C-CH₃) uracil, 5-propynylcytosine, 6-azouracil, 6-
10 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-benzoyl adenine, 2-N-isobutylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-
benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded
15 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*
20 *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.

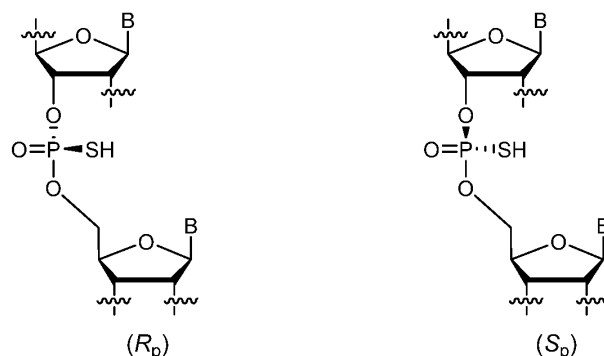
Publications that teach the preparation of certain of the above noted modified nucleobases as well as other
25 modified nucleobases include without limitation, Manoharan et al., US2003/0158403; Manoharan et al.,
US2003/0175906; Dinh et al., U.S. 4,845,205; Spielvogel et al., U.S. 5,130,302; Rogers et 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;
30 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., 6,166,199; and Matteucci et al., U.S. 6,005,096.

3. Certain Modified Internucleoside Linkages

35 In certain embodiments, nucleosides of modified oligonucleotides may be linked together using any
internucleoside linkage. 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
phosphodiester, which contain a phosphodiester bond ("P(O₂)=O") (also referred to as unmodified or naturally
occurring linkages), phosphotriesters, methylphosphonates, phosphoramidates, phosphorothioates ("P(O₂)=S"), and

phosphorodithioates ("HS-P=S"). Representative non-phosphorus containing internucleoside linking groups include but are not limited to methylenemethylimino (-CH₂-N(CH₃)-O-CH₂-), thiodiester, thionocarbamate (-O-C(=O)(NH)-S-); siloxane (-O-SiH₂-O-); and N,N'-dimethylhydrazine (-CH₂-N(CH₃)-N(CH₃)-). Modified internucleoside linkages, compared to naturally occurring phosphodiester internucleoside linkages, can be used to alter, typically increase, 5 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 10 chiral center can be prepared as populations of modified oligonucleotides comprising stereorandom internucleoside linkages, or as populations of modified oligonucleotides comprising phosphorothioate internucleoside 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 15 of the stereochemical configuration of each phosphorothioate internucleoside linkage. Nonetheless, as is well understood by those of skill in the art, 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 linkage in a particular, independently selected stereochemical configuration. In certain embodiments, the particular configuration of the 20 particular phosphorothioate internucleoside linkage is present in at least 65% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate internucleoside linkage is present in at least 70% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate internucleoside linkage is present in at least 80% of the molecules in the population. In certain 25 embodiments, the particular configuration of the particular phosphorothioate internucleoside linkage is present in at least 90% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate internucleoside 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*, 2003, 125, 8307, Wan et al., *Nuc. Acid. Res.*, 2014, 42, 13456, and WO 2017/015555. In certain embodiments, a population of modified oligonucleotides is enriched for modified 30 oligonucleotides having at least one indicated phosphorothioate in the (*Sp*) configuration. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one phosphorothioate in the (*Rp*) configuration. In certain embodiments, modified oligonucleotides comprising (*Rp*) and/or (*Sp*) phosphorothioates comprise one or more of the following formulas, respectively, wherein "B" indicates a nucleobase:



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'-CH₂-N(CH₃)-O-5'), amide-3 (3'-CH₂-C(=O)-N(H)-5'), amide-4 (3'-CH₂-N(H)-C(=O)-5'), formacetal (3'-O-CH₂-O-5'), methoxypropyl (MOP), and thioformacetal (3'-S-CH₂-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 CH₂ component parts.

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 portion 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.

In certain embodiments, modified oligonucleotides have 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).

5 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
10 nucleosides of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least five 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'-deoxyribosyl sugar moiety. In certain embodiments, at least six nucleosides of the gap of a gapmer comprise a 2'-β-D-deoxyribosyl sugar moiety. In certain embodiments, each
15 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, at least one nucleoside of the gap of a gapmer comprises a 2'-OMe 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
20 wing/gap junction comprise modified sugar moieties. In certain embodiments, at least six nucleosides of the gap of a gapmer comprise a 2'-β-D-deoxyribosyl sugar moiety. In certain embodiments, each nucleoside of the gap of a gapmer comprises a 2'-deoxyribosyl sugar moiety. In certain embodiments, each nucleoside of each wing 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.

25 In certain embodiments, modified oligonucleotides comprise or consist of a portion having a fully modified sugar motif. In such embodiments, each nucleoside of the fully modified portion of the modified oligonucleotide comprises a modified sugar moiety. In certain embodiments, each nucleoside of the entire modified oligonucleotide comprises a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise or consist of a portion having a fully modified sugar motif, wherein each nucleoside within the fully modified portion comprises the same
30 modified sugar moiety, referred to herein as a uniformly modified sugar motif. In certain embodiments, a fully modified oligonucleotide is a uniformly modified oligonucleotide. In certain embodiments, each nucleoside of a uniformly modified oligonucleotide comprises the same 2'-modification.

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 5-
35 10-5 gapmer consists of 5 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 comprises a 2'-β-D-deoxyribosyl sugar moiety. Thus, 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. 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 5-8-5 gapmer consists of 5 linked nucleosides comprising a modified sugar moiety in the 5'-wing, 8 linked a 2'- β -D-deoxynucleosides in the gap, and 5 linked nucleosides comprising a modified sugar moiety in the 3'-wing. A mixed wing gapmer has at least two different modified sugar moieties in the 5' and/or the 3' wing. A 5-8-5 or 5-8-4 mixed wing gapmer has at least two different modified sugar moieties in the 5'- and/or the 3'-wing.

In certain embodiments, modified oligonucleotides are 5-10-5 MOE gapmers. In certain embodiments, modified oligonucleotides are 6-10-4 MOE gapmers. In certain embodiments, modified oligonucleotides are 4-10-6 MOE gapmers. In certain embodiments, modified oligonucleotides are 4-8-6 MOE gapmers. In certain embodiments, modified oligonucleotides are 6-8-4 MOE gapmers. In certain embodiments, modified oligonucleotides are 5-8-4 MOE gapmers. In certain embodiments, modified oligonucleotides are 3-10-7 MOE gapmers. In certain embodiments, modified oligonucleotides are 7-10-3 MOE gapmers. In certain embodiments, modified oligonucleotides are 5-8-5 MOE gapmers. In certain embodiments, modified oligonucleotides are 5-9-5 MOE gapmers. In certain embodiments, modified oligonucleotides are X-Y-Z MOE gapmers, wherein X and Z are independently selected from 1, 2, 3, 4, 5, 6, or 7 linked 2'-MOE nucleosides and Y is selected from 7, 8, 9, 10, or 11 linked deoxynucleosides.

In certain embodiments, modified oligonucleotides have the following sugar motif (5' to 3'): eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, or eeeeeyeeeeeeeeee, wherein 'd' represents a 2'-deoxyribose sugar moiety, 'e' represents a 2'-MOE sugar moiety, and 'y' represents a 2'-OMe sugar moiety.

2. Certain Nucleobase Motifs

In certain embodiments, oligonucleotides comprise modified and/or unmodified nucleobases arranged along the oligonucleotide or portion 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-methyl cytosines. In certain embodiments, all of the cytosine nucleobases are 5-methyl cytosines 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 the nucleoside is a 2'-deoxyribose 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 portion 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 (*Sp*) phosphorothioate, and a (*Rp*) 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 internucleoside linkage is not a terminal internucleoside linkage, and the remaining internucleoside linkages are phosphorothioate internucleoside linkages. In certain such embodiments, all of the phosphorothioate internucleoside linkages are stereorandom. In certain embodiments, all of the phosphorothioate internucleoside 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.

In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of sooooooossssssooss or sooooooossssssooss wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

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*, 1992, 89, 7305-7309, 1992), a series of oligonucleotides 13-25 nucleobases in length were tested for their ability to induce cleavage of a target nucleic acid 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 nucleic acid, 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 29, 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.

In certain embodiments, oligonucleotides consist of 16 linked nucleosides. In certain embodiments, oligonucleotides consist of 17 linked nucleosides. In certain embodiments, oligonucleotides consist of 18 linked nucleosides. In certain embodiments, oligonucleotides consist of 19 linked nucleosides. In certain embodiments, oligonucleotides consist of 20 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 portion 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 portion 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.

I. 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, abasic nucleosides, 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, 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 palmitoyl 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 N-acetylgalactosamine (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.

1. Conjugate Moieties

Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates, vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterol, thiocholesterol, cholic acid moieties, folate, lipids, lipophilic groups, 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, folic acid, a benzothiadiazide, chlorothiazide, a diazepam, 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 oligomeric compounds, a conjugate moiety is attached to an oligonucleotide via a more complex conjugate linker comprising one or more conjugate linker moieties, which are sub-units making up a conjugate linker. In certain embodiments, the conjugate linker comprises a chain structure, such as a hydrocarbon chain, or an oligomer of repeating units such as ethylene glycol, nucleosides, or amino acid units.

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 parent 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 parent 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 (AHX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C₁-C₁₀ alkyl, substituted or

unsubstituted C₂-C₁₀ alkenyl or substituted or unsubstituted C₂-C₁₀ 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-methyl cytosine, 4-N-benzoyl-5-methyl cytosine, 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.

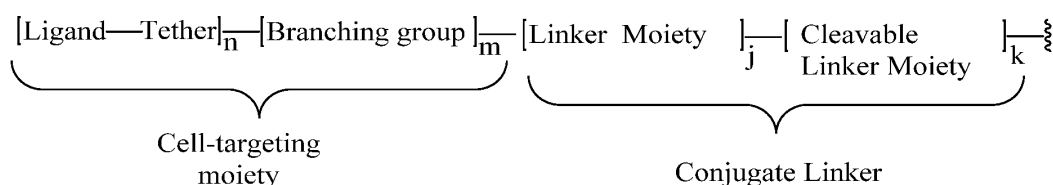
In certain embodiments, it is desirable for a conjugate group to be cleaved from the oligonucleotide. For example, in certain circumstances oligomeric compounds comprising a particular conjugate moiety are better taken up by a particular cell type, but once the oligomeric compound has been taken up, 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 or phosphodiester 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 phosphodiester internucleoside linkage and covalently attached to the remainder of the conjugate linker or conjugate moiety by a phosphate or phosphorothioate internucleoside 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 attached to a branching group. In certain embodiments, cell-targeting moieties comprise three tethered ligands covalently attached to a branching group.

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 nucleosides and/or inverted nucleosides. In certain embodiments, terminal groups comprise one or more 2'-linked nucleosides. In certain such embodiments, the 2'-linked nucleoside is an abasic nucleoside.

III. Oligomeric Duplexes

In certain embodiments, oligomeric compounds described herein comprise an oligonucleotide, having a nucleobase sequence complementary to that of a target nucleic acid. In certain embodiments, an oligomeric compound is paired with a second oligomeric compound to form an oligomeric duplex. Such oligomeric duplexes comprise a first oligomeric compound having a portion complementary to a target nucleic acid and a second oligomeric compound having a portion complementary to the first oligomeric compound. In certain embodiments, the first oligomeric compound of an oligomeric duplex comprises or consists of (1) a modified or unmodified oligonucleotide and optionally a conjugate group and (2) a second modified or unmodified oligonucleotide and optionally a conjugate group. Either or both oligomeric compounds of an oligomeric duplex may comprise a conjugate group. The oligonucleotides of each oligomeric compound of an oligomeric duplex may include non-complementary overhanging nucleosides.

10 **IV. 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 compounds. In certain embodiments, antisense compounds have antisense activity when they reduce the amount or activity of a target nucleic acid by 25% or more in the standard cell assay. In certain embodiments, antisense compounds selectively affect one or more target nucleic acid. Such antisense compounds 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 compound to a target nucleic acid results in recruitment of a protein that cleaves the target nucleic acid. For example, certain antisense compounds 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 compounds that 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 compound or a portion of an antisense compound is loaded into an RNA-induced silencing complex (RISC), ultimately resulting in cleavage of the target nucleic acid. For example, certain antisense compounds result in cleavage of the target nucleic acid by Argonaute. Antisense compounds that are loaded into RISC are RNAi compounds. RNAi compounds may be double-stranded (siRNA) or single-stranded (ssRNA).

In certain embodiments, hybridization of an antisense compound 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 compound to the target nucleic acid results in alteration of splicing of the target nucleic acid. In certain embodiments, hybridization of an antisense compound 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 compound 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 subject.

V. Certain Target Nucleic Acids

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a portion 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 nucleic acid 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

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 a 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 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 portion that is 100% or fully complementary to a target nucleic acid. In certain embodiments, the portion of full complementarity is 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 nucleobases in length.

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, 8, 9, 10, or 11 from the 5'-end of the gap region. In certain embodiments, the mismatch is at position 1, 2, 3, 4, 5, or 6 from the 5'-end of the 5' wing region or the 3' wing region.

B. PLP1

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 PLP1 nucleic acid. In certain embodiments, the PLP1 nucleic acid has the sequence set forth in SEQ ID NO: 1 (GENBANK Accession No. NM_001128834.2) or SEQ ID NO: 2 (GENBANK Accession No. NC_000023.11 truncated from nucleotides 103773001 to 103795000).

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 PLP1 RNA in a cell, and in certain embodiments reduces the amount of PLP1 protein in a cell. In certain embodiments, contacting a cell with a modified oligonucleotide complementary to SEQ ID

NO: 1 or SEQ ID NO: 2 reduces the amount of PLP1 RNA in a cell, and in certain embodiments reduces the amount of PLP1 protein in a cell. In certain embodiments, the cell is *in vitro*. In certain embodiments, the cell is in a subject. In certain embodiments, contacting a cell in a subject with an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 ameliorates one or more symptom or hallmark of a leukodystrophy. In certain embodiments, the

5 leukodystrophy is PMD. In certain embodiments, the symptom or hallmark is selected from hypotonia, nystagmus, optic atrophy, respiratory distress, motor delays, cognitive dysfunction, speech dysfunction, spasticity, ataxia, seizures, and choreiform movements. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide.

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 PLP1 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 *in vitro* assay. In certain

10 embodiments, an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 is capable of reducing the detectable amount of PLP1 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 the standard *in vitro* 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 PLP1

15 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% when administered according to the standard *in vivo* 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 PLP1 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% when administered according to the standard *in vivo* assay. In certain embodiments, an oligomeric

20 compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2, is capable of reducing the detectable amount of PLP1 RNA in the CSF of a subject 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 PLP1 protein in the CSF of a subject 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%.

25 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 (CNS). Such tissues include the brain and spinal cord. In certain embodiments, the

30 pharmacologically relevant tissues include white matter tracts across the brain and spinal cord, such tissues include the corpus callosum, cortex, cerebellum, hippocampus, brain stem, striatum, and spinal cord. In certain embodiments, the pharmacologically relevant tissues include the cortex, cerebellum, hippocampus, brain stem, and spinal cord. In certain embodiments, the pharmacologically relevant cells are oligodendrocytes and oligodendrocyte progenitor cells. In certain embodiments, the pharmacologically relevant cells are Schwann cells or Schwann cell progenitors.

35 VI. 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. 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, 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 a subject, 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. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium 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.

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” expressly includes all such forms that may be fully or partially protonated/de-protonated/in association with a cation. In certain instances, one or more specific cation is identified.

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
5 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
10 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. For example, 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
15 Na⁺ ions. However, the mass of the protons are nevertheless counted toward the weight of the dose, and the mass of the Na⁺ ions are not counted toward the weight of the dose. Thus, for example, a dose, or dosage unit, of 10 mg of Compound No. 1362458 equals the number of fully protonated molecules that weighs 10 mg. This would be equivalent to 10.47 mg of solvent-free, sodium acetate-free, anhydrous sodiated Compound No. 1362458. And, for example, a dose, or dosage unit, of 10 mg of Compound No. 1523605 equals the number of fully protonated molecules that weighs
20 10 mg. This would be equivalent to 10.59 mg of solvent-free, sodium acetate-free, anhydrous sodiated Compound No. 1523605. When an oligomeric compound comprises a conjugate group, the mass of the conjugate group is 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.

VII. Certain Compositions

1. Compound No. 1363235

In certain embodiments, Compound No. 1363235 is characterized as a 5-10-5 MOE gapmer having a sequence
30 (from 5' to 3') of TG TAGTACAAATCTTTCCTT (SEQ ID NO: 2101), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1363235 is represented by the following chemical notation:
35 T_{es}G_{eo}T_{eo}A_{eo}G_{eo}T_{ds}A_{ds}^mC_{ds}A_{ds}A_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}T_{eo}^mC_{eo}^mC_{es}T_{es}T_e (SEQ ID NO: 2101), wherein:

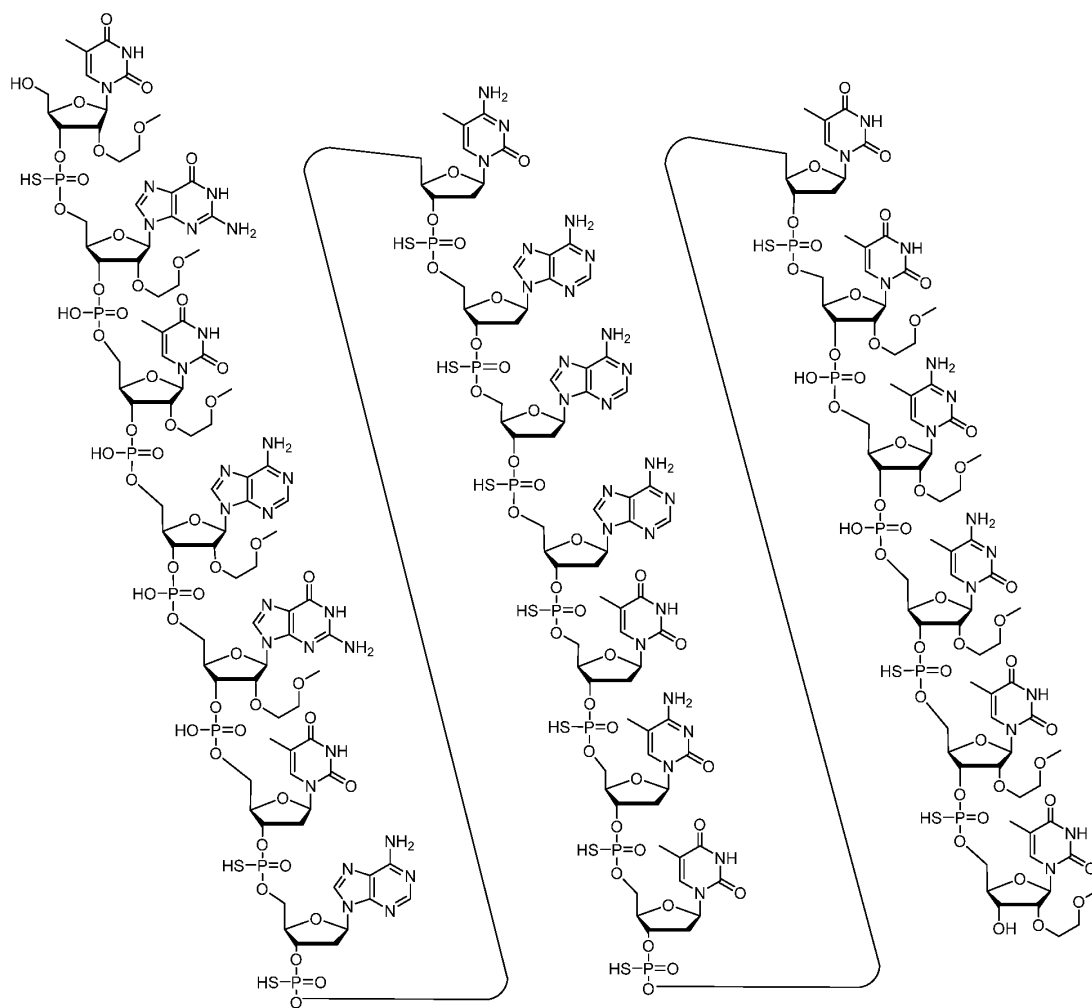
A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

- 5
- T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribose sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

In certain embodiments, Compound No. 1363235 is represented by the following chemical structure:

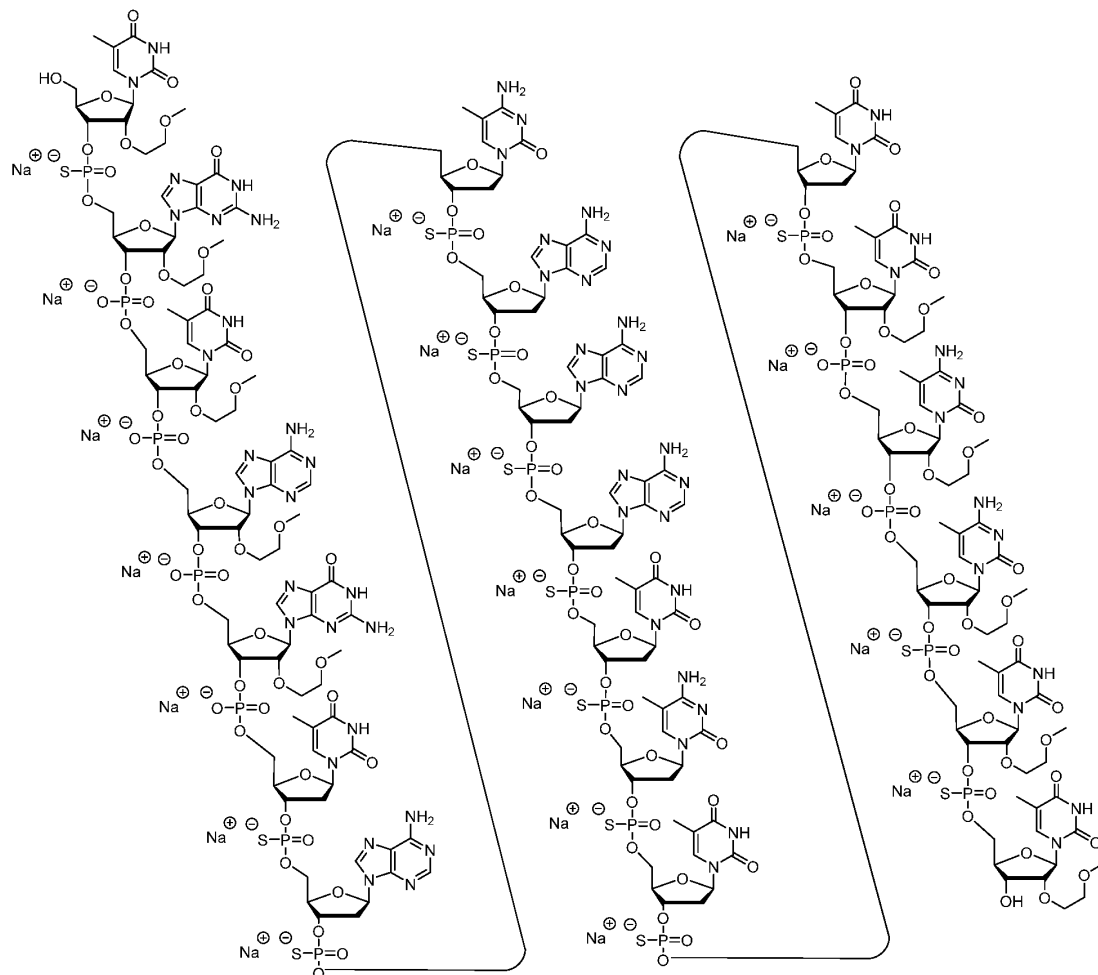


10

(SEQ ID NO: 2101).

Structure 1. Compound No. 1363235

In certain embodiments, the sodium salt of Compound No. 1363235 is represented by the following chemical structure:



5

(SEQ ID NO: 2101).

Structure 2. The sodium salt of Compound No. 1363235

2. Compound No. 1523601

In certain embodiments, Compound No. 1523601 is characterized as a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of ACAAATCTTTCCTTCAATTA (SEQ ID NO: 682), wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1523601 is represented by the following chemical notation:

$A_{es}{}^mC_{eo}A_{eo}A_{eo}A_{eo}T_{eo}{}^mC_{ds}T_{ds}T_{ds}T_{ds}{}^mC_{ds}{}^mC_{ds}T_{ds}T_{ds}{}^mC_{ds}A_{ds}A_{eo}T_{es}T_{es}A_e$ (SEQ ID NO: 682), wherein:

A = an adenine nucleobase,

${}^mC$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

5 T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

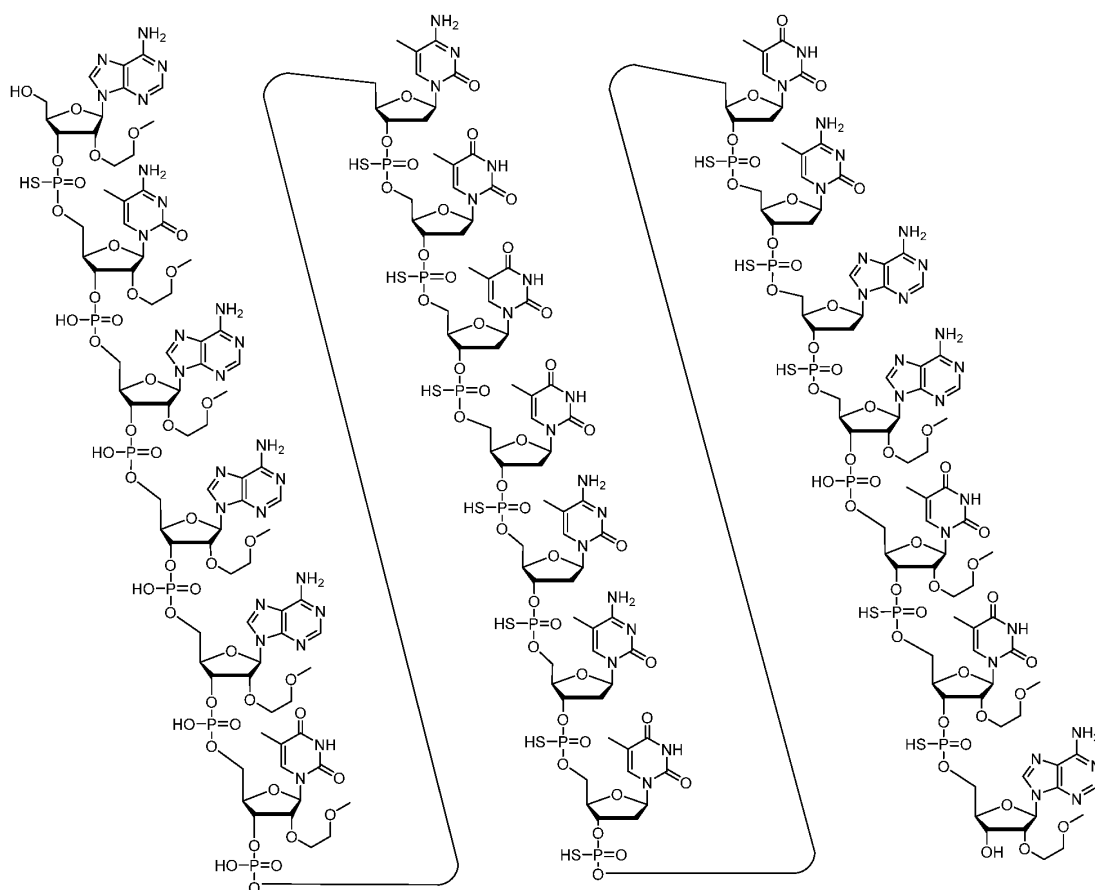
d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

10

In certain embodiments, Compound No. 1523601 is represented by the following chemical structure:

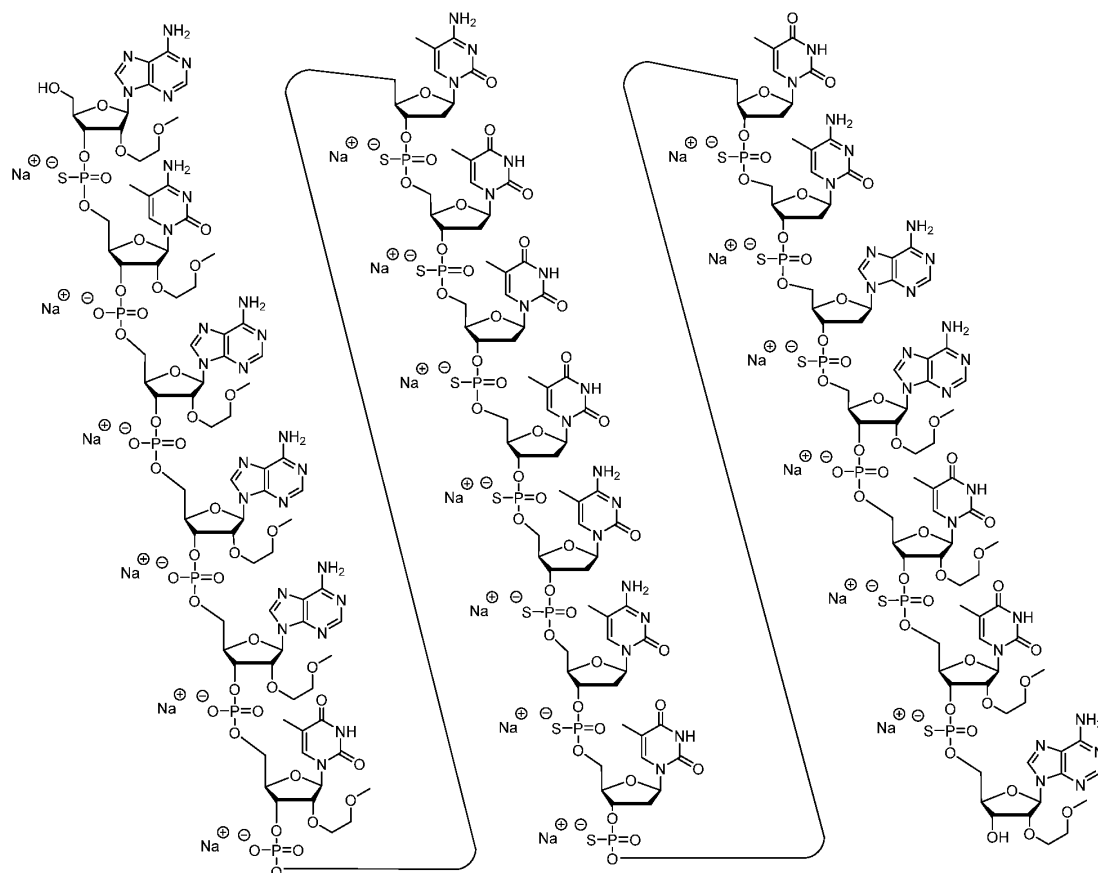


15

(SEQ ID NO: 682).

Structure 3. Compound No. 1523601

In certain embodiments, the sodium salt of Compound No. 1523601 is represented by the following chemical structure:



5

(SEQ ID NO: 682).

Structure 4. The sodium salt of Compound No. 1523601

3. Compound No. 1523605

In certain embodiments, Compound No. 1523605 is characterized as a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of CAGATGTTTCATCTCTTCACA (SEQ ID NO: 1124), wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1523605 is represented by the following chemical notation:

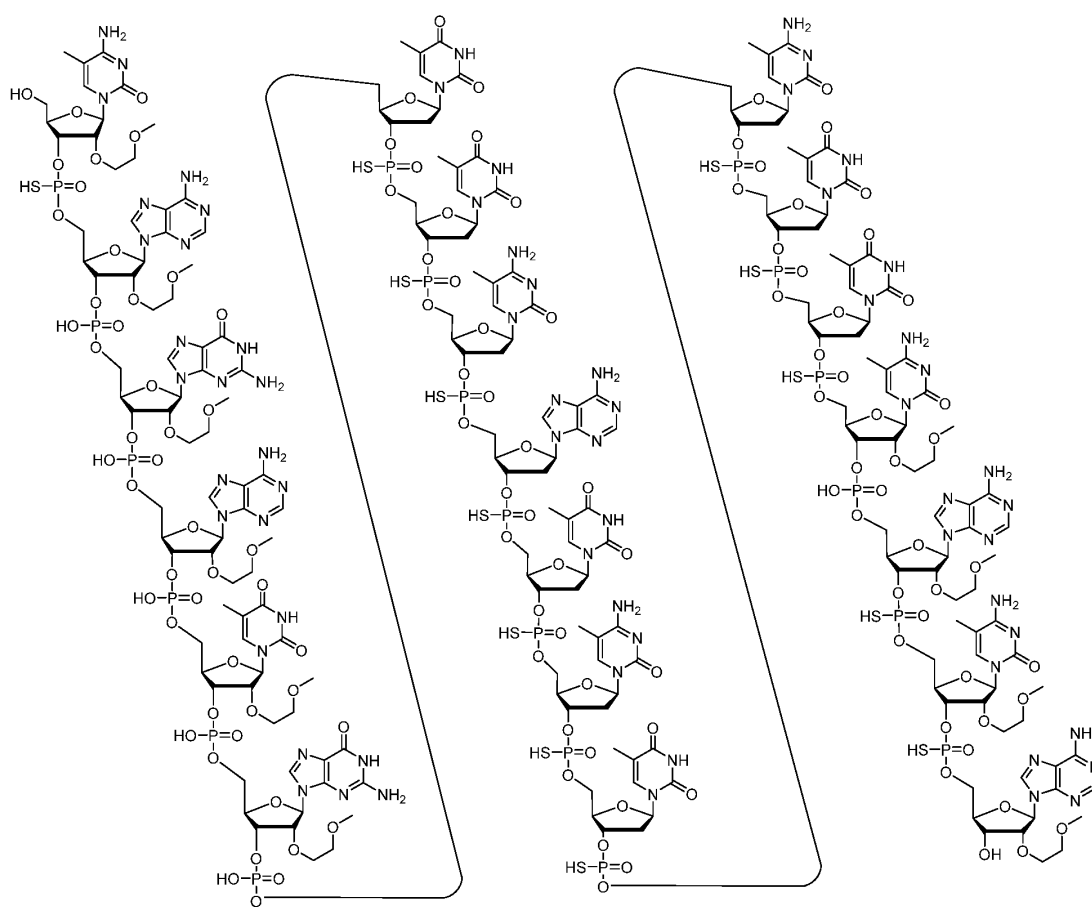
^mC_{es}A_{eo}G_{eo}A_{eo}T_{eo}G_{eo}T_{ds}T_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ds}T_{ds}^mC_{eo}A_{es}^mC_{es}A_e (SEQ ID NO: 1124), wherein:

A = an adenine nucleobase,

- ^mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 5 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

10

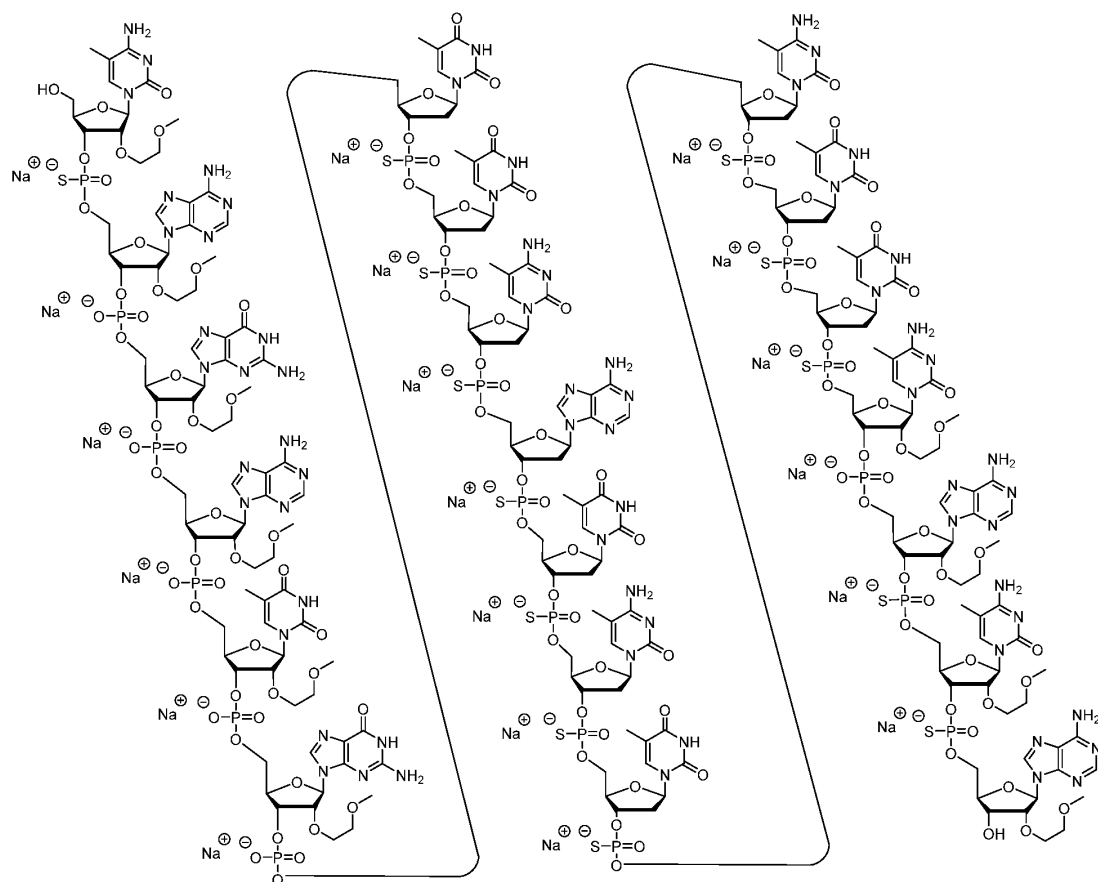
In certain embodiments, Compound No. 1523605 is represented by the following chemical structure:



(SEQ ID NO: 1124).

15 Structure 5. Compound No. 1523605

In certain embodiments, the sodium salt of Compound No. 1523605 is represented by the following chemical structure:



5

(SEQ ID NO: 1124).

Structure 6. The sodium salt of Compound No. 1523605

4. Compound No. 1523608

In certain embodiments, Compound No. 1523608 is characterized as a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of CATCAGATGTTTCATCTCTTC (SEQ ID NO: 2145), wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

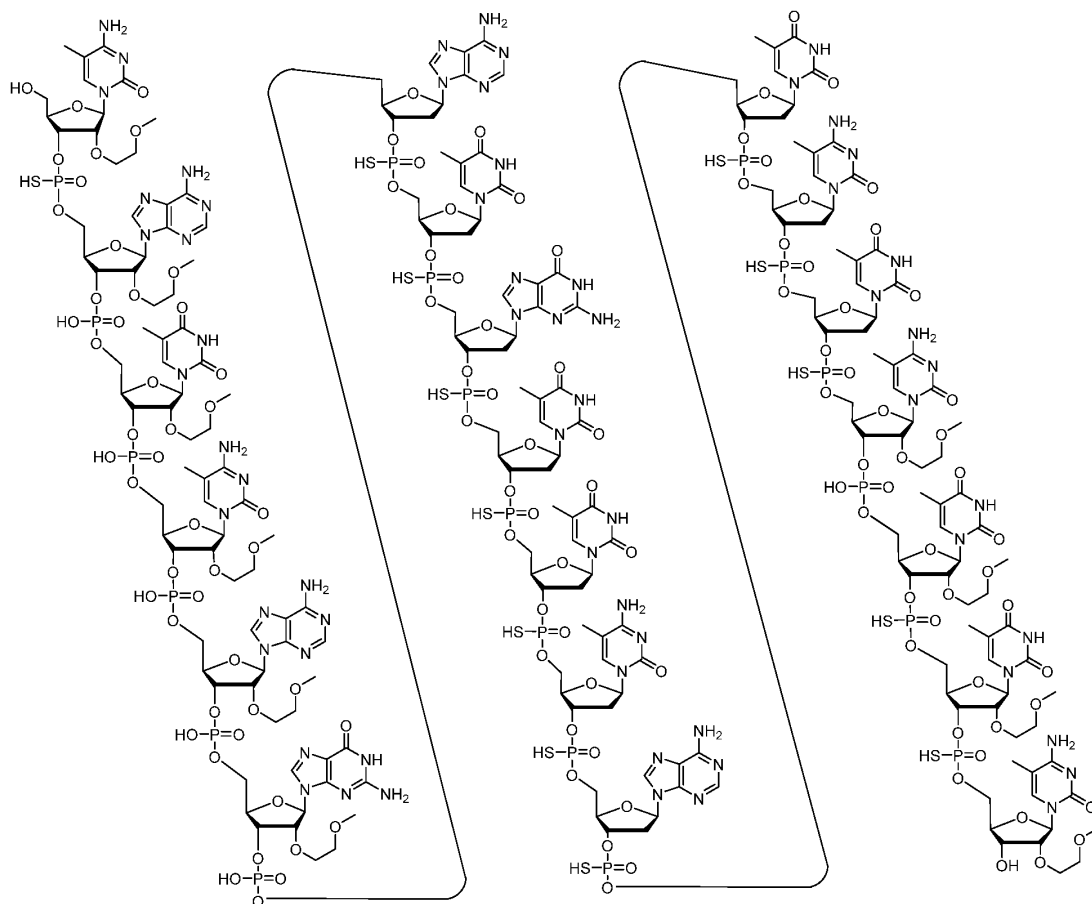
In certain embodiments, Compound No. 1523608 is represented by the following chemical notation:

^mC_{es}A_{eo}T_{eo}^mC_{eo}A_{eo}G_{eo}A_{ds}T_{ds}G_{ds}T_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{eo}T_{es}T_{es}^mC_e (SEQ ID NO: 2145), wherein:

A = an adenine nucleobase,

- ^mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 5 d = a 2'-β-D-deoxyribose sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

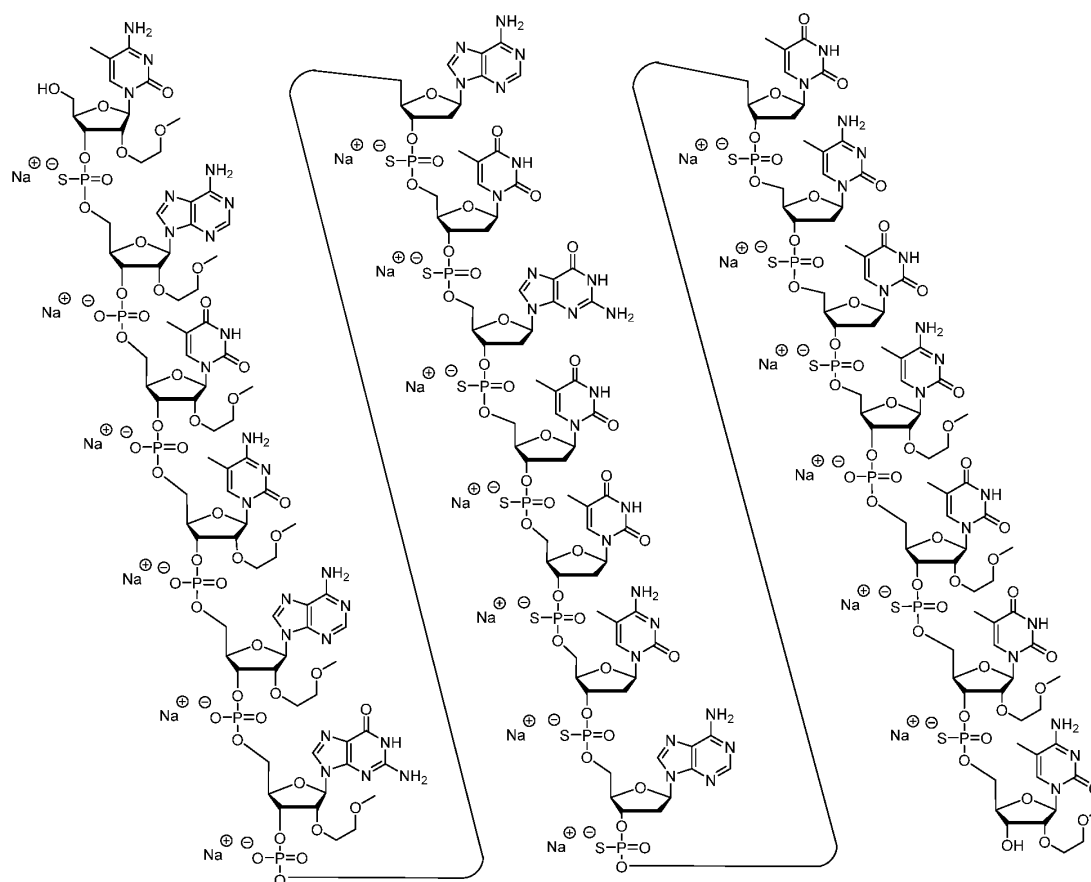
In certain embodiments, Compound No. 1523608 is represented by the following chemical structure:



(SEQ ID NO: 2145).

Structure 7. Compound No. 1523608

In certain embodiments, the sodium salt of Compound No. 1523608 is represented by the following chemical structure:



5

(SEQ ID NO: 2145).

Structure 8. The sodium salt of Compound No. 1523608

5. Compound No. 1362445

In certain embodiments, Compound No. 1362445 is characterized as a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of CCCAATAGATTCAACTAGCC (SEQ ID NO: 134), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

15 In certain embodiments, Compound No. 1362445 is represented by the following chemical notation:

${}^m\text{C}_{\text{es}}{}^m\text{C}_{\text{eo}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{eo}}\text{A}_{\text{eo}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}\text{G}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{A}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{eo}}\text{A}_{\text{eo}}\text{G}_{\text{es}}{}^m\text{C}_{\text{es}}{}^m\text{C}_{\text{e}}$ (SEQ ID NO: 134), wherein:

A = an adenine nucleobase,

${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribose sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

6. Compound No. 1362449

In certain embodiments, Compound No. 1362449 is characterized as a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of ACACAACCTCTTTACAACAAA (SEQ ID NO: 411), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1362449 is represented by the following chemical notation:

$A_{es}^m C_{eo} A_{eo}^m C_{eo} A_{eo} A_{ds}^m C_{ds} T_{ds} T_{ds} T_{ds} T_{ds} A_{ds}^m C_{ds} A_{ds} A_{eo}^m C_{eo} A_{es} A_{es} A_e$ (SEQ ID NO: 411), wherein:

A = an adenine nucleobase,
 mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribose sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

7. Compound No. 1362458

In certain embodiments, Compound No. 1362458 is characterized as a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of TCTCCAGACATTTCTGATGC (SEQ ID NO: 934), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1362458 is represented by the following chemical notation:

$T_{es}^m C_{eo} T_{eo}^m C_{eo}^m C_{eo} A_{ds} G_{ds} A_{ds}^m C_{ds} A_{ds} T_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds} G_{eo} A_{eo} T_{es} G_{es}^m C_e$ (SEQ ID NO: 934), wherein:

A = an adenine nucleobase,
 mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,

T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

8. Compound No. 1362602

In certain embodiments, Compound No. 1362602 is characterized as a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of GTGTGTTAAAATTGCAATTC (SEQ ID NO: 1238), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1362602 is represented by the following chemical notation: $G_{es}T_{eo}G_{eo}T_{eo}G_{eo}T_{ds}T_{ds}A_{ds}A_{ds}A_{ds}A_{ds}T_{ds}T_{ds}G_{ds}^mC_{ds}A_{eo}A_{eo}T_{es}T_{es}^mC_e$ (SEQ ID NO: 1238), wherein:

A = an adenine nucleobase,
 ^mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

9. Compound No. 1362842

In certain embodiments, Compound No. 1362842 is characterized as a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of ATTGCAATTCTATATCAGAA (SEQ ID NO: 2010), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1362842 is represented by the following chemical notation: $A_{es}T_{eo}T_{eo}G_{eo}^mC_{eo}A_{ds}A_{ds}T_{ds}T_{ds}^mC_{ds}T_{ds}A_{ds}T_{ds}A_{ds}T_{ds}^mC_{eo}A_{eo}G_{es}A_{es}A_e$ (SEQ ID NO: 2010), wherein:

A = an adenine nucleobase,
 ^mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,

T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

10. Compound No. 1362892

In certain embodiments, Compound No. 1362892 is characterized as a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of ATGTGATCTATATCAGGAGA (SEQ ID NO: 1772), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1362892 is represented by the following chemical notation:
 $A_{es}T_{eo}G_{eo}T_{eo}G_{eo}A_{ds}T_{ds}{}^mC_{ds}T_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^mC_{ds}A_{ds}G_{eo}G_{eo}A_{es}G_{es}A_e$ (SEQ ID NO: 1772), wherein:

A = an adenine nucleobase,
 ${}^mC$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

11. Compound No. 1363013

In certain embodiments, Compound No. 1363013 is characterized as a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of ACCAGAGGGCCATCTCAGGT (SEQ ID NO: 881), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1363013 is represented by the following chemical notation:
 $A_{es}{}^mC_{eo}{}^mC_{eo}A_{eo}G_{eo}A_{ds}G_{ds}G_{ds}G_{ds}{}^mC_{ds}{}^mC_{ds}A_{ds}{}^mC_{ds}T_{ds}{}^mC_{eo}A_{eo}G_{es}G_{es}T_e$ (SEQ ID NO: 881), wherein:

A = an adenine nucleobase,
 ${}^mC$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,

T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribose sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

12. Compound No. 1363398

In certain embodiments, Compound No. 1363398 is characterized as a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of GCATCAGATGTTCATCTCTT (SEQ ID NO: 1050), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1363398 is represented by the following chemical notation:

$G_{es}^m C_{eo} A_{eo} T_{eo}^m C_{eo} A_{ds} G_{ds} A_{ds} T_{ds} G_{ds} T_{ds}^m C_{ds} A_{ds} T_{ds}^m C_{eo} T_{eo}^m C_{es} T_{es} T_e$ (SEQ ID NO: 1050), wherein:

A = an adenine nucleobase,
 mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribose sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

13. Compound No. 1363557

In certain embodiments, Compound No. 1363557 is characterized as a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of CCTCCATTCCTTTGTGACTT (SEQ ID NO: 1449), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1363557 is represented by the following chemical notation:

$mC_{es}^m C_{eo} T_{eo}^m C_{eo}^m C_{eo} A_{ds} T_{ds} T_{ds}^m C_{ds}^m C_{ds} T_{ds} T_{ds} G_{ds} T_{ds} G_{eo} A_{eo}^m C_{es} T_{es} T_e$ (SEQ ID NO: 1449), wherein:

A = an adenine nucleobase,
 mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

5

VIII. Certain Hotspot Regions

In certain embodiments, nucleobases in the ranges specified below comprise a hotspot region of PLP1 nucleic acid. In certain embodiments, modified oligonucleotides that are complementary to a portion of a hotspot region of PLP1 nucleic acid achieve an average of 50% or greater reduction of PLP1 RNA *in vitro* in the standard *in vitro* assay.

10 In certain embodiments, modified oligonucleotides that are complementary to a portion of a hotspot region of PLP1 nucleic acid achieve an average of 50% or greater reduction of PLP1 RNA *in vivo* in the standard *in vivo* assay.

1. Nucleobases 9198-9222 of SEQ ID NO: 2

In certain embodiments, nucleobases 9198-9222 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 9198-9222 of SEQ ID NO: 2.

15 In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain
 20 embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribosyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted
 25 nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain
 30 embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': soooooossssssooss or soooooossssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 1050, 1124, 2145, 2151, 2152, and 2153 are complementary to a portion of nucleobases 9198-9222 of SEQ ID NO: 2.

35 The nucleobase sequences of Compound Nos.: 1363398, 1363516, 1523604, 1523605, 1523606, 1523607, 1523608, and 1523609 are complementary to a portion of nucleobases 9198-9222 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 9198-9222 of SEQ ID NO: 2 achieve at least 65% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 9198-9222 of SEQ ID NO: 2 achieve an average

of 71.5% reduction of PLP1 RNA in the standard *in vitro* assay.

2. Nucleobases 13702-13766 of SEQ ID NO: 2

In certain embodiments, nucleobases 13702-13766 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 13702-13766 of SEQ ID NO: 2.

5 In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain
10 embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeeeeeeeeee or eeeeeeeeeeeeeee, wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted
15 nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain
20 embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': sooooooooooooo or sooooooooooooo, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 36, 86, 114, 164, 191, 242, 269, 426, 523, 602, 691, and 780 are complementary to a portion of nucleobases 13702-13766 of SEQ ID NO: 2.

25 The nucleobase sequences of Compound Nos.: 1218139, 1218140, 1218141, 1218142, 1218341, 1218342, 1218343, 1362839, 1363565, 1363589, 1363758, and 1364150 are complementary to a portion of nucleobases 13702-13766 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 13702-13766 of SEQ ID NO: 2 achieve at least 60% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 13702-13766 of SEQ ID NO: 2 achieve an
30 average of 68.6% reduction of PLP1 RNA in the standard *in vitro* assay.

3. Nucleobases 14037-14062 of SEQ ID NO: 2

In certain embodiments, nucleobases 14037-14062 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 14037-14062 of SEQ ID NO: 2.

35 In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers

are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribsyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': soooooossssssooss or soooooossssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 89, 167, 245, 322, and 323 are complementary to a portion of nucleobases 14037-14062 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1218352, 1218353, 1218354, 1362909, 1362866, 1218355, and 1218356 are complementary to a portion of nucleobases 14037-14062 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 14037-14062 of SEQ ID NO: 2 achieve at least 64% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 14037-14062 of SEQ ID NO: 2 achieve an average of 79.9% reduction of PLP1 RNA in the standard *in vitro* assay.

4. Nucleobases 16761-16800 of SEQ ID NO: 2

In certain embodiments, nucleobases 16761-16800 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 16761-16800 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribsyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain

embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in the order from 5’ to 3’: sooooooossssssooss or sooooooossssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 720, 808, 904, 937, 1058, 1097, 1184, 1278, and 1340 are
5 complementary to a portion of nucleobases 16761-16800 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1362547, 1362649, 1362825, 1363052, 1363131, 1363205, 1363559, 1363590, and 1363607 are complementary to a portion of nucleobases 16761-16800 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 16761-16800 of SEQ ID NO: 2 achieve at least 60% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments,
10 modified oligonucleotides complementary to a portion of nucleobases 16761-16800 of SEQ ID NO: 2 achieve an average of 70.7% reduction of PLP1 RNA in the standard *in vitro* assay.

5. Nucleobases 17558-17602 of SEQ ID NO: 2

In certain embodiments, nucleobases 17558-17602 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 17558-17602 of SEQ ID NO: 2.
15 In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain
20 embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5’ to 3’: eeeeeedddddddeeeee or eeeeeedddddddeeeee, wherein ‘d’ represents a 2’-β-D-deoxyribose sugar moiety, and ‘e’ represents a 2’-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2’-substituted nucleoside in the gap. In certain embodiments, the 2’-substituted nucleoside comprises a 2’-OMe sugar moiety. In
25 certain embodiments, the 2’-substituted nucleoside is at position 2 of the gap (5’ to 3’).

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain
30 embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in the order from 5’ to 3’: sooooooossssssooss or sooooooossssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 40, 41, 117, 118, 195, 196, 273, 274, 588, 690 are complementary to a portion of nucleobases 17558-17602 of SEQ ID NO: 2.

The nucleobase sequence of Compound Nos.: 1218154, 1218155, 1218156, 1218157, 1218158, 1218159, 1218160, 1218161, 1363257, 1363439, and 1363756 are complementary to a portion of nucleobases 17558-17602 of
35 SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 17558-17602 of SEQ ID NO: 2 achieve at least 62% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments,

modified oligonucleotides complementary to a portion of nucleobases 17558-17602 of SEQ ID NO: 2 achieve an average of 74.6% reduction of PLP1 RNA in the standard *in vitro* assay.

6. Nucleobases 17615-17667 of SEQ ID NO: 2

In certain embodiments, nucleobases 17615-17667 of SEQ ID NO: 2 comprise a hotspot region. In certain
 5 embodiments, modified oligonucleotides are complementary to a portion of nucleobases 17615-17667 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are
 10 MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribsyl sugar
 15 moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified
 20 oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': soooooossssssooss or soooooossssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 42, 43, 119, 120, 197, 198, 275, 276, 373, 460, 1431, 1542, 1645,
 25 1850, 1965, and 2109 are complementary to a portion of nucleobases 17615-17667 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1218162, 1218163, 1218164, 1218165, 1218166, 1218167, 1218168, 1218169, 1362484, 1362497, 1362517, 1362591, 1362749, 1362970, 1363246, 1363342, 1363415, 1363474, 1363544, 1363725, and 1363736 are complementary to a portion of nucleobases 17615-17667 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 17615-17667 of
 30 SEQ ID NO: 2 achieve at least 28% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 17615-17667 of SEQ ID NO: 2 achieve an average of 74.4% reduction of PLP1 RNA in the standard *in vitro* assay.

7. Nucleobases 17853-17883 of SEQ ID NO: 2

In certain embodiments, nucleobases 17853-17883 of SEQ ID NO: 2 comprise a hotspot region. In certain
 35 embodiments, modified oligonucleotides are complementary to a portion of nucleobases 17853-17883 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are

MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': sooooooooooooo or sooooooooooooo, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 1451, 1499, 1543, 1654, 1733, 2154, and 2155 are complementary to a portion of nucleobases 17853-17883 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1362611, 1363392, 1363557, 1363795, 1364094, 1523610, 1523611, 1523612, and 1523613 are complementary to a portion of nucleobases 17853-17883 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 17853-17883 of SEQ ID NO: 2 achieve at least 65% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 17853-17883 of SEQ ID NO: 2 achieve an average of 73.5% reduction of PLP1 RNA in the standard *in vitro* assay.

8. Nucleobases 18097-18160 of SEQ ID NO: 2

In certain embodiments, nucleobases 18097-18160 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 18097-18160 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified

oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in the order from 5’ to 3’: sooooooooooooo or sooooooooooooo, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

5 The nucleobase sequences of SEQ ID NOs: 200, 420, 504, 620, 646, 709, 823, 980, 1029, 1149, 1196, 1253, 1323, 1423, 1476, 1605, 1613, 1728, and 1832 are complementary to a portion of nucleobases 18097-18160 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1218175, 1362441, 1362447, 1362750, 1362769, 1362774, 1362926, 1362945, 1362957, 1362963, 1362967, 1363191, 1363253, 1363427, 1363489, 1363691, 1363993, 1364083, 10 1364097, and 1364099 are complementary to a portion of nucleobases 18097-18160 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18097-18160 of SEQ ID NO: 2 achieve at least 53% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18097-18160 of SEQ ID NO: 2 achieve an average of 70.1% reduction of PLP1 RNA in the standard *in vitro* assay.

15 9. Nucleobases 18206-18237 of SEQ ID NO: 2

In certain embodiments, nucleobases 18206-18237 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 18206-18237 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 20 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain 25 embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5’ to 3’: eeeeeeeeeeeeeee or eeeeeeeeeeeeeee, wherein ‘d’ represents a 2’-β-D-deoxyribose sugar moiety, and ‘e’ represents a 2’-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2’-substituted nucleoside in the gap. In certain embodiments, the 2’-substituted nucleoside comprises a 2’-OMe sugar moiety. In certain embodiments, the 2’-substituted nucleoside is at position 2 of the gap (5’ to 3’).

30 In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in the order from 5’ to 3’: sooooooooooooo or sooooooooooooo, wherein each “s” represents a phosphorothioate 35 internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

The nucleobase sequences of 45, 46, 123, 124, 201, 202, 279, 280, 538, 562, and 2091 are complementary to a portion of nucleobases 18206-18237 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1218177, 1218178, 1218179, 1218180, 1218181, 1218182, 1218183, 1218184, 1362490, 1362584, 1362927, 1363103, 1363121, 1363314, and 1363983 are complementary to a

portion of nucleobases 18206-18237 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18206-18237 of SEQ ID NO: 2 achieve at least 64% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18206-18237 of SEQ ID NO: 2 achieve an average of 81.8% reduction of PLP1 RNA in the standard *in vitro* assay.

10. Nucleobases 18237-18340 of SEQ ID NO: 2

In certain embodiments, nucleobases 18237-18340 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 18237-18340 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeeee or eeeeeeddddddddeeeeee, wherein 'd' represents a 2'-β-D-deoxyribsyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': soooooossssssoosss or soooooossssssoosss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 48, 49, 50, 51, 52, 53, 125, 126, 127, 128, 129, 130, 131, 203, 204, 205, 206, 207, 208, 281, 282, 283, 284, 285, 286, 414, 459, 485, 503, 579, 580, 693, 724, 840, 873, 911, 1034, 1081, 1125, 1159, 1318, 1413, 1513, 1548, 1672, 1701, 1794, 1868, 1958, and 2002 are complementary to a portion of nucleobases 18237-18340 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1218186, 1218187, 1218188, 1218189, 1218190, 1218191, 1218192, 1218193, 1218194, 1218195, 1218196, 1218197, 1218198, 1218199, 1218200, 1218201, 1218202, 1218203, 1218204, 1218205, 1218206, 1218207, 1218208, 1218209, 1218210, 1362429, 1362468, 1362571, 1362623, 1362659, 1362697, 1362699, 1362710, 1362714, 1362723, 1362734, 1362821, 1362902, 1362924, 1362955, 1362977, 1363036, 1363051, 1363069, 1363149, 1363206, 1363269, 1363286, 1363355, 1363429, 1363518, 1363687, 1363748, 1363790, 1363856, 1363872, 1363884, 1364129, 1364227, and 1364246 are complementary to a portion of nucleobases 18237-18340 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18237-18340 of SEQ ID NO: 2 achieve at least 44% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments,

modified oligonucleotides complementary to a portion of nucleobases 18237-18340 of SEQ ID NO: 2 achieve an average of 70.9% reduction of PLP1 RNA in the standard *in vitro* assay.

11. Nucleobases 18350-18387 of SEQ ID NO: 2

In certain embodiments, nucleobases 18350-18387 of SEQ ID NO: 2 comprise a hotspot region. In certain
 5 embodiments, modified oligonucleotides are complementary to a portion of nucleobases 18350-18387 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are
 10 MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribsyl sugar
 15 moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified
 20 oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': soooooossssssooss or soooooossssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 209, 287, 335, 439, 506, 606, 659, 1922, 2033, and 2104 are
 25 complementary to a portion of nucleobases 18350-18387 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1218211, 1218212, 1362567, 1362579, 1362987, 1363166, 1363184, 1363310, 1363502, and 1363644 are complementary to a portion of nucleobases 18350-18387 of SEQ ID NO:
 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18350-18387 of
 30 SEQ ID NO: 2 achieve at least 64% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18350-18387 of SEQ ID NO: 2 achieve an average of 76.2% reduction of PLP1 RNA in the standard *in vitro* assay.

12. Nucleobases 18412-18469 of SEQ ID NO: 2

In certain embodiments, nucleobases 18412-18469 of SEQ ID NO: 2 comprise a hotspot region. In certain
 35 embodiments, modified oligonucleotides are complementary to a portion of nucleobases 18412-18469 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are

MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': soooooossssssoos or soooooossssssoos, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 784, 842, 869, 978, 1082, 1131, 1218, 1250, 1320, 1453, 1529, 1538, 1616, 1712, and 1821 are complementary to a portion of nucleobases 18412-18469 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1362519, 1362535, 1362684, 1362724, 1362885, 1363026, 1363457, 1363648, 1363838, 1363887, 1363933, 1364125, 1364192, 1364197, and 1364255 are complementary to a portion of nucleobases 18412-18469 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18412-18469 of SEQ ID NO: 2 achieve at least 67% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18412-18469 of SEQ ID NO: 2 achieve an average of 75% reduction of PLP1 RNA in the standard *in vitro* assay.

13. Nucleobases 18461-18506 of SEQ ID NO: 2

In certain embodiments, nucleobases 18461-18506 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 18461-18506 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in the order from 5’ to 3’: sooooooossssssooss or sooooooossssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 54, 55, 132, 133, 210, 288, 419, 499, 564, 665, 764, 800, 881, 993, 1059, 1200, 1295, 1354, 1422, 1465, 1544, 1705, 1802, and 2149 are complementary to a portion of nucleobases 18461-18506 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1218213, 1218214, 1218215, 1218216, 1218217, 1218218, 1362618, 1362620, 1362632, 1362704, 1362718, 1362815, 1363013, 1363023, 1363128, 1363328, 1363400, 1363431, 1363519, 1363533, 1363570, 1363709, 1363762, 1363975, 1364180, 1523591, 1523592, and 1523593 are complementary to a portion of nucleobases 18461-18506 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18461-18506 of SEQ ID NO: 2 achieve at least 40% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18461-18506 of SEQ ID NO: 2 achieve an average of 69.7% reduction of PLP1 RNA in the standard *in vitro* assay.

14. Nucleobases 18539-18579 of SEQ ID NO: 2

In certain embodiments, nucleobases 18539-18579 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 18539-18579 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5’ to 3’: eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein ‘d’ represents a 2’-β-D-deoxyribose sugar moiety, and ‘e’ represents a 2’-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2’-substituted nucleoside in the gap. In certain embodiments, the 2’-substituted nucleoside comprises a 2’-OMe sugar moiety. In certain embodiments, the 2’-substituted nucleoside is at position 2 of the gap (5’ to 3’).

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in the order from 5’ to 3’: sooooooossssssooss or sooooooossssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 338, 438, 525, 604, 658, 758, 813, 887, 977, 1043, 1108, 1199, 1258, 1336, 1395, 1514, 1557, 1668, 1697, and 2089 are complementary to a portion of nucleobases 18539-18579 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1362619, 1362637, 1362652, 1362830, 1362901, 1363079, 1363118, 1363143, 1363145, 1363146, 1363176, 1363193, 1363287, 1363422, 1363451, 1363569, 1363592, 1363611, 1363796, and 1363860 are complementary to a portion of nucleobases 18539-18579 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18539-18579 of SEQ ID NO: 2 achieve at least 62% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18539-18579 of SEQ ID NO: 2 achieve an average of 68.8% reduction of PLP1 RNA in the standard *in vitro* assay.

15. Nucleobases 18697-18727 of SEQ ID NO: 2

In certain embodiments, nucleobases 18697-18727 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 18697-18727 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': soooooossssssooss or soooooossssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 875, 934, 1047, 1110, 1229, 1243, 1373, 1438, 2146, and 2147 are complementary to a portion of nucleobases 18697-18727 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1362458, 1362696, 1362878, 1363179, 1363351, 1363697, 1364107, 1364147, 1523584, 1523586, and 1523587 are complementary to a portion of nucleobases 18697-18727 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18697-18727 of SEQ ID NO: 2 achieve at least 66% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18697-18727 of SEQ ID NO: 2 achieve an

average of 77.7% reduction of PLP1 RNA in the standard *in vitro* assay.

16. Nucleobases 18755-18793 of SEQ ID NO: 2

In certain embodiments, nucleobases 18755-18793 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 18755-18793 of SEQ ID NO: 2.

5 In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain
10 embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeeeeeeeeee or eeeeeeeeeeeeeee, wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted
15 nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain
20 embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': sooooooooooooo or sooooooooooooo, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 761, 798, 890, 946, 1022, 1120, 1198, 1293, 1358, 1398, and 1463 are complementary to a portion of nucleobases 18755-18793 of SEQ ID NO: 2.

25 The nucleobase sequences of Compound Nos.: 1362575, 1362680, 1362689, 1362856, 1363019, 1363172, 1363357, 1363391, 1363591, 1363639, and 1363889 are complementary to a portion of nucleobases 18755-18793 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18755-18793 of SEQ ID NO: 2 achieve at least 65% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18755-18793 of SEQ ID NO: 2 achieve an
30 average of 77.7% reduction of PLP1 RNA in the standard *in vitro* assay.

17. Nucleobases 18797-18819 of SEQ ID NO: 2

In certain embodiments, nucleobases 18797-18819 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 18797-18819 of SEQ ID NO: 2.

35 In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers

are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribsyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': soooooossssssooss or soooooossssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 56, 134, 683, and 718 are complementary to a portion of nucleobases 18797-18819 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1218221, 1218222, 1362445, 1362612, 1363487, and 1363656 are complementary to a portion of nucleobases 18797-18819 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18797-18819 of SEQ ID NO: 2 achieve at least 65% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18797-18819 of SEQ ID NO: 2 achieve an average of 75.4% reduction of PLP1 RNA in the standard *in vitro* assay.

18. Nucleobases 18839-18862 of SEQ ID NO: 2

In certain embodiments, nucleobases 18839-18862 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 18839-18862 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribsyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain

embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in the order from 5’ to 3’: soooooossssssooss or soooooossssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 1610, 1663, 1702, and 1786 are complementary to a portion of
5 nucleobases 18839-18862 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1363076, 1362712, 1363649, and 1364195 are complementary to a portion of nucleobases 18839-18862 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18839-18862 of SEQ ID NO: 2 achieve at least 66% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments,
10 modified oligonucleotides complementary to a portion of nucleobases 18839-18862 of SEQ ID NO: 2 achieve an average of 72.8% reduction of PLP1 RNA in the standard *in vitro* assay.

19. Nucleobases 18974-19021 of SEQ ID NO: 2

In certain embodiments, nucleobases 18974-19021 of SEQ ID NO: 2 comprise a hotspot region. In certain
embodiments, modified oligonucleotides are complementary to a portion of nucleobases 18974-19021 of SEQ ID NO: 2.
15 In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers
20 are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5’ to 3’: eeeeeedddddddeeeee or eeeeeedddddddeeeee, wherein ‘d’ represents a 2’-β-D-deoxyribose sugar moiety, and ‘e’ represents a 2’-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2’-substituted
25 nucleoside in the gap. In certain embodiments, the 2’-substituted nucleoside comprises a 2’-OMe sugar moiety. In certain embodiments, the 2’-substituted nucleoside is at position 2 of the gap (5’ to 3’).

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified
oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain
30 embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in the order from 5’ to 3’: soooooossssssooss or soooooossssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 212, 1060, 1090, 1181, 1277, 1446, 1510, 1589, 1646, 1693, 1772, and 2148 are complementary to a portion of nucleobases 18974-19021 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1218223, 1362460, 1362600, 1362805, 1362892, 1363007, 1363316, 1363581, 1363642, 1363664, 1363773, 1363984, 1523588, 1523589, and 1523590 are complementary to a
35 portion of nucleobases 18974-19021 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 18974-19021 of SEQ ID NO: 2 achieve at least 54% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments,

modified oligonucleotides complementary to a portion of nucleobases 18974-19021 of SEQ ID NO: 2 achieve an average of 71.5% reduction of PLP1 RNA in the standard *in vitro* assay.

20. Nucleobases 19028-19080 of SEQ ID NO: 2

In certain embodiments, nucleobases 19028-19080 of SEQ ID NO: 2 comprise a hotspot region. In certain
 5 embodiments, modified oligonucleotides are complementary to a portion of nucleobases 19028-19080 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are
 10 MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribsyl sugar
 15 moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified
 20 oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': soooooossssssooss or soooooossssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 57, 586, 666, 714, 812, 914, 951, 1052, 1138, 1162, 1248, 1363,
 25 and 1455 are complementary to a portion of nucleobases 19028-19080 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1218225, 1362492, 1362565, 1362817, 1362846, 1363141, 1363160, 1363346, 1363453, 1363550, 1363765, 1363835, 1363883, and 1364201 are complementary to a portion of nucleobases 19028-19080 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 19028-19080 of
 30 SEQ ID NO: 2 achieve at least 58% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 19028-19080 of SEQ ID NO: 2 achieve an average of 73.5% reduction of PLP1 RNA in the standard *in vitro* assay.

21. Nucleobases 19146-19173 of SEQ ID NO: 2

In certain embodiments, nucleobases 19146-19173 of SEQ ID NO: 2 comprise a hotspot region. In certain
 35 embodiments, modified oligonucleotides are complementary to a portion of nucleobases 19146-19173 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are

MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': soooooossssssooss or soooooossssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 385, 416, 545, 621, 682, 1968, 2055, 2101, and 2150 are complementary to a portion of nucleobases 19146-19173 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1362670, 1363235, 1363627, 1363734, 1363940, 1364008, 1364066, 1523601, 1523602, and 1523603 are complementary to a portion of nucleobases 19146-19173 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 19148-19173 of SEQ ID NO: 2 achieve at least 54% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 19146-19173 of SEQ ID NO: 2 achieve an average of 77.3% reduction of PLP1 RNA in the standard *in vitro* assay.

22. Nucleobases 19228-19253 of SEQ ID NO: 2

In certain embodiments, nucleobases 19228-19253 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 19228-19253 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in the order from 5’ to 3’: sooooooossssssooss or sooooooossssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 363, 467, 541, 2008, and 2111 are complementary to a portion of nucleobases 19228-19253 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1364015, 1363882, 1363157, 1363485, and 1362808 are complementary to a portion of nucleobases 19228-19253 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 19228-19253 of SEQ ID NO: 2 achieve at least 69% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 19228-19253 of SEQ ID NO: 2 achieve an average of 77.4% reduction of PLP1 RNA in the standard *in vitro* assay.

23. Nucleobases 19347-19393 of SEQ ID NO: 2

In certain embodiments, nucleobases 19347-19393 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 19347-19393 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5’ to 3’: eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein ‘d’ represents a 2’-β-D-deoxyribose sugar moiety, and ‘e’ represents a 2’-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2’-substituted nucleoside in the gap. In certain embodiments, the 2’-substituted nucleoside comprises a 2’-OMe sugar moiety. In certain embodiments, the 2’-substituted nucleoside is at position 2 of the gap (5’ to 3’).

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in the order from 5’ to 3’: sooooooossssssooss or sooooooossssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 58, 59, 136, 213, 214, 291, 292, 383, 417, 519, 612, 671, 730, 900, 986, 1019, 1136, 1353, 1457, 1504, 1546, and 2093 are complementary to a portion of nucleobases 19347-19393 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1218227, 1218228, 1218229, 1218230, 1218231, 1218232,

1218233, 1362526, 1362624, 1362677, 1362685, 1362799, 1362806, 1363094, 1363419, 1363425, 1363472, 1363499, 1363597, 1363628, 1363681, 1363744, 1363759, 1363800, and 1364257 are complementary to a portion of nucleobases 19347-19393 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 19347-19393 of SEQ ID NO: 2 achieve at least 52% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 19347-19393 of SEQ ID NO: 2 achieve an average of 71.6% reduction of PLP1 RNA in the standard *in vitro* assay.

24. Nucleobases 19500-19523 of SEQ ID NO: 2

In certain embodiments, nucleobases 19500-19523 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 19500-19523 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeee, wherein 'd' represents a 2'-β-D-deoxyribosyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': soooooossssssooss or soooooossssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 398, 435, 2095, 2010, and 2144 are complementary to a portion of nucleobases 19500-19523 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1362842, 1363110, 1363153, 1363982, 1523594, and 1523595 are complementary to a portion of nucleobases 19500-19523 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 19500-19523 of SEQ ID NO: 2 achieve at least 62% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 19500-19523 of SEQ ID NO: 2 achieve an average of 69.5% reduction of PLP1 RNA in the standard *in vitro* assay.

25. Nucleobases 19512-19534 of SEQ ID NO: 2

In certain embodiments, nucleobases 19512-19534 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 19512-19534 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddeeeee or eeeeeeddddddddeeeee, wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, all of the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in the order from 5' to 3': soooooossssssooss or soooooossssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 1201, 1238, 1341, and 1435 are complementary to a portion of nucleobases 19512-19534 of SEQ ID NO: 2.

The nucleobase sequences of Compound Nos.: 1362602, 1363268, 1363452, and 1363678 are complementary to a portion of nucleobases 19512-19534 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 19512-19534 of SEQ ID NO: 2 achieve at least 63% reduction of PLP1 RNA in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 19512-19534 of SEQ ID NO: 2 achieve an average of 80% reduction of PLP1 RNA 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, 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^mCGAUCG," wherein ^mC indicates a cytosine base comprising a methyl group at the 5-position.

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 ¹H hydrogen atoms. Isotopic substitutions encompassed by the compounds herein include but are not limited to: ²H or ³H in place of ¹H, ¹³C or ¹⁴C in place of ¹²C, ¹⁵N in place of ¹⁴N, ¹⁷O or ¹⁸O in place of ¹⁶O, and ³³S, ³⁴S, ³⁵S, or ³⁶S in place of ³²S. 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. For example, disclosure of an oligonucleotide having a particular motif provides reasonable support for additional oligonucleotides having the same or similar motif. And, for example, where a particular high-affinity modification appears at a particular position, other high-affinity modifications at the same position are considered suitable, unless otherwise indicated.

Example 1: Effect of 5-10-5 MOE gapmer modified oligonucleotides on human PLP1 RNA *in vitro*, single dose

Modified oligonucleotides complementary to human PLP1 nucleic acid were designed and tested for their single dose effects on PLP1 RNA *in vitro*. The modified oligonucleotides were tested in a series of experiments that had the same culture conditions, and the results for each experiment are presented in separate tables below.

5 The modified oligonucleotides in the tables below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment consists of ten 2'- β -D-deoxynucleosides and the 5' and 3' wing segments each consists of five 2'-MOE modified nucleosides. The sugar motif for the gapmers is (from 5' to 3'): eeeeeeeeeeeeeeeeee; wherein 'd' represents a 2'- β -D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. The internucleoside linkages throughout each modified oligonucleotide are phosphorothioate internucleoside
10 linkages. Each cytosine residue is a 5-methyl cytosine.

"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 Tables below is 100% complementary to either human PLP1 mRNA, designated herein as SEQ ID NO: 1 (GENBANK Accession No.
15 NM_001128834.2) or to the human PLP1 genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NC_000023.11 truncated from nucleotides 103773001 to 103795000), or to both. 'N/A' indicates that the modified oligonucleotide is not 100% complementary to that particular target nucleic acid sequence.

Cultured SK-MEL-28 cells were treated with modified oligonucleotide at a concentration of 7,000 nM using electroporation at a density of 20,000 cells per well. After a treatment period of approximately 24 hours, total RNA was
20 isolated from the cells and PLP1 RNA levels were measured by quantitative real-time RTPCR. PLP1 RNA levels were measured by Human PLP1 primer probe set RTS35092 (forward sequence CTGATGCCAGAATGTATGGTGT, designated herein as SEQ ID NO: 11; reverse sequence AGGTGGAAGGTCATTTGGAAC, designated herein as SEQ ID NO: 12; probe sequence TGCAGATGGACAGAAGGTTGGAGC, designated herein as SEQ ID NO: 13). PLP1 RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of PLP1 RNA is
25 presented in the tables below as percent PLP1 RNA relative to the amount in untreated control cells (% UTC). Each table represents results from an individual assay plate. The values marked with an "†" 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.

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Table 1

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with phosphorothioate internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1218077	N/A	N/A	3805	3824	AGCCAACCCCTTAAAGGGA	96	20
1218081	N/A	N/A	3815	3834	TCTGATTGACAGCCAACCCC	92	21
1218085	238	257	3948	3967	CCGGCTGGCTAGTCTGCTTT	43	22
1218089	249	268	3959	3978	TCCAATTGTAGCCGGCTGGC	62	23
1218093	305	324	12597	12616	CCCTACCAGACATCTGCAC	39	24

1218097	551	570	13539	13558	GCCGGTGGTGTAGAAGCCCT	67	25
1218101	564	583	13552	13571	TCTGCCTGACTGCGCCGGTG	31	26
1218105	577	596	13565	13584	TAGTCGCCAAAGATCTGCCT	50	27
1218109	589	608	13577	13596	ATGGTGGTCTTGTAGTCGCC	47	28
1218113	600	619	13588	13607	CCTTGCCGCAGATGGTGGTC	54	29
1218117	604	623	13592	13611	AGGCCCTTGCCGCAGATGGT	51	30
1218121	614	633	13602	13621	CGTTGCGCTCAGGCCCTTGC	70	31
1218125	620	639	13608	13627	TGTTACCGTTGCGCTCAGGC	64	32
1218129	624	643	13612	13631	CCCCTGTTACCGTTGCGCTC	76	33
1218133	656	675	13644	13663	ATGTTGGCCTCTGGAACCCC	51	34
1218137	689	708	13677	13696	ACAATGACACACCCGCTCCA	75	35
1218141	717	736	13705	13724	TGTCGGGATGTCCTAGCCAT	31	36
1218145	757	776	14816	14835	AGCCACACAACGGTCAGGGC	25	37
1218149	815	834	14874	14893	GGTGGTCCAGGTGTTGAAGT	75	38
1218153	907	926	15436	15455	GCATTCCATGGGAGAACACC	29†	39
1218157	1099	1118	17578	17597	CAGAACTTGGTGCCTCGGCC	16	40
1218161	1104	1123	17583	17602	GGGATCAGAACTTGGTGCCT	38	41
1218165	1151	1170	17630	17649	GCTGTGTGGTTAGAGCCTCG	19	42
1218169	1169	1188	17648	17667	GGAGACGCAGCATTGTAGGC	36	43
1218173	1528	1547	18007	18026	GGCCCTATAGATGGCAAGA	46	44
1218177	1727	1746	18206	18225	CAGTAGTCCATCGCCATCGG	28	45
1218181	1734	1753	18213	18232	AGGGCTTCAGTAGTCCATCG	12	46
1218185	1747	1766	18226	18245	GGTTGGCTGAGTTAGGGCTT	25	47
1218189	1764	1783	18243	18262	CCTTATGCTGTAAGTAAGGT	24	48
1218193	1770	1789	18249	18268	ACGCTCCCTTATGCTGTAAG	11	49
1218197	1774	1793	18253	18272	TTCTACGCTCCCTTATGCTG	40	50
1218201	1782	1801	18261	18280	TACACAGATTCTACGCTCCC	29	51
1218205	1807	1826	18286	18305	TGTAAGGCCAGATGCCCCCT	34	52
1218209	1824	1843	18303	18322	TCTCTCCCTAACGAGGTGT	9	53
1218213	1983	2002	18462	18481	AGGTTACACCATTAGCCACC	25	54
1218217	2005	2024	18484	18503	GTGTCTACCAGAGGGCCATC	27	55
1218221	2318	2337	18797	18816	CCAATAGATTCAACTAGCCA	22	56
1218225	2582	2601	19061	19080	GGAGCTATTCAGGTCTCAAA	12	57
1218229	2880	2899	19359	19378	TACGGATTACTTCACTGTCC	18	58
1218233	2888	2907	19367	19386	ACACAAGGTACGGATTACTT	23	59
1218237	36	55	3541	3560	TCCTTGGGTCTAATTGGTGT	93	60
1218241	115	134	3620	3639	TCGCTTTGCTGCAGAGACAT	88	61
1218245	N/A	N/A	1120	1139	TGGGCCCCCTTGATCATGGC	90	62
1218249	N/A	N/A	1412	1431	GCTCCCTACAGACCTCATAG	93	63
1218253	N/A	N/A	2172	2191	GGTCCTAGAGCCCCCTCGCCC	94	64
1218257	N/A	N/A	2814	2833	CCTGCCTTAGCAATAAGCTA	91	65
1218261	N/A	N/A	3457	3476	AACCTAGATATTAGCTCCCA	91	66
1218265	N/A	N/A	4445	4464	GCCCGATCCCCAGCTTCCCTA	78	67

1218269	N/A	N/A	5257	5276	GTTGTTATAGATCTTGCCCA	38	68
1218273	N/A	N/A	5479	5498	TGCACAACCTATCCAGTCAG	65	69
1218277	N/A	N/A	5871	5890	CCAATCCCGGATTCCATGAT	55	70
1218281	N/A	N/A	5994	6013	GTTGAAGTAGTAAGTTCCCT	34	71
1218285	N/A	N/A	6371	6390	GCCGCCACACTTTTTGCCTG	45	72
1218289	N/A	N/A	7095	7114	AGGGCCATTTTGCCGTAGGC	46	73
1218293	N/A	N/A	7523	7542	CGATTTAGTATTACCACGGC	24	74
1218297	N/A	N/A	7663	7682	GATATCAGCACTTATATACC	86	75
1218301	N/A	N/A	8082	8101	ACCAATTGTACCCTGCACAA	65	76
1218305	N/A	N/A	8355	8374	TTAAGCCCTTCTCACCAGCG	49	77
1218309	N/A	N/A	9005	9024	CCATTGGGCTCCCTTGATT	49	78
1218313	N/A	N/A	9645	9664	GTGCTTGTGCAGGTATGGTC	26	79
1218317	N/A	N/A	9713	9732	TCCACCCTAGCAAGTGACCA	68	80
1218321	N/A	N/A	10517	10536	GAGTCCTATTACCCACCATC	47	81
1218325	N/A	N/A	10523	10542	AGGAGTGAGTCCTATTACCC	56	82
1218329	N/A	N/A	11359	11378	CCCTCAGTTATACGCTGAGA	43	83
1218333	N/A	N/A	11465	11484	AGGAGGTTTGATATTACTCC	64	84
1218337	N/A	N/A	13224	13243	ACCTTGCTTACCCTGGGACC	50	85
1218341	N/A	N/A	13709	13728	ACCTTGTCGGGATGTCCTAG	39	86
1218345	N/A	N/A	13766	13785	ACTCGCGCCCAATTTTCCCC	50	87
1218349	N/A	N/A	13777	13796	CGAGGCCACAGACTCGCGCC	49	88
1218353	N/A	N/A	14039	14058	CCAGTTAGATCCACTCTTGT	29	89
1218357	N/A	N/A	14083	14102	GGTGCCCAAGTCTCAATCAC	43	90
1218361	N/A	N/A	14608	14627	TCTACTAGATAACTGGCCCC	64	91
1218365	N/A	N/A	14964	14983	CCCGTACCCTAACTCACCAT	77†	92
1218369	N/A	N/A	15536	15555	GGTATTAGCTACTCCCTTGT	40	93
1218373	N/A	N/A	15765	15784	CCATTAGGCTCTATCTTTAC	52	94
1218377	N/A	N/A	16150	16169	TCAGTGTACACCATAGCACC	37	95
1218381	N/A	N/A	16531	16550	AAGTACGGAGCCTCCACCCT	74	96
1218385	N/A	N/A	17129	17148	CAGTAGAGCTCTCCCTGGT	66	97

Table 2

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with phosphorothioate internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1218078	N/A	N/A	3806	3825	CAGCCAACCCCCTTAAAGGG	102	98
1218082	N/A	N/A	3816	3835	TTCTGATTGACAGCCAACCC	111	99
1218086	241	260	3951	3970	TAGCCGGCTGGCTAGTCTGC	45	100
1218090	251	270	3961	3980	ACTCCAATTGTAGCCGGCTG	67	101
1218094	307	326	12599	12618	GCCCCTACCAGACATCTTGC	34	102

1218098	557	576	13545	13564	GACTGCGCCGGTGGTGTAGA	66	103
1218102	566	585	13554	13573	GATCTGCCTGACTGCGCCGG	53	104
1218106	578	597	13566	13585	GTAGTCGCCAAAGATCTGCC	58	105
1218110	590	609	13578	13597	GATGGTGGTCTTGTAGTCGC	77	106
1218114	601	620	13589	13608	CCCTTGCCGCAGATGGTGGT	48	107
1218118	609	628	13597	13616	CGCTCAGGCCCTTGCCGCAG	21	108
1218122	617	636	13605	13624	TACCGTTGCGCTCAGGCCCT	71	109
1218126	621	640	13609	13628	CTGTTACCGTTGCGCTCAGG	90	110
1218130	625	644	13613	13632	CCCCCTGTTACCGTTGCGCT	76	111
1218134	657	676	13645	13664	GATGTTGGCCTCTGGAACCC	50	112
1218138	693	712	13681	13700	CCAAACAATGACACACCCGC	71	113
1218142	718	737	13706	13725	TTGTCGGGATGTCCTAGCCA	40	114
1218146	759	778	14818	14837	GGAGCCACACAACGGTCAGG	62	115
1218150	860	879	14919	14938	GCCTATACTGGCAGAGGTCT	38	116
1218154	1080	1099	17559	17578	CCATGAGTTTAAGGACGGCA	24	117
1218158	1100	1119	17579	17598	TCAGAACTTGGTGCCTCGGC	31	118
1218162	1144	1163	17623	17642	GGTTAGAGCCTCGCTATTAG	20	119
1218166	1164	1183	17643	17662	CGCAGCATTGTAGGCTGTGT	18	120
1218170	1180	1199	17659	17678	GAGTTAAGATGGGAGACGCA	46	121
1218174	1531	1550	18010	18029	TTTGGCCCCTATAGATGGCA	41	122
1218178	1728	1747	18207	18226	TCAGTAGTCCATCGCCATCG	21	123
1218182	1737	1756	18216	18235	GTTAGGGCTTCAGTAGTCCA	24	124
1218186	1758	1777	18237	18256	GCTGTAAGTAAGGTTGGCTG	17	125
1218190	1765	1784	18244	18263	CCCTTATGCTGTAAGTAAGG	20	126
1218194	1771	1790	18250	18269	TACGCTCCCTTATGCTGTAA	22	127
1218198	1778	1797	18257	18276	CAGATTCTACGCTCCCTTAT	52	128
1218202	1783	1802	18262	18281	CTACACAGATTCTACGCTCC	36	129
1218206	1808	1827	18287	18306	GTGTAAGGCCAGATGCCCCC	38	130
1218210	1825	1844	18304	18323	TTCTCTCCCTAACGAGGTG	25	131
1218214	1985	2004	18464	18483	TCAGGTTACACCATTAGCCA	23	132
1218218	2006	2025	18485	18504	TGTGTCTACCAGAGGGCCAT	26	133
1218222	2319	2338	18798	18817	CCCAATAGATTCAACTAGCC	16	134
1218226	2583	2602	19062	19081	GGGAGCTATTCAGGTCTCAA	16	135
1218230	2881	2900	19360	19379	GTACGGATTACTTCACTGTC	31	136
1218234	17	36	3522	3541	TGGGATATGCAGCACAAGCG	61	137
1218238	37	56	3542	3561	ATCCTTGGGTCTAATTGGTG	104	138
1218242	121	140	3626	3645	GGAATTCGCTTTGCTGCAG	98	139
1218246	N/A	N/A	1121	1140	CTGGGCCCCCTTGATCATGG	107	140
1218250	N/A	N/A	1468	1487	GCTCTGTACATCCCGACACT	91	141
1218254	N/A	N/A	2246	2265	CTGCCCTTGCAAAACGGTA	90	142
1218258	N/A	N/A	3019	3038	AGGTAGTCAGTATTCTATCC	101	143
1218262	N/A	N/A	3630	3649	GCCTGGAATTCGCTTTGCT	102	144
1218266	N/A	N/A	4450	4469	AGCTTGCCCCGATCCCCAGCT	55	145

1218270	N/A	N/A	5258	5277	AGTTGTTATAGATCTTGCCC	41	146
1218274	N/A	N/A	5642	5661	CGTGCCCTTATCTGTGGCAC	93	147
1218278	N/A	N/A	5880	5899	AAGTTCCTTCCAATCCCGGA	44	148
1218282	N/A	N/A	6231	6250	GCTTGCAGACAATGTTTTGC	54	149
1218286	N/A	N/A	6416	6435	ACTCAGTTAGTCTTCGGGCA	32	150
1218290	N/A	N/A	7164	7183	GGGACTCTTTTCTAGAGCCC	55	151
1218294	N/A	N/A	7527	7546	GACACGATTTAGTATTACCA	50	152
1218298	N/A	N/A	7859	7878	GCAGTAGTTGACAAGGCCGA	63	153
1218302	N/A	N/A	8084	8103	AGACCAATTGTACCCTGCAC	58	154
1218306	N/A	N/A	8367	8386	GATACTCCAACTTTAAGCCC	67	155
1218310	N/A	N/A	9421	9440	GAGTCACCAGATCATAGCCT	46	156
1218314	N/A	N/A	9691	9710	TTGGGCCTACTCACTCATCC	75	157
1218318	N/A	N/A	9750	9769	GCAGGACTGTTTGTGTTAGCC	51	158
1218322	N/A	N/A	10518	10537	TGAGTCCTATTACCCACCAT	68	159
1218326	N/A	N/A	11020	11039	CCTCTCGGCCAGATCCCTAA	92	160
1218330	N/A	N/A	11378	11397	AGCTTGGCTAATGTCCCCAC	59	161
1218334	N/A	N/A	12872	12891	CGGGAATCCGGTCTGGCTCC	72	162
1218338	N/A	N/A	13226	13245	ACACCTTGCTTACCCTGGGA	47	163
1218342	N/A	N/A	13719	13738	GAGGATGATCACCTTGTCGG	35	164
1218346	N/A	N/A	13767	13786	GACTCGCGCCCAATTTTCCC	64	165
1218350	N/A	N/A	13780	13799	GGACGAGGCCACAGACTCGC	69	166
1218354	N/A	N/A	14041	14060	GTCCAGTTAGATCCACTCTT	16	167
1218358	N/A	N/A	14181	14200	CCTCTGGGACCTCGAACTGT	88	168
1218362	N/A	N/A	14793	14812	GGTGATGCCCCACAACTAAA	91	169
1218366	N/A	N/A	14965	14984	ACCCGTACCCTAACTCACCA	91†	170
1218370	N/A	N/A	15540	15559	GTATGGTATTAGCTACTCCC	24	171
1218374	N/A	N/A	15985	16004	CCCCGATTTACTTTTATTC	55	172
1218378	N/A	N/A	16154	16173	GTCTTCAGTGTACACCATAG	37	173
1218382	N/A	N/A	16689	16708	ACCGTAATTTATGACTGCAA	24	174
1218386	N/A	N/A	17183	17202	TCCGAGTGACTTAGAGTCAT	32	175

Table 3

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with phosphorothioate internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1218079	N/A	N/A	3813	3832	TGATTGACAGCCAACCCCT	104	176
1218083	235	254	3945	3964	GCTGGCTAGTCTGCTTTGTG	34	177
1218087	244	263	3954	3973	TTGTAGCCGGCTGGCTAGTC	47	178
1218091	252	271	3962	3981	GACTCCAATTGTAGCCGGCT	62	179
1218095	309	328	12601	12620	GGGCCCCCTACCAGACATCTT	75	180

1218099	561	580	13549	13568	GCCTGACTGCGCCGGTGGTG	34	181
1218103	575	594	13563	13582	GTCGCCAAAGATCTGCCTGA	56	182
1218107	584	603	13572	13591	GGTCTTGTAGTCGCCAAAGA	62	183
1218111	593	612	13581	13600	GCAGATGGTGGTCTTGTAGT	68	184
1218115	602	621	13590	13609	GCCCTTGCCGCAGATGGTGG	30	185
1218119	610	629	13598	13617	GCGCTCAGGCCCTTGCCGCA	40	186
1218123	618	637	13606	13625	TTACCGTTGCGCTCAGGCC	53	187
1218127	622	641	13610	13629	CCTGTTACCGTTGCGCTCAG	76	188
1218131	629	648	13617	13636	CTGGCCCCCTGTTACCGTTG	53	189
1218135	677	696	13665	13684	CCGCTCCAAAGAATGAGCTT	32	190
1218139	714	733	13702	13721	CGGGATGTCCTAGCCATTTT	26	191
1218143	739	758	14798	14817	GCATAGGTGATGCCCCACAAA	77	192
1218147	762	781	14821	14840	CCAGGAGCCACACAACGGTC	43	193
1218151	861	880	14920	14939	TGCCTATACTGGCAGAGGTC	41	194
1218155	1091	1110	17570	17589	GGTGCCTCGGCCCATGAGTT	18	195
1218159	1102	1121	17581	17600	GATCAGAACTTGGTGCCTCG	34	196
1218163	1148	1167	17627	17646	GTGTGGTTAGAGCCTCGCTA	14	197
1218167	1165	1184	17644	17663	ACGCAGCATTTGTAGGCTGTG	17	198
1218171	1450	1469	17929	17948	AGTGGAAGTACCCTTTGAGA	39	199
1218175	1650	1669	18129	18148	TGCAATAGGCAGATTTGGGC	14	200
1218179	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	7	201
1218183	1738	1757	18217	18236	AGTTAGGGCTTCAGTAGTCC	19	202
1218187	1759	1778	18238	18257	TGCTGTAAGTAAGGTTGGCT	22	203
1218191	1768	1787	18247	18266	GCTCCCTTATGCTGTAAGTA	14	204
1218195	1772	1791	18251	18270	CTACGCTCCCTTATGCTGTA	23	205
1218199	1779	1798	18258	18277	ACAGATTCTACGCTCCCTTA	36	206
1218203	1784	1803	18263	18282	TCTACACAGATTCTACGCTC	17	207
1218207	1809	1828	18288	18307	GGTGTAAGGCCAGATGCCCC	22	208
1218211	1885	1904	18364	18383	GGTTGTCATGGTAGCTGTTA	22	209
1218215	1986	2005	18465	18484	CTCAGGTTACACCATTAGCC	16	210
1218219	2120	2139	18599	18618	GACTGAATGGATAATACCCC	9	211
1218223	2515	2534	18994	19013	GATGACTGGTGCATTCTGTT	17	212
1218227	2878	2897	19357	19376	CGGATTACTTCACTGTCCTT	27	213
1218231	2882	2901	19361	19380	GGTACGGATTACTTCACTGT	23	214
1218235	21	40	3526	3545	GGTGTGGGATATGCAGCACA	91	215
1218239	38	57	3543	3562	GATCCTTGGGTCTAATTGGT	53	216
1218243	N/A	N/A	900	919	AAGTGCCCAATCTAGTGGCC	58	217
1218247	N/A	N/A	1359	1378	ATCTACATACCCCCACCTAT	90	218
1218251	N/A	N/A	1537	1556	GGTGACCGTGTCTCACTCAT	98	219
1218255	N/A	N/A	2308	2327	TACTAGAACTCTAGATCCTT	101	220
1218259	N/A	N/A	3070	3089	CCAAGAAGGATAATCGACTT	72	221
1218263	N/A	N/A	4083	4102	CGACTCATTTAAACCATGGA	51	222
1218267	N/A	N/A	4974	4993	CCAGCTCAGTATAATTGCAA	23	223

1218271	N/A	N/A	5443	5462	TAGGATTCTGATGTTACCC	47	224
1218275	N/A	N/A	5668	5687	CCTGGGACCCAATGTGCATC	27	225
1218279	N/A	N/A	5947	5966	GTACGAACATTTAATTGGTT	39	226
1218283	N/A	N/A	6249	6268	GTTCTCAGACGACAACAGGC	43	227
1218287	N/A	N/A	6716	6735	TGTTATTACTCAGATCGCTC	45	228
1218291	N/A	N/A	7261	7280	GTAGCCATACCTTGTTCCCTC	33	229
1218295	N/A	N/A	7587	7606	GCTGGATAGTCAAATCATGT	45	230
1218299	N/A	N/A	7911	7930	AACCCACCCCTTAACCTTAC	91	231
1218303	N/A	N/A	8189	8208	TGGGCCCCGCTCAAGGACCA	71	232
1218307	N/A	N/A	8814	8833	CCAGTCTAAGTACAGACTGC	91	233
1218311	N/A	N/A	9519	9538	AGTGTATCTGATCCCTCAAT	65	234
1218315	N/A	N/A	9694	9713	ATCTTGGGCCTACTACTCA	75	235
1218319	N/A	N/A	9861	9880	TCCCCCGGACAAAGAAGCCT	50	236
1218323	N/A	N/A	10520	10539	AGTGAGTCCTATTACCCACC	45	237
1218327	N/A	N/A	11121	11140	TCCAAGTACTAGTCCCATGC	27	238
1218331	N/A	N/A	11463	11482	GAGGTTTGATATTACTCCCA	29	239
1218335	N/A	N/A	13022	13041	GCAATATGAACCACACCTAG	42	240
1218339	N/A	N/A	13230	13249	CGCCACACCTTGCTTACCCT	55	241
1218343	N/A	N/A	13747	13766	CCACCCCTTGTTATTGCCAC	40	242
1218347	N/A	N/A	13769	13788	CAGACTCGCGCCCAATTTTC	62	243
1218351	N/A	N/A	13969	13988	GGTCTGATTGTACAAAGCAT	22	244
1218355	N/A	N/A	14042	14061	TGTCCAGTTAGATCCACTCT	8	245
1218359	N/A	N/A	14289	14308	CGCCAAAGGATCTTTAACTC	30	246
1218363	N/A	N/A	14962	14981	CGTACCCTAACTCACCATAC	77†	247
1218367	N/A	N/A	14966	14985	CACCCGTACCCTAACTCACC	64†	248
1218371	N/A	N/A	15541	15560	TGTATGGTATTAGCTACTCC	23	249
1218375	N/A	N/A	15992	16011	CTGTCTCCCCCGGATTTACT	46	250
1218379	N/A	N/A	16434	16453	TACCCACACTATCTCAGGCC	23	251
1218383	N/A	N/A	16938	16957	GCACACTACATTACAGGGC	17	252
1218387	N/A	N/A	17196	17215	CCACATCAATATGTCCGAGT	12	253

Table 4

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with phosphorothioate internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1218080	N/A	N/A	3814	3833	CTGATTGACAGCCAACCCCC	98	254
1218084	236	255	3946	3965	GGCTGGCTAGTCTGCTTTGT	41	255
1218088	248	267	3958	3977	CCAATTGTAGCCGGCTGGCT	62	256
1218092	253	272	3963	3982	TGACTCCAATTGTAGCCGGC	80	257
1218096	550	569	13538	13557	CCGGTGGTGTAGAAGCCCTC	65	258

1218100	562	581	13550	13569	TGCCTGACTGCGCCGGTGGT	37	259
1218104	576	595	13564	13583	AGTCGCCAAAGATCTGCCTG	51	260
1218108	587	606	13575	13594	GGTGGTCTTGTAGTCGCCAA	44	261
1218112	595	614	13583	13602	CCGCAGATGGTGGTCTTGTA	50	262
1218116	603	622	13591	13610	GGCCCTTGCCGCAGATGGTG	52	263
1218120	612	631	13600	13619	TTGCGCTCAGGCCCTTGCCG	60	264
1218124	619	638	13607	13626	GTTACCGTTGCGCTCAGGCC	51	265
1218128	623	642	13611	13630	CCCTGTTACCGTTGCGCTCA	92	266
1218132	632	651	13620	13639	CTTCTGGCCCCCTGTTACCG	82	267
1218136	679	698	13667	13686	ACCCGCTCCAAAGAATGAGC	50	268
1218140	715	734	13703	13722	TCGGGATGTCCTAGCCATT	31	269
1218144	755	774	14814	14833	CCACACAACGGTCAGGGCAT	41	270
1218148	763	782	14822	14841	ACCAGGAGCCACACAACGGT	54	271
1218152	866	885	14925	14944	GAGACTGCCTATACTGGCAG	83	272
1218156	1096	1115	17575	17594	AACTTGGTGCCTCGGCCCAT	23	273
1218160	1103	1122	17582	17601	GGATCAGAACTTGGTGCCTC	22	274
1218164	1149	1168	17628	17647	TGTGTGGTTAGAGCCTCGCT	21	275
1218168	1168	1187	17647	17666	GAGACGCAGCATTGTAGGCT	17	276
1218172	1452	1471	17931	17950	TCAGTGGAAGTACCCTTTGA	69	277
1218176	1681	1700	18160	18179	AAGATCCTTGCTTTGACCCC	61	278
1218180	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	16	279
1218184	1739	1758	18218	18237	GAGTTAGGGCTTCAGTAGTC	21	280
1218188	1760	1779	18239	18258	ATGCTGTAAGTAAGGTTGGC	19	281
1218192	1769	1788	18248	18267	CGCTCCCTTATGCTGTAAGT	17	282
1218196	1773	1792	18252	18271	TCTACGCTCCCTTATGCTGT	32	283
1218200	1781	1800	18260	18279	ACACAGATTCTACGCTCCCT	24	284
1218204	1785	1804	18264	18283	GTCTACACAGATTCTACGCT	19	285
1218208	1818	1837	18297	18316	CCCTAACGAGGTGTAAGGCC	8	286
1218212	1887	1906	18366	18385	AGGGTTGTCATGGTAGCTGT	22	287
1218216	1994	2013	18473	18492	AGGGCCATCTCAGGTTACAC	13	288
1218220	2141	2160	18620	18639	GACCTTCAAATCACCTACGA	17	289
1218224	2541	2560	19020	19039	CCTGGAAGCTTACCAACTGA	25	290
1218228	2879	2898	19358	19377	ACGGATTACTTCACTGTCCT	14	291
1218232	2883	2902	19362	19381	AGGTACGGATTACTTCACTG	20	292
1218236	30	49	3535	3554	GGTCTAATTGGTGTGGGATA	90	293
1218240	114	133	3619	3638	CGCTTTGCTGCAGAGACATC	93	294
1218244	N/A	N/A	974	993	TCATTGTGTAGACTGAACTC	91	295
1218248	N/A	N/A	1400	1419	CCTCATAGGGTATCTTCCCA	105	296
1218252	N/A	N/A	2020	2039	ATCGCCAAATGTGTCTCCTC	100	297
1218256	N/A	N/A	2563	2582	GGTATGGTCTCCTGGAACCT	104	298
1218260	N/A	N/A	3444	3463	GCTCCCAAAGTCCTTCCGAA	104	299
1218264	N/A	N/A	4366	4385	GGCTAGACAGTGCTCAGTGG	40	300
1218268	N/A	N/A	5141	5160	GGTGATTCACTGACCTGTCC	39	301

1218272	N/A	N/A	5473	5492	ACCTATCCAGTCAGCTCGGC	85	302
1218276	N/A	N/A	5793	5812	GTCCAGTACCTTGTTAGAGA	29	303
1218280	N/A	N/A	5956	5975	GCAGAGGCTGTACGAACATT	29	304
1218284	N/A	N/A	6350	6369	GCTACACCCACTTACTGCAA	45	305
1218288	N/A	N/A	6780	6799	GAGTTCTACCTTAATGGGTT	57	306
1218292	N/A	N/A	7468	7487	CACTCCTCTTCAGACGCGCA	69	307
1218296	N/A	N/A	7636	7655	AGTGCTGGAAAACAGTCCCG	69	308
1218300	N/A	N/A	7949	7968	GGTCTCGAATCTGCACTACA	50	309
1218304	N/A	N/A	8273	8292	TCAAGGGACTGTGTTGATCC	63	310
1218308	N/A	N/A	8959	8978	GGTATGTGTGAACAATAGCC	56	311
1218312	N/A	N/A	9521	9540	TGAGTGTATCTGATCCCTCA	45	312
1218316	N/A	N/A	9709	9728	CCCTAGCAAGTGACCATCTT	90	313
1218320	N/A	N/A	9868	9887	CCATAGCTCCCCCGACAAA	77	314
1218324	N/A	N/A	10522	10541	GGAGTGAGTCCTATTACCCA	49	315
1218328	N/A	N/A	11125	11144	GTGTTCCAAGTACTAGTCCC	58	316
1218332	N/A	N/A	11464	11483	GGAGGTTTGATATTACTCCC	50	317
1218336	N/A	N/A	13056	13075	CTCCATACCTACTACGCTGG	48	318
1218340	N/A	N/A	13361	13380	CCAGAGCGAGCACCTTAACA	55	319
1218344	N/A	N/A	13762	13781	GCGCCCAATTTCCCCCACC	46	320
1218348	N/A	N/A	13776	13795	GAGGCCACAGACTCGCGCCC	55	321
1218352	N/A	N/A	14037	14056	AGTTAGATCCACTCTTGTTGG	36	322
1218356	N/A	N/A	14043	14062	TTGTCCAGTTAGATCCACTC	23	323
1218360	N/A	N/A	14402	14421	TGTTCCCTAGCCATTGAACA	67	324
1218364	N/A	N/A	14963	14982	CCGTACCCTAACTACCATA	94†	325
1218368	N/A	N/A	15173	15192	GTAGGCCAATGTGAATGGCC	95	326
1218372	N/A	N/A	15542	15561	TTGTATGGTATTAGCTACTC	45	327
1218376	N/A	N/A	16130	16149	TGGCCCATTAACACCCAGAT	49	328
1218380	N/A	N/A	16529	16548	GTACGGAGCCTCCACCCCTT	50	329
1218384	N/A	N/A	17128	17147	AGTAGAGCTCTCCCTGGTT	66	330
1218388	N/A	N/A	17329	17348	AGTCCGATGTCTCTGAGGCA	42	331

Example 2: Effect of 5-10-5 MOE gapmer modified oligonucleotides on human PLP1 RNA *in vitro*, single dose

Modified oligonucleotides complementary to human PLP1 nucleic acid were designed and tested for their single dose effects on PLP1 RNA *in vitro*. The modified oligonucleotides were tested in a series of experiments that had the same culture conditions, and the results for each experiment are presented in separate tables below.

The modified oligonucleotides in the tables below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment consists of ten 2'-β-D-deoxynucleosides and the 5' and 3' wing segments each consists of five 2'-MOE modified nucleosides. The sugar motif for the gapmers is (from 5' to 3'):

eeeeedddddddeeeeee; wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. The internucleoside linkage motif for the gapmers is (from 5' to 3'): "soooooossssssoos"; wherein each 'o'

represents a phosphodiester internucleoside linkage and each 's' represents a phosphorothioate internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

"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 Tables below is 100% complementary to either human PLP1 mRNA (SEQ ID NO: 1) or to the human PLP1 genomic sequence (SEQ ID NO: 2), or to both. 'N/A' indicates that the modified oligonucleotide is not 100% complementary to that particular target nucleic acid sequence.

Cultured SK-MEL-28 cells were treated with modified oligonucleotide at a concentration of 4,000 nM using electroporation at a density of 20,000 cells per well. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and PLP1 RNA levels were measured by quantitative real-time RTPCR. PLP1 RNA levels were measured by Human PLP1 primer probe set RTS35092, described in Example 1 above. PLP1 RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of PLP1 RNA is presented in the tables below as percent PLP1 RNA relative to the amount in untreated control cells (% UTC). Each table represents results from an individual assay plate. The values marked with an "†" 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.

Table 5

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362432	N/A	N/A	8998	9017	GCTCCCTTTGATTTTCACA	37	332
1362464	2489	2508	18968	18987	TCTATATCAGGAGAAAATAA	62	333
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	20	201
1362496	1917	1936	18396	18415	TCCTTCTATTCTCAGCTCCT	15	334
1362567	1879	1898	18358	18377	CATGGTAGCTGTTATCAAGG	21	335
1362568	2408	2427	18887	18906	CATTAGCTAGAAAGAACGAT	33	336
1362595	N/A	N/A	16249	16268	CATGAATACAGCTTTCTGAA	47	337
1362652	2080	2099	18559	18578	AAGATATGACAGAGGCCAGA	30	338
1362658	1217	1236	17696	17715	TCAAGTAAGAAGAGGGCCAG	56	339
1362661	N/A	N/A	10078	10097	AGATTCAGCCTATAAGTCAA	53	340
1362687	N/A	N/A	9225	9244	CAATTCAGTAATATCAGCAT	55	341
1362731	2016	2035	18495	18514	TTATCTATCCTGTGTCTACC	49	342
1362740	2300	2319	18779	18798	CAATTTTAAATATCATTTGT	57	343
1362755	2844	2863	19323	19342	TCTTACAAAACATTTTCCCT	40	344
1362763	2350	2369	18829	18848	TTTCTGCAAAGGCAGAATAC	58	345
1362775	2325	2344	18804	18823	GAAAATCCCAATAGATTCAA	49	346
1362803	2159	2178	18638	18657	CATTCTAAACAAATCAAGA	68	347

1362827	N/A	N/A	11747	11766	CTAACAATTCAGGCAGCCAA	57	348
1362850	N/A	N/A	17152	17171	TGTAGACACACAGCCACATC	57	349
1362884	1439	1458	17918	17937	CCTTTGAGAAGAAATTACTT	70	350
1362923	1254	1273	17733	17752	TTAATCACTGCAAGACTCTC	51	351
1362925	N/A	N/A	16906	16925	TCAGCAAGACCTGGGACATA	39	352
1362979	N/A	N/A	8166	8185	CCATGATGGAAATTCAGTGT	58	353
1363002	2699	2718	19178	19197	AACACAACCTTTTACAACAA	49	354
1363018	N/A	N/A	13294	13313	TCACCTTATCTTTGTTGAAA	55	355
1363035	1052	1071	17531	17550	AGTGGCAGCAATCATGAAGG	35	356
1363043	N/A	N/A	4770	4789	TCTGAGTAGAAACTACCACC	32	357
1363080	1843	1862	18322	18341	ATGCTGACAACACCCTGTTT	46	358
1363081	N/A	N/A	10740	10759	GCCACACTCACTTTTCTATA	48	359
1363103	1734	1753	18213	18232	AGGGCTTCAGTAGTCCATCG	11	46
1363134	1481	1500	17960	17979	TGAGCATCTTTCCTTCCACT	14	360
1363136	1520	1539	17999	18018	TAGATGGCAAGAGGACCAAA	70	361
1363137	2793	2812	19272	19291	TTGTATACTGGTTTGAAAAC	62	362
1363157	2752	2771	19231	19250	AAAGCTCTTACATCTCCTTA	27	363
1363158	2436	2455	18915	18934	GATAACATTGCTAAGTAAAA	42	364
1363161	3121	3140	19600	19619	TTTGATTGAGAACATTCTTA	43	365
1363177	N/A	N/A	5117	5136	TCACATAGTTCATAAGTAGC	40	366
1363206	1784	1803	18263	18282	TCTACACAGATTCTACGCTC	25	207
1363219	2135	2154	18614	18633	CAAATCACCTACGATGACTG	51	367
1363230	N/A	N/A	7394	7413	CATTCCAATTTATGTGCAAG	48	368
1363240	2237	2256	18716	18735	TCAAAGAATTATTCTCCAGA	42	369
1363259	2381	2400	18860	18879	CTCAAATTGAGATTCAAATT	59	370
1363272	2994	3013	19473	19492	ACTTTCAGTTGATTAACCTCT	37	371
1363291	N/A	N/A	13758	13777	CCAATTTTCCCCACCCCTT	56	372
1363342	1137	1156	17616	17635	GCCTCGCTATTAGAGAAAAGG	34	373
1363383	1298	1317	17777	17796	TGACTAAAAGAGGTACATAA	52	374
1363396	N/A	N/A	15298	15317	CCAACAATCAGGATCCTCTT	73	375
1363437	N/A	N/A	11123	11142	GTTCCAAGTACTAGTCCCAT	40	376
1363466	N/A	N/A	14343	14362	CTAAGCTAACTGCTGGCCAC	45	377
1363495	2262	2281	18741	18760	TTCTAGTTTAAAAAACAGT	59	378
1363529	N/A	N/A	5830	5849	TTGAACAGCAGTGCACTCCA	69	379
1363539	1554	1573	18033	18052	TTTTGTACACCAAAGAGAAT	62	380
1363641	N/A	N/A	16661	16680	GCAACATTACATGTTCTATA	11	381
1363679	N/A	N/A	11910	11929	CTTATTTTAGTCATTTCATCA	47	382
1363681	2894	2913	19373	19392	AACAAAACACAAGGTACGGA	20	383
1363730	1363	1382	17842	17861	TGCAGTTGGGAAGTCATCTT	36	384
1363734	2672	2691	19151	19170	GTAGTACAAATCTTTCCTTC	15	385
1363751	2624	2643	19103	19122	TTTAACCCAAAGTTAACAAA	50	386
1363767	2107	2126	18586	18605	ATACCCCATGAAATGAGCAC	23	387
1363797	1403	1422	17882	17901	TGCTTGAAAATTCAATTAGA	45	388

1363843	N/A	N/A	8643	8662	CAGTACAAGAATTAAGCACA	41	389
1363858	1185	1204	17664	17683	GCAAAGAGTTAAGATGGGAG	27	390
1363892	1976	1995	18455	18474	ACCATTAGCCACCAGCAACT	47	391
1363900	2586	2605	19065	19084	TCTGGGAGCTATTCAAGTCT	19	392
1363907	3060	3079	19539	19558	AAGTTTCTAAAAGTTTATCC	29	393
1363921	1593	1612	18072	18091	CTATCTTCAGTGGTAATAGA	35	394
1363922	N/A	N/A	15670	15689	GGTGTTTTACCTTCTATGCT	73	395
1363937	1664	1683	18143	18162	CCCCTTCTCCAGCTGCAAT	44	396
1363951	2535	2554	19014	19033	AGCTTACCAACTGAATAGCT	33	397
1363982	3022	3041	19501	19520	GCAATTCTATATCAGAAATG	21	398
1363998	N/A	N/A	7041	7060	TTGATGTAAGTTTGGCACTG	35	399
1364032	1324	1343	17803	17822	TAGCAGGAACCAGCTATGAA	56	400
1364046	2202	2221	18681	18700	CCCAAAATAAGTAATAAACAA	46	401
1364111	N/A	N/A	6222	6241	CAATGTTTGTCTGTTCAATA	50	402
1364117	2053	2072	18532	18551	ACTAATTAACAGAAAAAAG	74	403
1364223	N/A	N/A	5446	5465	AGATAGGATTCCTGATGTTA	62	404
1364232	2462	2481	18941	18960	GTAAACCTAACTCTTAACA	49	405
1364251	N/A	N/A	6414	6433	TCAGTTAGTCTTCGGGCATT	34	406

Table 6

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
805577	1253	1272	17732	17751	TAATCACTGCAAGACTCTCC	35	407
1362428	N/A	N/A	7391	7410	TCCAATTATGTGCAAGCAT	24	408
1362431	2488	2507	18967	18986	CTATATCAGGAGAAAATAAC	50	409
1362443	N/A	N/A	6215	6234	TTGCTGTTCAATAATGGCAT	26	410
1362449	2698	2717	19177	19196	ACACAACCTTTTACAACAAA	16	411
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	13	201
1362498	N/A	N/A	5445	5464	GATAGGATTCCTGATGTTAC	48	412
1362508	N/A	N/A	5115	5134	ACATAGTTCATAAGTAGCAG	29	413
1362623	1780	1799	18259	18278	CACAGATTCTACGCTCCCTT	16	414
1362629	N/A	N/A	13281	13300	GTTGAAATAAGTGAAGACAG	53	415
1362670	2671	2690	19150	19169	TAGTACAAATCTTTCCTTCA	18	416
1362677	2893	2912	19372	19391	ACAAAACACAAGGTACGGAT	21	417
1362711	2435	2454	18914	18933	ATAACATTGCTAAGTAAAAT	77	418
1362718	2008	2027	18487	18506	CCTGTGTCTACCAGAGGGCC	21	419
1362750	1662	1681	18141	18160	CCTTCTCCAGCTGCAATAG	30	420
1362756	N/A	N/A	16905	16924	CAGCAAGACCTGGGACATAG	33	421
1362765	N/A	N/A	5828	5847	GAACAGCAGTGCCTCCACA	36	422

1362766	1323	1342	17802	17821	AGCAGGAACCAGCTATGAAG	33	423
1362809	2236	2255	18715	18734	CAAAGAATTATTCTCCAGAC	23	424
1362812	3119	3138	19598	19617	TGATTGAGAACATTCTTAAT	48	425
1362839	N/A	N/A	13743	13762	CCCTTGTTATTGCCACAAAA	32	426
1362880	2843	2862	19322	19341	CTTACAAAACATTTTCCCTC	30	427
1362922	2461	2480	18940	18959	TTAAACCTAACTCTTAACAC	50	428
1362933	1553	1572	18032	18051	TTTGTAACCAAAGAGAATA	50	429
1362995	1591	1610	18070	18089	ATCTTCAGTGGTAATAGAGA	34	430
1363011	N/A	N/A	4769	4788	CTGAGTAGAACTACCACCA	27	431
1363046	N/A	N/A	16597	16616	TCCTCATACCACTTTTCTTG	87	432
1363055	1216	1235	17695	17714	CAAGTAAGAAGAGGGCCAGT	69	433
1363058	2380	2399	18859	18878	TCAAATTGAGATTCAAATTC	63	434
1363110	3021	3040	19500	19519	CAATTCTATATCAGAAATGA	35	435
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	11	279
1363140	1361	1380	17840	17859	CAGTTGGGAAGTCATCTTCT	27	436
1363170	2534	2553	19013	19032	GCTTACCAACTGAATAGCTG	18	437
1363176	2079	2098	18558	18577	AGATATGACAGAGGCCAGAG	32	438
1363184	1874	1893	18353	18372	TAGCTGTTATCAAGGAGAAG	11	439
1363188	1519	1538	17998	18017	AGATGGCAAGAGGACCAAAG	34	440
1363209	1051	1070	17530	17549	GTGGCAGCAATCATGAAGGT	23	441
1363223	1297	1316	17776	17795	GACTAAAAGAGGTACATAAG	39	442
1363224	N/A	N/A	9224	9243	AATTCAGTAATATCAGCATA	71	443
1363225	N/A	N/A	16248	16267	ATGAATACAGCTTTTCTGAAT	64	444
1363244	3059	3078	19538	19557	AGTTTCTAAAAGTTTATCCT	19	445
1363263	2261	2280	18740	18759	TCCTAGTTTAAAAAACAGTC	21	446
1363264	N/A	N/A	6399	6418	GCATTTTATAAACTGGACC	40	447
1363279	2158	2177	18637	18656	ATTCTAAAACAAATCAAGAC	63	448
1363331	1436	1455	17915	17934	TTGAGAAGAAATTACTTTCT	64	449
1363332	2583	2602	19062	19081	GGGAGCTATTTCAGGTCTCAA	88	135
1363350	N/A	N/A	10033	10052	ACTGCCATTTTCCTTCTCTG	34	450
1363354	1184	1203	17663	17682	CAAAGAGTTAAGATGGGAGA	44	451
1363362	N/A	N/A	7027	7046	GCACTGAGTAGGCTCTGAAA	18	452
1363388	N/A	N/A	15221	15240	TGTTATTGAAATGTGCTGCT	47	453
1363416	N/A	N/A	15669	15688	GTGTTTTACCTTCTATGCTC	27	454
1363510	2407	2426	18886	18905	ATTAGCTAGAAAGAACGATC	19	455
1363545	1975	1994	18454	18473	CCATTAGCCACCAGCAACTG	40	456
1363634	N/A	N/A	11120	11139	CCAAGTACTAGTCCCATGCT	48	457
1363645	2623	2642	19102	19121	TTAACCCAAAGTTAACAAAA	56	458
1363687	1842	1861	18321	18340	TGCTGACAACACCCTGTTTC	28	459
1363736	1136	1155	17615	17634	CCTCGCTATTAGAGAAAGGG	13	460
1363755	2201	2220	18680	18699	CCAAATAAGTAATAAACAAA	60	461
1363761	1402	1421	17881	17900	GCTTGAAAATTCAATTAGAG	17	462
1363798	N/A	N/A	8641	8660	GTACAAGAATTAAGCACACT	38	463

1363806	2349	2368	18828	18847	TTCTGCAAAGGCAGAATACT	63	464
1363823	2134	2153	18613	18632	AAATCACCTACGATGACTGA	45	465
1363851	N/A	N/A	8994	9013	CCTTTGATTTTTCACAGTCC	28	466
1363882	2750	2769	19229	19248	AGCTCTTACATCTCCTTAAA	16	467
1363930	2324	2343	18803	18822	AAAATCCCAATAGATTCAAC	29	468
1363932	2792	2811	19271	19290	TGTATACTGGTTTGAAAACA	32	469
1363934	N/A	N/A	8160	8179	TGGAAATTCAGTGTGAATCT	37	470
1363959	2106	2125	18585	18604	TACCCCATGAAATGAGCACC	13	471
1364007	1916	1935	18395	18414	CCTTCTATTCTCAGCTCCTT	14	472
1364041	N/A	N/A	14308	14327	GAACCCACACATGTTTCAGCC	17	473
1364067	N/A	N/A	11746	11765	TAACAATTCAGGCAGCCAAG	38	474
1364100	N/A	N/A	17151	17170	GTAGACACACAGCCACATCA	31	475
1364146	2052	2071	18531	18550	CTAATTAACAGAAAAAAGA	107	476
1364156	2299	2318	18778	18797	AATTTTTAATATCATTTGTG	71	477
1364174	N/A	N/A	10688	10707	TTCTGTTAACATTAGTTACA	30	478
1364235	1478	1497	17957	17976	GCATCTTTCCTTCCACTTTG	13	479
1364240	N/A	N/A	11907	11926	ATTTTAGTCATTTCATCAACT	43	480
1364269	2993	3012	19472	19491	CTTTCAGTTGATTAACCTCTC	17	481

Table 7

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362427	N/A	N/A	7390	7409	CCAATTTATGTGCAAGCATT	34	482
1362453	1551	1570	18030	18049	TGTACACCAAAGAGAATATA	43	483
1362467	N/A	N/A	4548	4567	CTACCCATATCTGTTTCCCA	60	484
1362468	1841	1860	18320	18339	GCTGACAACACCCTGTTTCT	21	485
1362481	N/A	N/A	5826	5845	ACAGCAGTGCACTCCACATC	59	486
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	11	201
1362500	1049	1068	17528	17547	GGCAGCAATCATGAAGGTGA	19	487
1362524	N/A	N/A	7024	7043	CTGAGTAGGCTCTGAAAGCA	66	488
1362566	2460	2479	18939	18958	TAAACCTAACTCTTAACACA	51	489
1362577	1913	1932	18392	18411	TCTATTCTCAGCTCCTTGGA	38	490
1362578	1473	1492	17952	17971	TTTCCTTCCACTTTGTTTCC	60	491
1362604	N/A	N/A	16191	16210	TAACTAAGTTTTCACTTCCC	88	492
1362613	N/A	N/A	16540	16559	TGCAAGTAGAAGTACGGAGC	34	493
1362621	N/A	N/A	9221	9240	TCAGTAATATCAGCATAAGC	43	494
1362636	1215	1234	17694	17713	AAGTAAGAAGAGGGCCAGTT	63	495
1362641	2791	2810	19270	19289	GTATACTGGTTTGAAAACAA	14	496
1362650	1183	1202	17662	17681	AAAGAGTTAAGATGGGAGAC	61	497

1362690	N/A	N/A	9918	9937	CCACTGTTCCCTTTCTCCCC	94	498
1362704	2007	2026	18486	18505	CTGTGTCTACCAGAGGGCCA	24	499
1362706	N/A	N/A	11119	11138	CAAGTACTAGTCCCATGCTC	62	500
1362822	3058	3077	19537	19556	GTTTCTAAAAGTTTATCCTT	26	501
1362831	2433	2452	18912	18931	AACATTGCTAAGTAAAATCA	43	502
1362955	1777	1796	18256	18275	AGATTCTACGCTCCCTTATG	53	503
1362957	1661	1680	18140	18159	CTTCTCCAGCTGCAATAGG	36	504
1362980	N/A	N/A	10680	10699	ACATTAGTTACAGTTTGTTT	48	505
1362987	1873	1892	18352	18371	AGCTGTTATCAAGGAGAAGG	16	506
1363016	N/A	N/A	5114	5133	CATAGTTCATAAGTAGCAGA	37	507
1363061	N/A	N/A	15220	15239	GTTATTGAAATGTGCTGCTT	62	508
1363071	N/A	N/A	11738	11757	CAGGCAGCCAAGTAAGTGGT	36	509
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	13	279
1363165	1518	1537	17997	18016	GATGGCAAGAGGACCAAAGA	39	510
1363174	2379	2398	18858	18877	CAAATTGAGATTCAAATTCA	80	511
1363182	1296	1315	17775	17794	ACTAAAAGAGGTACATAAGA	82	512
1363243	N/A	N/A	14287	14306	CCAAAGGATCTTTAACTCCA	42	513
1363276	1322	1341	17801	17820	GCAGGAACCAGCTATGAAGC	50	514
1363300	3020	3039	19499	19518	AATTCTATATCAGAAATGAA	84	515
1363308	N/A	N/A	11904	11923	TTAGTCATTCATCAACTATT	36	516
1363344	N/A	N/A	16863	16882	TTCTAATAATGTTAGGAGGT	27	517
1363410	2105	2124	18584	18603	ACCCCATGAAATGAGCACCA	14	518
1363425	2892	2911	19371	19390	CAAAACACAAGGTACGGATT	48	519
1363434	N/A	N/A	15661	15680	CCTTCTATGCTCATTGGCTC	65	520
1363439	1099	1118	17578	17597	CAGAACTTGGTGCCTCGGCC	15	40
1363443	N/A	N/A	5441	5460	GGATTCCTGATGTTACCCAG	41	521
1363542	N/A	N/A	6211	6230	TGTTCAATAATGGCATTGTG	50	522
1363550	2582	2601	19061	19080	GGAGCTATTCAGGTCTCAAA	20	57
1363589	N/A	N/A	13739	13758	TGTTATTGCCACAAAATCCT	40	523
1363610	2842	2861	19321	19340	TTACAAAACATTTTCCCTCT	53	524
1363611	2078	2097	18557	18576	GATATGACAGAGGCCAGAGT	30	525
1363631	1974	1993	18453	18472	CATTAGCCACCAGCAACTGC	50	526
1363711	N/A	N/A	6368	6387	GCCACACTTTTTGCCTGGGC	27	527
1363746	1435	1454	17914	17933	TGAGAAGAAATTACTTTCTG	101	528
1363825	2622	2641	19101	19120	TAACCCAAAGTTAACAAAAA	74	529
1363829	2235	2254	18714	18733	AAAGAATTATTCTCCAGACA	37	530
1363888	2406	2425	18885	18904	TTAGCTAGAAAGAACGATCA	29	531
1363891	2298	2317	18777	18796	ATTTTAAATATCATTTGTGA	78	532
1363897	2157	2176	18636	18655	TTCTAAACAAATCAAGACC	55	533
1363899	2487	2506	18966	18985	TATATCAGGAGAAAATAACC	63	534
1363968	N/A	N/A	8085	8104	GAGACCAATTGTACCCTGCA	59	535
1363969	2260	2279	18739	18758	CCTAGTTTAAAAAACAGTCA	38	536
1363980	1401	1420	17880	17899	CTTGAAAATTCAATTAGAGC	62	537

1363983	1730	1749	18209	18228	CTTCAGTAGTCCATCGCCAT	21	538
1364000	N/A	N/A	12823	12842	CTGAAGAGTTCTCTATCTCC	59	539
1364002	3118	3137	19597	19616	GATTGAGAACATTCTTAATT	57	540
1364015	2749	2768	19228	19247	GCTCTTACATCTCCTTAAAT	28	541
1364024	2133	2152	18612	18631	AATCACCTACGATGACTGAA	33	542
1364047	N/A	N/A	8993	9012	CTTTGATTTTTCACAGTCCA	43	543
1364052	1360	1379	17839	17858	AGTTGGGAAGTCATCTTCTT	53	544
1364066	2670	2689	19149	19168	AGTACAAATCTTTCCTTCAA	16	545
1364084	N/A	N/A	17150	17169	TAGACACACAGCCACATCAT	67	546
1364089	N/A	N/A	8640	8659	TACAAGAATTAAGCACACTA	77	547
1364093	2051	2070	18530	18549	TAATTAACAGAAAAAAGAC	103	548
1364155	2323	2342	18802	18821	AAATCCCAATAGATTCAACT	44	549
1364158	1252	1271	17731	17750	AATCACTGCAAGACTCTCCT	36	550
1364162	1590	1609	18069	18088	TCTTCAGTGGTAATAGAGAG	43	551
1364178	2197	2216	18676	18695	ATAAGTAATAAACAAACTGG	79	552
1364181	2348	2367	18827	18846	TCTGCAAAGGCAGAATACTT	73	553
1364189	2532	2551	19011	19030	TTACCAACTGAATAGCTGAT	32	554
1364248	2989	3008	19468	19487	CAGTTGATTAAGTCTCTTTG	21	555
1364262	2696	2715	19175	19194	ACAACCTCTTACAACAAAAG	49	556

Table 8

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362437	2156	2175	18635	18654	TCTAAAACAAATCAAGACCT	45	557
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	13	201
1362518	2621	2640	19100	19119	AACCCAAAGTTAACAAAAAC	62	558
1362534	1470	1489	17949	17968	CCTTCCACTTTGTTTCCATC	64	559
1362548	2790	2809	19269	19288	TATACTGGTTTGAAAACAAG	55	560
1362580	1912	1931	18391	18410	CTATTCTCAGCTCCTTGGA	36	561
1362584	1729	1748	18208	18227	TTCAGTAGTCCATCGCCATC	36	562
1362597	2378	2397	18857	18876	AAATTGAGATTCAAATTCAC	59	563
1362632	2004	2023	18483	18502	TGTCTACCAGAGGGCCATCT	25	564
1362664	2347	2366	18826	18845	CTGCAAAGGCAGAATACTTG	38	565
1362691	2322	2341	18801	18820	AATCCCAATAGATTCAACTA	45	566
1362735	2531	2550	19010	19029	TACCAACTGAATAGCTGATG	32	567
1362748	N/A	N/A	7382	7401	TGTGCAAGCATTGGGAAGCT	36	568
1362791	N/A	N/A	9728	9747	GGGTAAGAAGAGCCATCCAC	68	569
1362826	N/A	N/A	17523	17542	CAATCATGAAGGTGAGCTGT	72	570
1362849	N/A	N/A	6986	7005	GCTCCATTACCTACCATGG	38	571

1362860	2405	2424	18884	18903	TAGCTAGAAAGAACGATCAG	51	572
1362900	2104	2123	18583	18602	CCCCATGAAATGAGCACCAT	19	573
1362913	2259	2278	18738	18757	CTAGTTTAAAAAACAGTCAT	41	574
1362961	1295	1314	17774	17793	CTAAAAGAGGTACATAAGAG	76	575
1362962	1973	1992	18452	18471	ATTAGCCACCAGCAACTGCT	39	576
1362965	1589	1608	18068	18087	CTTCAGTGGTAATAGAGAGA	32	577
1363027	N/A	N/A	11067	11086	GCCAAGTAGATGACTGACTA	33	578
1363036	1776	1795	18255	18274	GATTCTACGCTCCCTTATGC	54	579
1363069	1840	1859	18319	18338	CTGACAACACCCTGTTTCTC	32	580
1363077	N/A	N/A	11656	11675	TTGTCAGACAGGATTTTAGC	45	581
1363082	N/A	N/A	4537	4556	TGTTTCCCATGGTCAAGCCA	51	582
1363091	N/A	N/A	8053	8072	TGTCCTTGAATCCAGCTGA	67	583
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	12	279
1363123	2132	2151	18611	18630	ATCACCTACGATGACTGAAT	36	584
1363126	3117	3136	19596	19615	ATTGAGAACATTCTTAATTT	75	585
1363141	2581	2600	19060	19079	GAGCTATTCAAGGTCTCAAAC	21	586
1363200	2432	2451	18911	18930	ACATTGCTAAGTAAAATCAT	50	587
1363257	1081	1100	17560	17579	CCCATGAGTTTAAGGACGGC	22	588
1363295	2045	2064	18524	18543	ACAGAAAAAAGACATGCTA	63	589
1363323	2486	2505	18965	18984	ATATCAGGAGAAAATAACCT	49	590
1363333	1400	1419	17879	17898	TTGAAAATTCAATTAGAGCC	47	591
1363340	N/A	N/A	6184	6203	GCAGAGAATAATCAGCTACT	62	592
1363367	1517	1536	17996	18015	ATGGCAAGAGGACCAAAGAC	65	593
1363436	N/A	N/A	8990	9009	TGATTTTTTACAGTCCAAGA	55	594
1363441	2297	2316	18776	18795	TTTTTAATATCATTGTGTAT	84	595
1363454	N/A	N/A	5435	5454	CTGATGTTACCCAGGGCAGG	44	596
1363455	N/A	N/A	14282	14301	GGATCTTTAACTCCAGAGAC	26	597
1363491	N/A	N/A	5817	5836	CACTCCACATCAGAAGTAGT	65	598
1363493	1550	1569	18029	18048	GTACACCAAAGAGAATATAT	18	599
1363504	N/A	N/A	5111	5130	AGTTCATAAGTAGCAGATCT	32	600
1363506	2987	3006	19466	19485	GTTGATTAACTCTCTTTGTG	33	601
1363565	N/A	N/A	13734	13753	TTGCCACAAAATCCTGAGGA	21	602
1363568	2234	2253	18713	18732	AAGAATTATTCTCCAGACAT	26	603
1363592	2077	2096	18556	18575	ATATGACAGAGGCCAGAGTA	38	604
1363623	3055	3074	19534	19553	TCTAAAAGTTTATCCTTTAT	37	605
1363644	1872	1891	18351	18370	GCTGTTATCAAGGAGAAGGG	23	606
1363650	2459	2478	18938	18957	AAACCTAACTCTTAACACAC	45	607
1363688	N/A	N/A	16190	16209	AACTAAGTTTTCACTTCCCT	72	608
1363704	1321	1340	17800	17819	CAGGAACCAGCTATGAAGCA	37	609
1363776	2194	2213	18673	18692	AGTAATAAACAACTGGAAT	68	610
1363783	1359	1378	17838	17857	GTTGGGAAGTCATCTTCTTA	45	611
1363800	2891	2910	19370	19389	AAAACACAAGGTACGGATTA	38	612
1363852	N/A	N/A	10586	10605	AAATTATCTCTGTCATGGGA	55	613

1363865	3019	3038	19498	19517	ATTCTATATCAGAAATGAAG	64	614
1363879	2841	2860	19320	19339	TACAAAACATTTTCCCTCTC	59	615
1363901	N/A	N/A	16498	16517	AGAAGCTTCCCTCCAGCATT	84	616
1363953	1214	1233	17693	17712	AGTAAGAAGAGGGCCAGTTG	75	617
1363956	N/A	N/A	15143	15162	CCACCACTTCCAAGTTCCCT	69	618
1363972	N/A	N/A	6367	6386	CCACACTTTTTGCCTGGGCT	25	619
1363993	1655	1674	18134	18153	CCAGCTGCAATAGGCAGATT	21	620
1364008	2668	2687	19147	19166	TACAAATCTTTCCTTCAATT	43	621
1364009	N/A	N/A	8638	8657	CAAGAATTAAGCACACTAGC	77	622
1364035	1434	1453	17913	17932	GAGAAGAAATTACTTTCTGA	113	623
1364039	1182	1201	17661	17680	AAGAGTTAAGATGGGAGACG	66	624
1364042	N/A	N/A	17149	17168	AGACACACAGCCACATCATG	57	625
1364065	N/A	N/A	11896	11915	TCATCAACTATTTATGGAAT	67	626
1364073	N/A	N/A	9220	9239	CAGTAATATCAGCATAAGCA	23	627
1364112	N/A	N/A	12817	12836	AGTTCTCTATCTCCAGGATG	56	628
1364128	1250	1269	17729	17748	TCACTGCAAGACTCTCCTTT	45	629
1364159	2695	2714	19174	19193	CAACTCTTTACAACAAAAGA	75	630
1364171	2748	2767	19227	19246	CTCTTACATCTCCTTAAATA	43	631
1364185	N/A	N/A	16858	16877	ATAATGTTAGGAGGTCTCC	33	632
1364187	N/A	N/A	15658	15677	TCTATGCTCATTGGCTCAGG	70	633

Table 9

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362479	3115	3134	19594	19613	TGAGAACATTCTTAATTTTA	84	634
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	14	201
1362499	1469	1488	17948	17967	CTTCCACTTTGTTTCCATCA	70	635
1362545	N/A	N/A	11653	11672	TCAGACAGGATTTTAGCATG	65	636
1362561	N/A	N/A	16189	16208	ACTAAGTTTTCACTTCCCTA	72	637
1362586	N/A	N/A	6181	6200	GAGAATAATCAGCTACTGCT	76	638
1362634	N/A	N/A	7948	7967	GTCTCGAATCTGCACTACAG	57	639
1362635	1516	1535	17995	18014	TGGCAAGAGGACCAAAGACA	62	640
1362638	2985	3004	19464	19483	TGATTAACCTCTCTTTGTGTG	49	641
1362669	2840	2859	19319	19338	ACAAAACATTTTCCCTCTCC	57	642
1362681	1294	1313	17773	17792	TAAAAGAGGTACATAAGAGG	84	643
1362695	2155	2174	18634	18653	CTAAAACAAATCAAGACCTT	62	644
1362737	2746	2765	19225	19244	CTTACATCTCCTTAAATATT	38	645
1362769	1654	1673	18133	18152	CAGCTGCAATAGGCAGATTT	41	646
1362802	N/A	N/A	10560	10579	AGGTAGAGGCATTTGCCTCT	85	647
1362852	N/A	N/A	17360	17379	GCTTGGCTTTCTCCATATAC	34	648

1362863	2377	2396	18856	18875	AATTGAGATTCAAATTCACC	46	649
1362872	N/A	N/A	7378	7397	CAAGCATTGGGAAGCTGAGG	42	650
1362893	N/A	N/A	5108	5127	TCATAAGTAGCAGATCTGGG	44	651
1362939	2346	2365	18825	18844	TGCAAAGGCAGAATACTTGT	60	652
1362942	1399	1418	17878	17897	TGAAAATTCAATTAGAGCCT	43	653
1362943	2044	2063	18523	18542	CAGAAAAAAGACATGCTAT	78	654
1363003	1181	1200	17660	17679	AGAGTTAAGATGGGAGACGC	52	655
1363075	N/A	N/A	15624	15643	ATGTTGTAGAAGGCAATCGG	59	656
1363093	2296	2315	18775	18794	TTTTAATATCATTTGTGATG	73	657
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	15	279
1363146	2076	2095	18555	18574	TATGACAGAGGCCAGAGTAC	22	658
1363166	1871	1890	18350	18369	CTGTTATCAAGGAGAAGGGA	24	659
1363178	N/A	N/A	15110	15129	ACCTCTCTGGTTTCAGTAGG	67	660
1363185	2485	2504	18964	18983	TATCAGGAGAAAATAACCTT	44	661
1363201	1249	1268	17728	17747	CACTGCAAGACTCTCCTTTC	34	662
1363251	2103	2122	18582	18601	CCCATGAAATGAGCACCATT	43	663
1363285	N/A	N/A	17148	17167	GACACACAGCCACATCATGC	57	664
1363314	1728	1747	18207	18226	TCAGTAGTCCATCGCCATCG	23	123
1363328	2002	2021	18481	18500	TCTACCAGAGGGCCATCTCA	50	665
1363346	2580	2599	19059	19078	AGCTATTCAAGGTCTCAAAC	39	666
1363347	2404	2423	18883	18902	AGCTAGAAAGAACGATCAGA	38	667
1363364	N/A	N/A	4532	4551	CCCATGGTCAAGCCATTGAG	63	668
1363380	N/A	N/A	14246	14265	CCTCACTCAAAGCATGGATA	26	669
1363406	N/A	N/A	9219	9238	AGTAATATCAGCATAAGCAT	46	670
1363419	2890	2909	19369	19388	AAACACAAGGTACGGATTAC	40	671
1363448	2620	2639	19099	19118	ACCCAAAGTTAACAAAAACA	52	672
1363462	N/A	N/A	5421	5440	GGCAGGAATTGAGTTCCTCC	35	673
1363480	N/A	N/A	11894	11913	ATCAACTATTTATGGAATAC	62	674
1363507	2193	2212	18672	18691	GTAATAAACAACTGGAATA	88	675
1363527	N/A	N/A	8637	8656	AAGAATTAAGCACACTAGCA	80	676
1363551	2233	2252	18712	18731	AGAATTATTCTCCAGACATT	35	677
1363604	3054	3073	19533	19552	CTAAAAGTTTATCCTTTATG	60	678
1363608	1213	1232	17692	17711	GTAAGAAGAGGGCCAGTTGG	80	679
1363613	1433	1452	17912	17931	AGAAGAAATTACTTTCTGAT	115	680
1363636	N/A	N/A	6979	6998	TCACCTACCATGGCTGCTGT	66	681
1363654	2667	2686	19146	19165	ACAAATCTTTCCTTCAATTA	59	682
1363656	2321	2340	18800	18819	ATCCCAATAGATTCAACTAG	35	683
1363676	2258	2277	18737	18756	TAGTTTAAAAAACAGTCATA	94	684
1363686	2530	2549	19009	19028	ACCAACTGAATAGCTGATGA	27	685
1363706	342	361	12634	12653	AACACAATCCAGTGCCACC	67	686
1363721	2131	2150	18610	18629	TCACCTACGATGACTGAATG	56	687
1363732	N/A	N/A	8983	9002	TCACAGTCCAAGAAATGTCC	62	688
1363742	N/A	N/A	9634	9653	GGTATGGTCAGGGATGGAGG	55	689

1363756	1079	1098	17558	17577	CATGAGTTTAAGGACGGCAA	36	690
1363758	N/A	N/A	13732	13751	GCCACAAAATCCTGAGGATG	14	691
1363814	1320	1339	17799	17818	AGGAACCAGCTATGAAGCAA	26	692
1363856	1839	1858	18318	18337	TGACAACACCCTGTTTCTCT	24	693
1363876	N/A	N/A	6330	6349	GCCAGCCAAAACACTACTGC	53	694
1363991	2431	2450	18910	18929	CATTGCTAAGTAAAATCATT	47	695
1364012	1588	1607	18067	18086	TTCAGTGGTAATAGAGAGAC	64	696
1364018	2458	2477	18937	18956	AACCTAACTCTTAACACACC	34	697
1364028	1972	1991	18451	18470	TTAGCCACCAGCAACTGCTG	43	698
1364071	1911	1930	18390	18409	TATTCTCAGCTCCTTGAAA	72	699
1364081	1358	1377	17837	17856	TTGGGAAGTCATCTTCTTAG	61	700
1364139	2693	2712	19172	19191	ACTCTTTACAACAAAAGAAC	48	701
1364163	N/A	N/A	16489	16508	CCTCCAGCATTTCAAGGATG	79	702
1364196	3018	3037	19497	19516	TTCTATATCAGAAATGAAGG	49	703
1364213	N/A	N/A	10960	10979	TGTCTTAATTCATATGTATG	61	704
1364246	1770	1789	18249	18268	ACGCTCCCTTATGCTGTAAG	13	49
1364249	N/A	N/A	16791	16810	GGATTCATATTGATAGTATA	76	705
1364260	1549	1568	18028	18047	TACACCAAAGAGAATATATT	79	706
1364263	N/A	N/A	5816	5835	ACTCCACATCAGAAGTAGTG	53	707
1364272	2789	2808	19268	19287	ATACTGGTTTGAAAACAAGT	35	708

Table 10

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362447	1652	1671	18131	18150	GCTGCAATAGGCAGATTTGG	29	709
1362477	N/A	N/A	5416	5435	GAATTGAGTTCCTCCAACAT	73	710
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	16	201
1362491	N/A	N/A	6303	6322	ACAGCCACTTTTGGATGGAG	55	711
1362533	2129	2148	18608	18627	ACCTACGATGACTGAATGGA	49	712
1362559	2376	2395	18855	18874	ATTGAGATTCAAATTCACCA	18	713
1362565	2578	2597	19057	19076	CTATTCAGGTCTCAAACCTCT	30	714
1362569	N/A	N/A	15623	15642	TGTTGTAGAAGGCAATCGGC	75	715
1362588	N/A	N/A	16065	16084	GGTTCCTACAGTTGTGCC	37	716
1362599	1355	1374	17834	17853	GGAAAGTCATCTTCTTAGGCA	44	717
1362612	2320	2339	18799	18818	TCCAATAGATTCAACTAGC	22	718
1362642	2666	2685	19145	19164	CAAATCTTCTTCAATTAA	72	719
1362649	N/A	N/A	16781	16800	TGATAGTATATAGAATTCCA	23	720
1362651	N/A	N/A	8627	8646	CACACTAGCAGTGACATAGA	75	721
1362665	3114	3133	19593	19612	GAGAACATTCTTAATTTTAT	68	722
1362707	2484	2503	18963	18982	ATCAGGAGAAAATAACCTTT	30	723

1362714	1838	1857	18317	18336	GACAACACCCTGTTTCTCTT	30	724
1362715	2430	2449	18909	18928	ATTGCTAAGTAAAATCATTT	50	725
1362744	N/A	N/A	7940	7959	TCTGCACTACAGTCTTACCC	67	726
1362747	2745	2764	19224	19243	TTACATCTCCTTAAATATTG	56	727
1362757	2619	2638	19098	19117	CCCAAAGTTAACAAAAACAG	36	728
1362761	N/A	N/A	4531	4550	CCATGGTCAAGCCATTGAGG	61	729
1362799	2889	2908	19368	19387	AACACAAGGTACGGATTACT	41	730
1362874	2042	2061	18521	18540	GAAAAAAGACATGCTATCC	64	731
1362906	2102	2121	18581	18600	CCATGAAATGAGCACCATTG	26	732
1362924	1769	1788	18248	18267	CGCTCCCTTATGCTGTAAGT	21	282
1362985	3053	3072	19532	19551	TAAAAGTTTATCCTTTATGT	85	733
1363066	N/A	N/A	5814	5833	TCCACATCAGAAGTAGTGGC	59	734
1363074	1248	1267	17727	17746	ACTGCAAGACTCTCCTTTCT	38	735
1363108	1432	1451	17911	17930	GAAGAAATTACTTTCTGATC	111	736
1363113	N/A	N/A	10892	10911	AAACACAGTATACACATGCA	71	737
1363116	2403	2422	18882	18901	GCTAGAAAGAACGATCAGAT	39	738
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	21	279
1363169	1870	1889	18349	18368	TGTTATCAAGGAGAAGGGAG	43	739
1363197	N/A	N/A	6179	6198	GAATAATCAGCTACTGCTCT	89	740
1363207	N/A	N/A	11650	11669	GACAGGATTTTAGCATGAAG	66	741
1363213	1398	1417	17877	17896	GAAAAATCAATTAGAGCCTC	43	742
1363270	N/A	N/A	6925	6944	TCTTCTTTAGACCTGAAGTG	74	743
1363280	1909	1928	18388	18407	TTCTCAGCTCCTTGGAACCC	52	744
1363303	1179	1198	17658	17677	AGTTAAGATGGGAGACGCAG	47	745
1363326	1467	1486	17946	17965	TCCACTTTGTTTCCATCAGT	72	746
1363438	2956	2975	19435	19454	GTGTATGTATGCATGTGAGG	29	747
1363440	1293	1312	17772	17791	AAAAGAGGTACATAAGAGGG	68	748
1363449	N/A	N/A	5046	5065	TCCTGTTTTACCTGAACACA	66	749
1363473	2192	2211	18671	18690	TAATAAACAAACTGGAATAC	90	750
1363482	N/A	N/A	16486	16505	CCAGCATTTCAAGGATGGAA	55	751
1363488	N/A	N/A	15073	15092	AGACCCAATCATTCATCATC	70	752
1363496	1708	1727	18187	18206	GGGTCAGTGCTCTCTTTCTG	37	753
1363509	1211	1230	17690	17709	AAGAAGAGGGCCAGTTGGTG	77	754
1363525	2692	2711	19171	19190	CTCTTTACAACAAAAGAACT	78	755
1363543	2528	2547	19007	19026	CAACTGAATAGCTGATGACT	58	756
1363556	N/A	N/A	9617	9636	AGGAACTTGAACCTCTTGCTA	47	757
1363569	2075	2094	18554	18573	ATGACAGAGGCCAGAGTACA	44	758
1363605	1587	1606	18066	18085	TCAGTGGTAATAGAGAGACC	54	759
1363620	2257	2276	18736	18755	AGTTTAAAAAACAGTCATAA	96	760
1363639	2295	2314	18774	18793	TTTAATATCATTTGTGATGC	30	761
1363661	3017	3036	19496	19515	TCTATATCAGAAATGAAGGA	47	762
1363677	N/A	N/A	17147	17166	ACACACAGCCACATCATGCA	61	763
1363709	2001	2020	18480	18499	CTACCAGAGGGCCATCTCAG	51	764

1363754	2788	2807	19267	19286	TACTGGTTTGGAAAACAAGTA	38	765
1363771	2154	2173	18633	18652	TAAACAAATCAAGACCTTC	55	766
1363781	N/A	N/A	11893	11912	TCAACTATTTATGGAATACT	69	767
1363799	1078	1097	17557	17576	ATGAGTTTAAGGACGGCAAA	55	768
1363810	1515	1534	17994	18013	GGCAAGAGGACCAAAGACAT	40	769
1363864	N/A	N/A	8958	8977	GTATGTGTGAACAATAGCCT	56	770
1363895	N/A	N/A	14243	14262	CACTCAAAGCATGGATAACC	54	771
1363931	2838	2857	19317	19336	AAAACATTTTCCTCTCCTC	58	772
1363950	340	359	12632	12651	CACAATCCAGTGGCCACCAG	72	773
1363997	2232	2251	18711	18730	GAATTATTCTCCAGACATTT	42	774
1363999	1319	1338	17798	17817	GGAACCAGCTATGAAGCAAA	32	775
1364010	2345	2364	18824	18843	GCAAAGGCAGAATACTTGTA	50	776
1364104	2457	2476	18936	18955	ACCTAACTCTTAACACACCA	32	777
1364114	N/A	N/A	17351	17370	TCTCCATATACACTTGACTG	46	778
1364130	N/A	N/A	10367	10386	GCTGCCAGGAACTTGGCCT	41	779
1364150	N/A	N/A	13731	13750	CCACAAAATCCTGAGGATGA	28	780
1364153	N/A	N/A	9218	9237	GTAATATCAGCATAAGCATC	57	781
1364169	N/A	N/A	7343	7362	TAAAACTTATCCTTGGCACA	93	782
1364252	1548	1567	18027	18046	ACACCAAAGAGAATATATTT	71	783
1364255	1971	1990	18450	18469	TAGCCACCAGCAACTGCTGC	31	784

Table 11

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362445	2319	2338	18798	18817	CCCAATAGATTCAACTAGCC	24	134
1362482	N/A	N/A	16485	16504	CAGCATTTCAAGGATGGAAG	51	785
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	30	201
1362513	1869	1888	18348	18367	GTTATCAAGGAGAAGGGAGT	37	786
1362549	N/A	N/A	5045	5064	CCTGTTTTACCTGAACACAT	53	787
1362550	2041	2060	18520	18539	AAAAAAAGACATGCTATCCA	63	788
1362560	2455	2474	18934	18953	CTAACTCTTAACACACCAAG	49	789
1362564	N/A	N/A	9215	9234	ATATCAGCATAAGCATCAGA	73	790
1362603	N/A	N/A	7337	7356	TTATCCTTGGCACATTGTCT	74	791
1362617	2344	2363	18823	18842	CAAAGGCAGAATACTTGTAG	53	792
1362699	1768	1787	18247	18266	GCTCCCTTATGCTGTAAGTA	35	204
1362804	1318	1337	17797	17816	GAACCAGCTATGAAGCAAAA	40	793
1362835	2618	2637	19097	19116	CCAAAGTTAACAAAAACAGG	63	794
1362840	2256	2275	18735	18754	GTTTAAAAAACAGTCATAAT	97	795
1362844	N/A	N/A	10891	10910	AACACAGTATACACATGCAC	48	796

1362996	2483	2502	18962	18981	TCAGGAGAAAATAACCTTTA	28	797
1363019	2294	2313	18773	18792	TTAATATCATTGTGTGATGCT	25	798
1363020	1466	1485	17945	17964	CCACTTTGTTTCCATCAGTG	64	799
1363023	2000	2019	18479	18498	TACCAGAGGGCCATCTCAGG	53	800
1363032	3016	3035	19495	19514	CTATATCAGAAATGAAGGAA	56	801
1363037	2189	2208	18668	18687	TAAACAAACTGGAATACATG	93	802
1363086	2787	2806	19266	19285	ACTGGTTTGAAAACAAGTAT	49	803
1363090	N/A	N/A	17146	17165	CACACAGCCACATCATGCAG	89	804
1363095	N/A	N/A	4528	4547	TGGTCAAGCCATTGAGGACT	41	805
1363097	N/A	N/A	16064	16083	GTTCCCTACAGTTGTGCCCA	41	806
1363109	2375	2394	18854	18873	TTGAGATTCAAATTCACCAA	44	807
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	22	279
1363131	N/A	N/A	16780	16799	GATAGTATATAGAATTCCAG	40	808
1363135	304	323	12596	12615	CCTACCAGACATCTTGCACA	44	809
1363147	1547	1566	18026	18045	CACCAAAGAGAATATATTTG	58	810
1363148	1431	1450	17910	17929	AAGAAATTACTTTCTGATCC	79	811
1363160	2577	2596	19056	19075	TATTCAGGTCTCAAACCTCTT	42	812
1363193	2074	2093	18553	18572	TGACAGAGGCCAGAGTACAC	43	813
1363217	1908	1927	18387	18406	TCTCAGCTCCTTGGAACCA	38	814
1363250	N/A	N/A	11542	11561	CTTCTTAGTTTACATATGGG	40	815
1363256	3089	3108	19568	19587	TTAATTTTATAAAATACACT	99	816
1363271	2665	2684	19144	19163	AAATCTTTCCTTCAATTTAA	80	817
1363296	N/A	N/A	6302	6321	CAGCCACTTTTGGATGGAGG	54	818
1363343	1178	1197	17657	17676	GTTAAGATGGGAGACGCAGC	46	819
1363363	2402	2421	18881	18900	CTAGAAAGAACGATCAGATT	69	820
1363376	N/A	N/A	8952	8971	GTGAACAATAGCCTAAAGCC	59	821
1363386	N/A	N/A	15072	15091	GACCCAATCATTATCATCT	60	822
1363427	1651	1670	18130	18149	CTGCAATAGGCAGATTTGGG	24	823
1363469	2230	2249	18709	18728	ATTATTCTCCAGACATTTCT	66	824
1363579	N/A	N/A	9615	9634	GAACTTGAACCTTTGCTAGC	69	825
1363583	1586	1605	18065	18084	CAGTGGTAATAGAGAGACCA	24	826
1363586	2153	2172	18632	18651	AAAACAAATCAAGACCTTCA	57	827
1363609	2100	2119	18579	18598	ATGAAATGAGCACCATTGTG	45	828
1363614	N/A	N/A	7936	7955	CACTACAGTCTTACCCTCCT	83	829
1363632	2837	2856	19316	19335	AAACATTTTCCCTCTCCTCC	57	830
1363652	2691	2710	19170	19189	TCTTTACAACAAAAGAACTG	73	831
1363660	3052	3071	19531	19550	AAAAGTTTATCCTTTATGTG	69	832
1363665	1275	1294	17754	17773	GGGAGAGTCCAAAGAGAGAC	77	833
1363668	1695	1714	18174	18193	CTTTCTGTGGGTGAAAGATC	70	834
1363715	1246	1265	17725	17744	TGCAAGACTCTCCTTTCTTG	51	835
1363727	N/A	N/A	8625	8644	CACTAGCAGTGACATAGACA	71	836
1363759	2888	2907	19367	19386	ACACAAGGTACGGATTACTT	42	59
1363775	N/A	N/A	5812	5831	CACATCAGAAGTAGTGGCAG	66	837

1363805	2954	2973	19433	19452	GTATGTATGCATGTGAGGTT	60	838
1363811	N/A	N/A	17349	17368	TCCATATACACTTGACTGGA	50	839
1363872	1834	1853	18313	18332	ACACCCTGTTTCTCTCCCT	39	840
1363917	N/A	N/A	15622	15641	GTTGTAGAAGGCAATCGGCT	63	841
1363933	1969	1988	18448	18467	GCCACCAGCAACTGCTGCTC	29	842
1363947	N/A	N/A	6003	6022	TTCTATATGGTTGAAGTAGT	61	843
1363957	2743	2762	19222	19241	ACATCTCCTTAAATATTGCT	33	844
1364023	N/A	N/A	5411	5430	GAGTTCCTCCAACATTCACC	39	845
1364038	1077	1096	17556	17575	TGAGTTTAAGGACGGCAAAG	80	846
1364060	1397	1416	17876	17895	AAAATTCAATTAGAGCCTCC	49	847
1364098	1210	1229	17689	17708	AGAAGAGGGCCAGTTGGTGG	69	848
1364106	1350	1369	17829	17848	TCATCTTCTTAGGCATTTCC	45	849
1364119	1514	1533	17993	18012	GCAAGAGGACCAAAGACATT	77	850
1364123	2527	2546	19006	19025	AACTGAATAGCTGATGACTG	55	851
1364138	N/A	N/A	14242	14261	ACTCAAAGCATGGATAACCC	38	852
1364145	609	628	13597	13616	CGCTCAGGCCCTTGCCGCAG	43	108
1364170	2428	2447	18907	18926	TGCTAAGTAAAATCATTTTC	47	853
1364193	2128	2147	18607	18626	CCTACGATGACTGAATGGAT	49	854
1364202	N/A	N/A	10364	10383	GCCAGGAACTTGGCCTCTA	22	855
1364204	N/A	N/A	11892	11911	CAACTATTTATGGAATACTC	59	856
1364210	N/A	N/A	6923	6942	TTCTTTAGACCTGAAGTGCT	85	857

Table 12

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362483	N/A	N/A	17145	17164	ACACAGCCACATCATGCAGT	59	858
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	10	201
1362505	N/A	N/A	17348	17367	CCATATACACTTGACTGGAA	42	859
1362507	582	601	13570	13589	TCTTGTAAGTCGCCAAAGATC	75	860
1362538	N/A	N/A	9212	9231	TCAGCATAAAGCATCAGATGT	46	861
1362539	1274	1293	17753	17772	GGAGAGTCCAAAGAGAGACC	61	862
1362556	2482	2501	18961	18980	CAGGAGAAAATAACCTTTAT	15	863
1362557	1243	1262	17722	17741	AAGACTCTCCTTTCTTGTTA	52	864
1362558	3015	3034	19494	19513	TATATCAGAAATGAAGGAAA	73	865
1362622	N/A	N/A	7890	7909	CCATGAACAGAGGCCTCCTT	84	866
1362647	2152	2171	18631	18650	AAACAAATCAAGACCTTCAA	38	867
1362678	1464	1483	17943	17962	ACTTTGTTTCCATCAGTGGA	47	868
1362684	1968	1987	18447	18466	CCACCAGCAACTGCTGCTCC	24	869
1362692	1429	1448	17908	17927	GAAATTACTTTCTGATCCTC	70	870
1362741	N/A	N/A	9613	9632	ACTTGAACCTTGCTAGCCA	44	871

1362782	N/A	N/A	15070	15089	CCCAATCATTTCATCATCTTA	55	872
1362821	1766	1785	18245	18264	TCCCTTATGCTGTAAGTAAG	32	873
1362829	303	322	12595	12614	CTACCAGACATCTTGACAG	53	874
1362878	2229	2248	18708	18727	TTATTCTCCAGACATTTCTG	36	875
1362895	2617	2636	19096	19115	CAAAGTTAACAAAAACAGGA	71	876
1362911	N/A	N/A	6914	6933	CCTGAAGTGCTGTGGGCAGG	78	877
1362938	2255	2274	18734	18753	TTTAAAAAACAGTCATAATC	81	878
1362967	1650	1669	18129	18148	TGCAATAGGCAGATTTGGGC	22	200
1362973	1546	1565	18025	18044	ACCAAAGAGAATATATTTGG	49	879
1363004	N/A	N/A	16483	16502	GCATTTCAAGGATGGAAGCA	53	880
1363013	1999	2018	18478	18497	ACCAGAGGGCCATCTCAGGT	15	881
1363073	N/A	N/A	5811	5830	ACATCAGAAAGTAGTGGCAGT	66	882
1363084	1316	1335	17795	17814	ACCAGCTATGAAGCAAAATG	30	883
1363104	2040	2059	18519	18538	AAAAAAGACATGCTATCCAA	51	884
1363106	1396	1415	17875	17894	AAATTCAATTAGAGCCTCCA	40	885
1363114	1209	1228	17688	17707	GAAGAGGGCCAGTTGGTGGC	44	886
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	16	279
1363143	2073	2092	18552	18571	GACAGAGGCCAGAGTACACA	10	887
1363159	N/A	N/A	10303	10322	AGTTTACTCAGCATGAACTT	85	888
1363168	1513	1532	17992	18011	CAAGAGGACCAAAGACATTC	85	889
1363172	2293	2312	18772	18791	TAATATCATTGTGTGATGCTT	25	890
1363220	2662	2681	19141	19160	TCTTCCTTCAATTAACC	27	891
1363231	2454	2473	18933	18952	TAAGTCTTAACACACCAAGA	40	892
1363293	N/A	N/A	6299	6318	CCACTTTTGGATGGAGGCAT	38	893
1363294	2690	2709	19169	19188	CTTTACAACAAAAGAACTGT	39	894
1363305	2374	2393	18853	18872	TGAGATTCAAATTCACCAA	22	895
1363306	N/A	N/A	16061	16080	CCCTACAGTTGTGCCAGGG	47	896
1363322	2427	2446	18906	18925	GCTAAGTAAAATCATTTTCC	13	897
1363356	2953	2972	19432	19451	TATGTATGCATGTGAGGTTT	58	898
1363421	N/A	N/A	8590	8609	GGGAATTAAAAGGCCAGTCC	57	899
1363472	2887	2906	19366	19385	CACAAGGTACGGATTACTTC	26	900
1363475	2786	2805	19265	19284	CTGGTTTGAAAAACAAGTATC	25	901
1363487	2318	2337	18797	18816	CCAATAGATTCAACTAGCCA	29	56
1363528	N/A	N/A	11540	11559	TCTTAGTTTACATATGGGAG	38	902
1363577	2188	2207	18667	18686	AAACAACTGGAATACATGA	53	903
1363590	N/A	N/A	16778	16797	TAGTATATAGAATTCCAGGC	23	904
1363601	N/A	N/A	5929	5948	TTGTTGTAAAAATGAATCCC	48	905
1363630	3050	3069	19529	19548	AAGTTTATCCTTTATGTGTG	36	906
1363666	2127	2146	18606	18625	CTACGATGACTGAATGGATA	44	907
1363675	3086	3105	19565	19584	ATTTTATAAAAATACACTTTG	78	908
1363682	N/A	N/A	5407	5426	TCCTCCAACATTCACCTCTC	43	909
1363722	2526	2545	19005	19024	ACTGAATAGCTGATGACTGG	44	910
1363748	1827	1846	18306	18325	GTTTCTCTTCCCTAACGAGG	27	911

1363826	2836	2855	19315	19334	AACATTTTCCCTCTCCTCCT	31	912
1363847	2401	2420	18880	18899	TAGAAAGAACGATCAGATTA	66	913
1363883	2573	2592	19052	19071	CAGGTCTCAAACCTTTCTG	18	914
1363902	2742	2761	19221	19240	CATCTCCTTAAATATTGCTG	20	915
1363904	N/A	N/A	15616	15635	GAAGGCAATCGGCTAATTCA	54	916
1363929	2343	2362	18822	18841	AAAGGCAGAATACTTGTAGA	58	917
1363958	N/A	N/A	7332	7351	CTTGGCACATTGTCTCCACC	79	918
1363965	N/A	N/A	8924	8943	TCCATTTTCAGAACCCCTCCT	55	919
1363976	1585	1604	18064	18083	AGTGGTAATAGAGAGACCAG	25	920
1364070	1906	1925	18385	18404	TCAGCTCCTTGGAACACACA	19	921
1364109	1868	1887	18347	18366	TTATCAAGGAGAAGGGAGTG	67	922
1364132	N/A	N/A	11891	11910	AACTATTTATGGAATACTCA	71	923
1364134	1694	1713	18173	18192	TTTCTGTGGGTGAAAGATCC	56	924
1364141	1347	1366	17826	17845	TCTTCTTAGGCATTTCCTCAT	30	925
1364191	N/A	N/A	10875	10894	GCACACACACAAATACTCAG	34	926
1364208	N/A	N/A	14236	14255	AGCATGGATAACCCCTCAGGC	18	927
1364218	N/A	N/A	5044	5063	CTGTTTTACCTGAACACATG	64	928
1364225	1076	1095	17555	17574	GAGTTTAAGGACGGCAAAGT	30	929
1364243	1177	1196	17656	17675	TTAAGATGGGAGACGCAGCA	39	930
1364245	2099	2118	18578	18597	TGAAATGAGCACCATTGTGA	42	931
1364247	N/A	N/A	4470	4489	CCATAGCCAAGCCTGAGTCC	72	932

Table 13

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362426	2661	2680	19140	19159	CTTTCCTTCAATTAAAACCA	49	933
1362458	2225	2244	18704	18723	TCTCCAGACATTTCTGATGC	18	934
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	25	201
1362510	2098	2117	18577	18596	GAAATGAGCACCATTGTGAA	72	935
1362528	1241	1260	17720	17739	GACTCTCCTTTCTTGTTACA	38	936
1362547	N/A	N/A	16777	16796	AGTATATAGAATTCCAGGCT	30	937
1362573	2614	2633	19093	19112	AGTTAACAAAAACAGGAAAA	89	938
1362587	N/A	N/A	17343	17362	TACACTTGACTGGAAGTCCG	43	939
1362590	1175	1194	17654	17673	AAGATGGGAGACGCAGCATT	55	940
1362606	2342	2361	18821	18840	AAGGCAGAATACTTGTAGAA	61	941
1362625	2946	2965	19425	19444	GCATGTGAGGTTTTTCAGGGA	30	942
1362626	N/A	N/A	10872	10891	CACACACAAATACTCAGCAA	53	943
1362644	2785	2804	19264	19283	TGGTTTGAAAACAAGTATCA	47	944
1362671	N/A	N/A	8923	8942	CCATTTTCAGAACCCCTCCTG	81	945
1362680	2292	2311	18771	18790	AATATCATTTGTGATGCTTA	18	946

1362694	N/A	N/A	16481	16500	ATTTC AAGGATGGAAGCAGT	88	947
1362720	N/A	N/A	5761	5780	CAAAGTACTTTAGATACTCT	71	948
1362779	1545	1564	18024	18043	CCAAAGAGAATATATTTGGC	65	949
1362810	2317	2336	18796	18815	CAATAGATTCAACTAGCCAA	44	950
1362817	2571	2590	19050	19069	GGTCTCAAACCTCTTCTGCC	21	951
1362833	2740	2759	19219	19238	TCTCCTTAAATATTGCTGAA	27	952
1362836	N/A	N/A	11392	11411	TCCTCCTATAATGCAGCTTG	39	953
1362858	2125	2144	18604	18623	ACGATGACTGAATGGATAAT	41	954
1362902	1765	1784	18244	18263	CCCTTATGCTGTAAGTAAGG	27	126
1362936	3042	3061	19521	19540	CCTTTATGTGTGTTAAAATT	41	955
1362946	3081	3100	19560	19579	ATAAAATACACTTTGTAAGA	86	956
1362975	N/A	N/A	15615	15634	AAGGCAATCGGCTAATTCAA	54	957
1363012	1584	1603	18063	18082	GTGGTAATAGAGAGACCAGA	26	958
1363025	1208	1227	17687	17706	AAGAGGGCCAGTTGGTGGCA	37	959
1363033	N/A	N/A	8458	8477	GCAAAATGTAAGCAAAGGGA	60	960
1363105	1428	1447	17907	17926	AAATTACTTTCTGATCCTCA	91	961
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	18	279
1363183	1075	1094	17554	17573	AGTTTAAGGACGGCAAAGTT	58	962
1363189	N/A	N/A	15954	15973	TTGTATATAATATCTGTTCT	61	963
1363192	2689	2708	19168	19187	TTTACAACAAAAGAACTGTA	76	964
1363211	N/A	N/A	6295	6314	TTTTGGATGGAGGCATCACA	72	965
1363214	N/A	N/A	14235	14254	GCATGGATAACCCTCAGGCA	27	966
1363215	2400	2419	18879	18898	AGAAAGAACGATCAGATTAC	65	967
1363239	2151	2170	18630	18649	AACAAATCAAGACCTTCAAA	63	968
1363255	1904	1923	18383	18402	AGCTCCTTGGAACCACAGG	20	969
1363261	2187	2206	18666	18685	AACAAACTGGAATACATGAA	54	970
1363288	N/A	N/A	5403	5422	CCAACATTACCTCTCATCT	59	971
1363298	2481	2500	18960	18979	AGGAGAAAAATAACCTTTATG	40	972
1363355	1824	1843	18303	18322	TCTCTTCCCTAACGAGGTGT	36	53
1363359	2453	2472	18932	18951	AACTCTTAACACACCAAGAT	41	973
1363382	2524	2543	19003	19022	TGAATAGCTGATGACTGGTG	49	974
1363445	1463	1482	17942	17961	CTTTGTTTCCATCAGTGGAA	71	975
1363450	N/A	N/A	7773	7792	AACAACAATTATCAAGAGGT	60	976
1363451	2071	2090	18550	18569	CAGAGGCCAGAGTACACAAC	31	977
1363457	1967	1986	18446	18465	CACCAGCAACTGCTGCTCCT	29	978
1363476	3013	3032	19492	19511	TATCAGAAATGAAGGAAACA	78	979
1363489	1649	1668	18128	18147	GCAATAGGCAGATTTGGGCA	31	980
1363490	N/A	N/A	15068	15087	CAATCATTCATCATCTTATA	68	981
1363546	1273	1292	17752	17771	GAGAGTCCAAAGAGAGACCT	50	982
1363575	2828	2847	19307	19326	CCCTCTCCTCCTTCTATGCA	54	983
1363578	N/A	N/A	6800	6819	GAAAGTGATGTTACTGGCTG	52	984
1363595	N/A	N/A	5928	5947	TGTTGTA AAAATGAATCCCG	48	985
1363597	2886	2905	19365	19384	ACAAGGTACGGATTACTTCA	45	986

1363626	301	320	12593	12612	ACCAGACATCTTGCACAGCA	39	987
1363640	1315	1334	17794	17813	CCAGCTATGAAGCAAATGA	24	988
1363680	2254	2273	18733	18752	TTAAAAACAGTCATAATCA	86	989
1363685	2426	2445	18905	18924	CTAAGTAAATCATTTTCCA	18	990
1363694	1346	1365	17825	17844	CTTCTTAGGCATTTCCCAT	40	991
1363720	1692	1711	18171	18190	TCTGTGGGTGAAAGATCCTT	33	992
1363762	1998	2017	18477	18496	CCAGAGGGCCATCTCAGGTT	22	993
1363841	N/A	N/A	5041	5060	TTTTACCTGAACACATGCTT	85	994
1363885	573	592	13561	13580	CGCCAAAGATCTGCCTGACT	61	995
1364003	N/A	N/A	9601	9620	GCTAGCCAAAAGAGAACTCC	86	996
1364031	N/A	N/A	17018	17037	TGTCTGATCACTGCTTATAA	44	997
1364043	N/A	N/A	9206	9225	TAAGCATCAGATGTTTCATCT	42	998
1364044	N/A	N/A	11881	11900	GGAATACTCACTATATGCCC	49	999
1364049	1866	1885	18345	18364	ATCAAGGAGAAGGGAGTGAG	50	1000
1364101	2039	2058	18518	18537	AAAAAGACATGCTATCCAAA	57	1001
1364131	N/A	N/A	10296	10315	TCAGCATGAACTTTGCAAAC	76	1002
1364136	N/A	N/A	4469	4488	CATAGCCAAGCCTGAGTCCA	88	1003
1364175	1512	1531	17991	18010	AAGAGGACCAAGACATTCC	59	1004
1364182	2373	2392	18852	18871	GAGATTCAAATTCACCAAAT	16	1005
1364188	N/A	N/A	7288	7307	GGGAAGTAACTGGTACTAGA	57	1006
1364265	1395	1414	17874	17893	AATTCAATTAGAGCCTCCAT	48	1007

Table 14

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362486	2827	2846	19306	19325	CCTCTCCTCTTCTATGCAG	30	1008
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	12	201
1362511	N/A	N/A	8895	8914	GGTGTGAGTTTGATTCAAGA	64	1009
1362514	2038	2057	18517	18536	AAAAGACATGCTATCCAAAG	68	1010
1362521	2150	2169	18629	18648	ACAAATCAAGACCTTCAAAT	57	1011
1362527	N/A	N/A	15952	15971	GTATATAATATCTGTTCTCA	39	1012
1362582	2372	2391	18851	18870	AGATTCAAATTCACCAAATC	38	1013
1362630	2945	2964	19424	19443	CATGTGAGGTTTTTCAGGGAA	36	1014
1362683	1544	1563	18023	18042	CAAAGAGAATATATTTGGCC	69	1015
1362703	1207	1226	17686	17705	AGAGGGCCAGTTGGTGGCAA	55	1016
1362758	2784	2803	19263	19282	GGTTTGAAAACAAGTATCAA	35	1017
1362792	1865	1884	18344	18363	TCAAGGAGAAGGGAGTGAGA	45	1018
1362806	2885	2904	19364	19383	CAAGGTACGGATTACTTCAC	36	1019
1362843	2425	2444	18904	18923	TAAGTAAATCATTTTCCAT	56	1020

1362854	2452	2471	18931	18950	ACTCTTAACACACCAAGATA	52	1021
1362856	2289	2308	18768	18787	ATCATTTGTGATGCTTAATG	11	1022
1362877	N/A	N/A	4403	4422	GTTTGCATCAAGCAAGCAGT	40	1023
1362887	2688	2707	19167	19186	TTACAACAAAAGAACTGTAG	65	1024
1362908	1462	1481	17941	17960	TTTGTTCATCAGTGGAAG	72	1025
1362932	N/A	N/A	5927	5946	GTTGTAAAAATGAATCCCCG	35	1026
1362934	N/A	N/A	10871	10890	ACACACAAATACTCAGCAAA	58	1027
1362953	N/A	N/A	6796	6815	GTGATGTTACTGGCTGGAGT	52	1028
1362963	1648	1667	18127	18146	CAATAGGCAGATTTGGGCAA	47	1029
1362966	N/A	N/A	15608	15627	TCGGCTAATTCAAAATCCAG	37	1030
1362978	N/A	N/A	16478	16497	TCAAGGATGGAAGCAGTCTA	77	1031
1362983	299	318	12591	12610	CAGACATCTTGCACAGCACT	34	1032
1363008	3079	3098	19558	19577	AAAAATACACTTTGTAAGATA	80	1033
1363051	1822	1841	18301	18320	TCTTCCCTAACGAGGTGTAA	31	1034
1363064	N/A	N/A	11880	11899	GAATACTCACTATATGCCCA	65	1035
1363101	1903	1922	18382	18401	GCTCCTTGGAACCACAGGG	23	1036
1363115	N/A	N/A	14089	14108	AGATCAGGTGCCCAAGTCTC	43	1037
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	12	279
1363129	N/A	N/A	7771	7790	CAACAATTATCAAGAGGTGC	40	1038
1363144	2253	2272	18732	18751	TAAAAAACAGTCATAATCAA	107	1039
1363167	2097	2116	18576	18595	AAATGAGCACCATTGTGAAG	68	1040
1363187	1583	1602	18062	18081	TGGTAATAGAGAGACCAGAA	29	1041
1363283	1314	1333	17793	17812	CAGCTATGAAGCAAAATGAC	50	1042
1363287	2070	2089	18549	18568	AGAGGCCAGAGTACACAACT	18	1043
1363290	1394	1413	17873	17892	ATTCAATTAGAGCCTCCATT	60	1044
1363311	1272	1291	17751	17770	AGAGTCCAAAGAGAGACCTT	51	1045
1363320	N/A	N/A	5038	5057	TACCTGAACACATGCTTCAA	87	1046
1363351	2224	2243	18703	18722	CTCCAGACATTTCTGATGCA	20	1047
1363389	1174	1193	17653	17672	AGATGGGAGACGCAGCATTG	50	1048
1363395	N/A	N/A	5758	5777	AGTACTTTAGATACTCTGTT	24	1049
1363398	N/A	N/A	9203	9222	GCATCAGATGTTTCATCTCTT	22	1050
1363408	N/A	N/A	10147	10166	AAATCGATGTGTTCTCAG	60	1051
1363453	2569	2588	19048	19067	TCTCAAACCTTTCTGCCTG	24	1052
1363460	872	891	14931	14950	AGCACAGAGACTGCCTATAC	67†	1053
1363467	2124	2143	18603	18622	CGATGACTGAATGGATAATA	28	1054
1363513	572	591	13560	13579	GCCAAAGATCTGCCTGACTG	45	1055
1363534	2399	2418	18878	18897	GAAAGAACGATCAGATTACT	53	1056
1363558	1427	1446	17906	17925	AATTACTTTCTGATCCTCAG	88	1057
1363559	N/A	N/A	16776	16795	GTATATAGAATTCCAGGCTA	32	1058
1363570	1997	2016	18476	18495	CAGAGGGCCATCTCAGGTTA	45	1059
1363642	2523	2542	19002	19021	GAATAGCTGATGACTGGTGC	23	1060
1363651	1239	1258	17718	17737	CTCTCCTTTCTTGTTACACT	36	1061
1363716	2480	2499	18959	18978	GGAGAAAATAACCTTTATGT	33	1062

1363735	2184	2203	18663	18682	AAACTGGAATACATGAAATG	73	1063
1363737	N/A	N/A	11389	11408	TCCTATAATGCAGCTTGGCT	60	1064
1363760	2316	2335	18795	18814	AATAGATTCAACTAGCCAAT	48	1065
1363809	3041	3060	19520	19539	CTTTATGTGTGTTAAAATTG	72	1066
1363812	2739	2758	19218	19237	CTCCTTAAATATTGCTGAAA	32	1067
1363817	N/A	N/A	5402	5421	CAACATTCACCTCTCATCTG	77	1068
1363831	N/A	N/A	9597	9616	GCCAAAAGAGAACTCCACTT	49	1069
1363836	3012	3031	19491	19510	ATCAGAAATGAAGGAAACAC	61	1070
1363846	2341	2360	18820	18839	AGGCAGAATACTTGTAGAAA	58	1071
1363848	1691	1710	18170	18189	CTGTGGGTGAAAGATCCTTG	29	1072
1363854	N/A	N/A	7272	7291	TAGAGACAATAGTAGCCATA	73	1073
1363886	N/A	N/A	16994	17013	ACTTCAGATAAATCACTTCA	53	1074
1364056	N/A	N/A	17340	17359	ACTTGACTGGAAGTCCGATG	29	1075
1364078	2613	2632	19092	19111	GTTAACAAAAACAGGAAAAG	79	1076
1364079	1511	1530	17990	18009	AGAGGACCAAAGACATTCTT	48	1077
1364086	N/A	N/A	8419	8438	GCTACATTTGTATACAAACT	36	1078
1364091	1074	1093	17553	17572	GTTTAAGGACGGCAAAGTTG	55	1079
1364126	N/A	N/A	6291	6310	GGATGGAGGCATCACAGTCT	47	1080
1364129	1762	1781	18241	18260	TTATGCTGTAAGTAAGGTTG	42	1081
1364192	1966	1985	18445	18464	ACCAGCAACTGCTGCTCCTC	33	1082
1364205	2658	2677	19137	19156	TCCTTCAATTAACCAATC	38	1083
1364244	1345	1364	17824	17843	TTCTTAGGCATTTCCCATT	52	1084

Table 15

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362433	296	315	12588	12607	ACATCTTGACAGCACTCTA	34	1085
1362442	N/A	N/A	5303	5322	CTGTATACACATTATTGTCT	46	1086
1362446	1864	1883	18343	18362	CAAGGAGAAGGGAGTGAGAA	60	1087
1362448	1234	1253	17713	17732	CTTTCTTGTTACACTCATCA	28	1088
1362450	2783	2802	19262	19281	GTTTGAAAACAAGTATCAAG	29	1089
1362460	2520	2539	18999	19018	TAGCTGATGACTGGTGCATT	26	1090
1362485	2738	2757	19217	19236	TCCTTAAATATTGCTGAAAC	40	1091
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	13	201
1362516	N/A	N/A	10143	10162	CGATTGTTGTTCTCAGAAAA	49	1092
1362738	2183	2202	18662	18681	AACTGGAATACATGAAATGT	78	1093
1362745	N/A	N/A	8416	8435	ACATTTGTATACAAACTCCC	46	1094
1362767	N/A	N/A	17254	17273	CCTCTGTTTGATCTAGCACT	31	1095
1362816	2657	2676	19136	19155	CCTTCAATTAACCAATCA	39	1096
1362825	N/A	N/A	16765	16784	TCCAGGCTATAGCAAGTCAT	23	1097

1362857	1073	1092	17552	17571	TTTAAGGACGGCAAAGTTGT	66	1098
1362866	N/A	N/A	14042	14061	TGTCCAGTTAGATCCACTCT	16	245
1362899	N/A	N/A	10870	10889	CACACAAATACTCAGCAAAT	66	1099
1362916	1205	1224	17684	17703	AGGGCCAGTTGGTGGCAAAG	34	1100
1362951	3039	3058	19518	19537	TTATGTGTGTTAAAAATTGCA	55	1101
1362982	N/A	N/A	11388	11407	CCTATAATGCAGCTTGGCTA	54	1102
1363000	N/A	N/A	5037	5056	ACCTGAACACATGCTTCAAA	59	1103
1363031	N/A	N/A	5728	5747	TGAAAACCTCAGTGGCTGCTC	47	1104
1363039	2315	2334	18794	18813	ATAGATTCAACTAGCCAATT	61	1105
1363059	2037	2056	18516	18535	AAAGACATGCTATCCAAAGA	46	1106
1363100	1543	1562	18022	18041	AAAGAGAATATATTTGGCCC	58	1107
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	15	279
1363145	2069	2088	18548	18567	GAGGCCAGAGTACACAATA	15	1108
1363151	2371	2390	18850	18869	GATTCAAATTCACCAAATCT	28	1109
1363179	2223	2242	18702	18721	TCCAGACATTTCTGATGCAA	14	1110
1363199	N/A	N/A	16993	17012	CTTCAGATAAATCACTTCAC	40	1111
1363216	N/A	N/A	7714	7733	TGGTCAGACAATGCCCTGCC	56	1112
1363221	N/A	N/A	16474	16493	GGATGGAAGCAGTCTACCTT	44	1113
1363234	1343	1362	17822	17841	CTTAGGCATTTCCATTCT	47	1114
1363237	3011	3030	19490	19509	TCAGAAATGAAGGAAACACT	51	1115
1363248	1425	1444	17904	17923	TTACTTTCTGATCCTCAGGA	66	1116
1363273	1459	1478	17938	17957	GTTTCCATCAGTGGAAGTAC	16	1117
1363292	2929	2948	19408	19427	GGAAGGGTTGGTTATTTGTT	41	1118
1363338	N/A	N/A	7271	7290	AGAGACAATAGTAGCCATAC	69	1119
1363357	2286	2305	18765	18784	ATTTGTGATGCTTAATGTCC	30	1120
1363361	1901	1920	18380	18399	TCCTTGGAACCACAGGGTT	49	1121
1363424	N/A	N/A	9511	9530	TGATCCCCTCAATCATCATCC	56	1122
1363486	N/A	N/A	15607	15626	CGGCTAATTCAAAATCCAGC	19	1123
1363516	N/A	N/A	9199	9218	CAGATGTTTCATCTCTTCACA	35	1124
1363518	1821	1840	18300	18319	CTTCCCTAACGAGGTGTAAG	33	1125
1363519	1994	2013	18473	18492	AGGGCCATCTCAGGTTACAC	10	288
1363521	N/A	N/A	5912	5931	CCCGCATTGAAGGTTGGCTC	32	1126
1363584	2398	2417	18877	18896	AAAGAACGATCAGATTACTC	28	1127
1363598	2122	2141	18601	18620	ATGACTGAATGGATAATACC	37	1128
1363638	2823	2842	19302	19321	TCCTCCTTCTATGCAGCCTG	21	1129
1363646	N/A	N/A	6282	6301	CATCACAGTCTGGTTACCAG	68	1130
1363648	1965	1984	18444	18463	CCAGCAACTGCTGCTCCTCA	17	1131
1363655	871	890	14930	14949	GCACAGAGACTGCCTATACT	77†	1132
1363663	478	497	13466	13485	ACATACTGGAAGGCATGGAT	36	1133
1363693	N/A	N/A	8893	8912	TGTGAGTTTGATTCAAGAAG	52	1134
1363714	1393	1412	17872	17891	TTCAATTAGAGCCTCCATTC	50	1135
1363744	2884	2903	19363	19382	AAGGTACGGATTACTTCACT	26	1136
1363764	1271	1290	17750	17769	GAGTCCAAAGAGAGACCTTA	43	1137

1363835	2566	2585	19045	19064	CAAACCTCTTTCTGCCTGTCC	31	1138
1363866	3078	3097	19557	19576	AAATACACTTTGTAAGATAA	55	1139
1363920	N/A	N/A	6767	6786	ATGGGTTTGAGACTATATT	61	1140
1363945	2612	2631	19091	19110	TTAACAAAAACAGGAAAAGA	86	1141
1363952	2687	2706	19166	19185	TACAACAAAAGAACTGTAGT	49	1142
1363971	1582	1601	18061	18080	GGTAATAGAGAGACCAGAAT	21	1143
1363996	2451	2470	18930	18949	CTCTTAACACACCAAGATAA	58	1144
1364006	N/A	N/A	15913	15932	AAATGTACTTATTTTACCTC	65	1145
1364054	1313	1332	17792	17811	AGCTATGAAGCAAAATGACT	41	1146
1364059	2424	2443	18903	18922	AAGTAAAATCATTTTCCATT	47	1147
1364082	2096	2115	18575	18594	AATGAGCACCATTGTGAAGA	44	1148
1364083	1647	1666	18126	18145	AATAGGCAGATTTGGGCAAA	36	1149
1364135	N/A	N/A	11875	11894	CTCACTATATGCCCAGCATT	66	1150
1364140	2479	2498	18958	18977	GAGAAAATAACCTTTATGTT	56	1151
1364160	N/A	N/A	4399	4418	GCATCAAGCAAGCAGTTATT	23	1152
1364161	2340	2359	18819	18838	GGCAGAATACTTGTAGAAAA	28	1153
1364217	2149	2168	18628	18647	CAAATCAAGACCTTCAAATC	68	1154
1364224	1173	1192	17652	17671	GATGGGAGACGCAGCATTGT	58	1155
1364227	1760	1779	18239	18258	ATGCTGTAAGTAAGGTTGGC	24	281
1364229	1689	1708	18168	18187	GTGGGTGAAAGATCCTTGCT	26	1156
1364242	1510	1529	17989	18008	GAGGACCAAAGACATTCCTT	49	1157
1364264	2252	2271	18731	18750	AAAAAACAGTCATAATCAAA	118	1158

Table 16

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362429	1820	1839	18299	18318	TTCCCTAACGAGGTGTAAGG	34	1159
1362430	863	882	14922	14941	ACTGCCTATACTGGCAGAGG	70	1160
1362465	2181	2200	18660	18679	CTGGAATACATGAAATGTGC	30	1161
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	15	201
1362492	2565	2584	19044	19063	AAACTCTTTCTGCCTGTCCT	26	1162
1362515	2370	2389	18849	18868	ATTCAAATTCACCAAATCTG	45	1163
1362526	2880	2899	19359	19378	TACGGATTACTTCACTGTCC	27	58
1362676	2478	2497	18957	18976	AGAAAATAACCTTTATGTTA	83	1164
1362682	N/A	N/A	8412	8431	TTGTATACAACTCCCAAAA	69	1165
1362701	3010	3029	19489	19508	CAGAAATGAAGGAAACACTT	34	1166
1362725	N/A	N/A	4382	4401	ATTTTGTACATCTGAGGGCT	72	1167
1362726	2397	2416	18876	18895	AAGAACGATCAGATTACTCA	34	1168
1362770	1688	1707	18167	18186	TGGGTGAAAGATCCTTGCTT	32	1169

1362796	N/A	N/A	17246	17265	TGATCTAGCACTGAGTTTTTC	69	1170
1362801	N/A	N/A	6275	6294	GTCTGGTTACCAGGGTAACA	28	1171
1362814	N/A	N/A	16992	17011	TTCAGATAAATCACTTCACC	62	1172
1362864	2035	2054	18514	18533	AGACATGCTATCCAAAGAGT	53	1173
1362909	N/A	N/A	14041	14060	GTCCAGTTAGATCCACTCTT	13	167
1362976	N/A	N/A	11326	11345	GCTACAAACAGACTTTATAC	69	1174
1362984	N/A	N/A	10139	10158	TGTTGTTCTCAGAAAACATT	70	1175
1362986	1458	1477	17937	17956	TTTCCATCAGTGGAAGTACC	66	1176
1362994	1204	1223	17683	17702	GGGCCAGTTGGTGGCAAAGG	36	1177
1362997	N/A	N/A	8889	8908	AGTTTGATTCAAGAAGGCTG	52	1178
1362999	2095	2114	18574	18593	ATGAGCACCATTGTGAAGAT	32	1179
1363005	N/A	N/A	9425	9444	TTCTGAGTCACCAGATCATA	78	1180
1363007	2517	2536	18996	19015	CTGATGACTGGTGCATTCTG	24	1181
1363009	N/A	N/A	12528	12547	CCAGTAGGTAGTCTCATGCCA	93	1182
1363029	1312	1331	17791	17810	GCTATGAAGCAAAATGACTA	39	1183
1363052	N/A	N/A	16764	16783	CCAGGCTATAGCAAGTCATG	33	1184
1363060	2782	2801	19261	19280	TTTGAAAACAAGTATCAAGT	60	1185
1363068	N/A	N/A	13455	13474	GGCATGGATCCTGCATTAAC	73	1186
1363083	1423	1442	17902	17921	ACTTTCTGATCCTCAGGAGA	87	1187
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	22	279
1363127	N/A	N/A	10862	10881	TACTCAGCAAATGTACTGGG	46	1188
1363139	3077	3096	19556	19575	AATACACTTTGTAAGATAAG	70	1189
1363154	1270	1289	17749	17768	AGTCCAAAGAGAGACCTTAA	70	1190
1363196	2819	2838	19298	19317	CCTTCTATGCAGCCTGGAAG	13	1191
1363204	1072	1091	17551	17570	TTAAGGACGGCAAAGTTGTA	78	1192
1363227	2928	2947	19407	19426	GAAGGGTTGGTTATTTGTTA	55	1193
1363245	1392	1411	17871	17890	TCAATTAGAGCCTCCATTCC	64	1194
1363247	2314	2333	18793	18812	TAGATTCAACTAGCCAATTT	71	1195
1363253	1646	1665	18125	18144	ATAGGCAGATTTGGGCAAAC	42	1196
1363337	1542	1561	18021	18040	AAGAGAATATATTTGGCCCC	62	1197
1363391	2285	2304	18764	18783	TTTGTGATGCTTAATGTCCA	20	1198
1363422	2067	2086	18546	18565	GGCCAGAGTACACAATAAT	32	1199
1363429	1758	1777	18237	18256	GCTGTAAGTAAGGTTGGCTG	15	125
1363431	1993	2012	18472	18491	GGGCCATCTCAGGTTACACC	17	1200
1363452	3036	3055	19515	19534	TGTGTGTTAAAATTGCAATT	20	1201
1363479	2423	2442	18902	18921	AGTAAAATCATTTTCCATTA	44	1202
1363501	2251	2270	18730	18749	AAAAACAGTCATAATCAAAG	77	1203
1363523	2148	2167	18627	18646	AAATCAAGACCTTCAAATCA	71	1204
1363524	2450	2469	18929	18948	TCTTAACACACCAAGATAAC	79	1205
1363531	2609	2628	19088	19107	ACAAAAACAGGAAAAGACTG	91	1206
1363566	1900	1919	18379	18398	CCTTGAAACCACAGGGTTG	46	1207
1363580	1861	1880	18340	18359	GGAGAAGGGAGTGAGAAGAT	56	1208
1363622	1172	1191	17651	17670	ATGGGAGACGCAGCATTGTA	56	1209

1363635	2737	2756	19216	19235	CCTTAAATATTGCTGAAACC	44	1210
1363647	N/A	N/A	5036	5055	CCTGAACACATGCTTCAAAG	73	1211
1363729	N/A	N/A	5727	5746	GAAAACCTCAGTGGCTGCTCC	41	1212
1363733	N/A	N/A	9155	9174	GGGCATTTAAGTTCAGCAGA	45	1213
1363768	1342	1361	17821	17840	TTAGGCATTTCCCATTCTA	40	1214
1363770	N/A	N/A	11874	11893	TCACTATATGCCCAGCATTA	103	1215
1363794	N/A	N/A	7270	7289	GAGACAATAGTAGCCATACC	68	1216
1363840	1581	1600	18060	18079	GTAATAGAGAGACCAGAATG	55	1217
1363887	1961	1980	18440	18459	CAACTGCTGCTCCTCAGGCC	23	1218
1363903	N/A	N/A	15907	15926	ACTTATTTTACCTCTCATTT	57	1219
1363915	N/A	N/A	7700	7719	CCTGCCTATAATCTTGTCTT	72	1220
1363935	2121	2140	18600	18619	TGACTGAATGGATAATACCC	25	1221
1363964	N/A	N/A	6763	6782	GTTTGGAGACTATATTTCCC	67	1222
1363994	1232	1251	17711	17730	TTCTTGTTACACTCATCAAG	45	1223
1364048	N/A	N/A	16470	16489	GGAAGCAGTCTACCTTCTTG	52	1224
1364063	N/A	N/A	5302	5321	TGTATACACATTATTGTCTA	71	1225
1364105	2686	2705	19165	19184	ACAACAAAAGAACTGTAGTA	61	1226
1364113	N/A	N/A	5905	5924	TGAAGGTTGGCTCAGACAAC	51	1227
1364115	N/A	N/A	15606	15625	GGCTAATTCAAATCCAGCA	20	1228
1364147	2222	2241	18701	18720	CCAGACATTTCTGATGCAAC	13	1229
1364177	1509	1528	17988	18007	AGGACCAAAGACATTCCTTC	35	1230
1364179	2656	2675	19135	19154	CTTCAATTAAAACCAATCAG	53	1231
1364261	2338	2357	18817	18836	CAGAATACTTGTAGAAAATC	78	1232

Table 17

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362451	N/A	N/A	15605	15624	GCTAATTCAAATCCAGCAA	39	1233
1362466	N/A	N/A	8393	8412	ACAAGTCTAATCAATCTGTG	102	1234
1362476	N/A	N/A	16991	17010	TCAGATAAATCACTTCACCC	44	1235
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	16	201
1362509	N/A	N/A	11863	11882	CCAGCATTATGCTGGGTGTT	102	1236
1362531	2422	2441	18901	18920	GTAAAATCATTTTCCATTAG	61	1237
1362571	1818	1837	18297	18316	CCCTAACGAGGTGTAAGGCC	32	286
1362602	3035	3054	19514	19533	GTGTGTTAAAATTGCAATTC	14	1238
1362615	1421	1440	17900	17919	TTTCTGATCCTCAGGAGATG	87	1239
1362624	2879	2898	19358	19377	ACGGATTACTTCACTGTCCT	27	291
1362653	862	881	14921	14940	CTGCCTATACTGGCAGAGGT	72	1240
1362660	2917	2936	19396	19415	TATTTGTTATGTTATTAAAT	126	1241

1362686	N/A	N/A	11317	11336	AGACTTTATACAAAGTCAGC	101	1242
1362696	2221	2240	18700	18719	CAGACATTTCTGATGCAACC	28	1243
1362776	2147	2166	18626	18645	AATCAAGACCTTCAAATCAC	79	1244
1362794	N/A	N/A	5033	5052	GAACACATGCTTCAAAGTGT	45	1245
1362823	2685	2704	19164	19183	CAACAAAAGAACTGTAGTAC	57	1246
1362838	1269	1288	17748	17767	GTCCAAAGAGAGACCTTAAT	61	1247
1362846	2553	2572	19032	19051	CCTGTCCTTTTCTGGAAG	41	1248
1362875	3009	3028	19488	19507	AGAAATGAAGGAAACACTTT	87	1249
1362885	1958	1977	18437	18456	CTGCTGCTCCTCAGGCCAGT	31	1250
1362928	1340	1359	17819	17838	AGGCATTTCCCATTCTAGC	18	1251
1362940	2449	2468	18928	18947	CTTAACACACCAAGATAACA	66	1252
1362945	1645	1664	18124	18143	TAGGCAGATTTGGGCAAACG	39	1253
1362950	1508	1527	17987	18006	GGACCAAAGACATTCCTTCT	47	1254
1363030	1860	1879	18339	18358	GAGAAGGGAGTGAGAAGATG	70	1255
1363038	N/A	N/A	7655	7674	CACTTATATACCACATTCAA	79	1256
1363063	N/A	N/A	5724	5743	AACTCAGTGGCTGCTCCATC	89	1257
1363079	2066	2085	18545	18564	GCCAGAGTACACAATAATT	23	1258
1363092	1171	1190	17650	17669	TGGGAGACGCAGCATTGTAG	57	1259
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	13	279
1363142	N/A	N/A	10856	10875	GCAAATGTACTGGGAAGCTG	61	1260
1363212	2736	2755	19215	19234	CTTAAATATTGCTGAAACCA	62	1261
1363252	N/A	N/A	9422	9441	TGAGTCACCAGATCATAGCC	77	1262
1363281	1231	1250	17710	17729	TCTTGTTACACTCATCAAGT	56	1263
1363289	1311	1330	17790	17809	CTATGAAGCAAAATGACTAA	84	1264
1363307	N/A	N/A	4251	4270	GGACACATGACCACATCCAT	38	1265
1363309	N/A	N/A	15889	15908	TTGAGATAAAGAAGTTCCAA	57	1266
1363319	N/A	N/A	9153	9172	GCATTTAAGTTCAGCAGAAG	71	1267
1363349	N/A	N/A	7268	7287	GACAATAGTAGCCATACCTT	76	1268
1363405	2477	2496	18956	18975	GAAAATAACCTTTATGTTAA	67	1269
1363428	N/A	N/A	6757	6776	AGACTATATTTCCCCTCCCA	78	1270
1363446	N/A	N/A	13454	13473	GCATGGATCCTGCATTAACA	93	1271
1363464	1203	1222	17682	17701	GGCCAGTTGGTGGCAAAGGC	46	1272
1363492	N/A	N/A	16466	16485	GCAGTCTACCTTCTTGCCCTT	58	1273
1363500	3074	3093	19553	19572	ACACTTTGTAAGATAAGTTT	29	1274
1363536	1899	1918	18378	18397	CTTGGAACCACAGGGTTGT	82	1275
1363553	1456	1475	17935	17954	TCCATCAGTGGAAGTACCCT	27	1276
1363581	2516	2535	18995	19014	TGATGACTGGTGCATTCTGT	34	1277
1363607	N/A	N/A	16763	16782	CAGGCTATAGCAAGTCATGT	30	1278
1363674	2369	2388	18848	18867	TTCAAATTCACCAAATCTGT	43	1279
1363698	N/A	N/A	10136	10155	TGTTCTCAGAAAACATTCCA	48	1280
1363703	2180	2199	18659	18678	TGGAATACATGAAATGTGCA	38	1281
1363718	2250	2269	18729	18748	AAAACAGTCATAATCAAAGA	70	1282
1363728	N/A	N/A	6274	6293	TCTGGTTACCAGGGTAACAG	43	1283

1363782	1391	1410	17870	17889	CAATTAGAGCCTCCATTCTCT	75	1284
1363786	2313	2332	18792	18811	AGATTCAACTAGCCAATTTT	61	1285
1363789	2034	2053	18513	18532	GACATGCTATCCAAAGAGTT	48	1286
1363803	1070	1089	17549	17568	AAGGACGGCAAAGTTGTAAG	37	1287
1363804	N/A	N/A	5901	5920	GGTTGGCTCAGACAACCTTCT	44	1288
1363816	2094	2113	18573	18592	TGAGCACCATTGTGAAGATA	51	1289
1363857	1687	1706	18166	18185	GGGTGAAAGATCCTTGCTTT	52	1290
1363871	N/A	N/A	8854	8873	GAGAAGTTCCTTGCTCTCT	56	1291
1363875	1541	1560	18020	18039	AGAGAATATATTTGGCCCCCT	52	1292
1363889	2282	2301	18761	18780	GTGATGCTTAATGTCCAATT	20	1293
1363946	2655	2674	19134	19153	TTCAATTAAAACCAATCAGA	75	1294
1363975	1991	2010	18470	18489	GCCATCTCAGGTTACACCAT	25	1295
1364016	N/A	N/A	13995	14014	GGGATACCAACAGATGGCTT	43	1296
1364017	N/A	N/A	17242	17261	CTAGCACTGAGTTTCTCTCA	49	1297
1364020	1580	1599	18059	18078	TAATAGAGAGACCAGAATGA	88	1298
1364021	2602	2621	19081	19100	CAGGAAAAGACTGAAATCTG	52	1299
1364061	1757	1776	18236	18255	CTGTAAGTAAGGTTGGCTGA	38	1300
1364085	N/A	N/A	5301	5320	GTATACACATTATTGTCTAA	53	1301
1364116	2120	2139	18599	18618	GACTGAATGGATAATACCCC	20	211
1364118	2781	2800	19260	19279	TTGAAAACAAGTATCAAGTG	39	1302
1364124	2818	2837	19297	19316	CTTCTATGCAGCCTGGAAGC	62	1303
1364165	2337	2356	18816	18835	AGAATACTTGTAGAAAATCC	70	1304
1364166	N/A	N/A	12527	12546	CAGTAGGTAGCTCATGCCAC	90	1305
1364230	2396	2415	18875	18894	AGAACGATCAGATTACTCAA	36	1306

Table 18

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362454	2684	2703	19163	19182	AACAAAAGAACTGTAGTACA	52	1307
1362473	2179	2198	18658	18677	GGAATACATGAAATGTGCAT	8	1308
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	15	201
1362503	N/A	N/A	10840	10859	GCTGCTATTTTGAATAAGC	24	1309
1362517	1168	1187	17647	17666	GAGACGCAGCATTGTAGGCT	9	276
1362543	N/A	N/A	5898	5917	TGGCTCAGACAACCTCTAAA	36	1310
1362551	N/A	N/A	17239	17258	GCACTGAGTTTCTCAGGG	23	1311
1362593	1418	1437	17897	17916	CTGATCCTCAGGAGATGCTT	26	1312
1362609	2735	2754	19214	19233	TTAAATATTGCTGAAACCAC	43	1313
1362610	2312	2331	18791	18810	GATTCAACTAGCCAATTTTT	48	1314
1362656	N/A	N/A	9142	9161	CAGCAGAAGTGAAGAATCTC	54	1315
1362657	N/A	N/A	6756	6775	GACTATATTTCCCTCCCAC	81	1316

1362662	N/A	N/A	5298	5317	TACACATTATTGTCTAATAG	66	1317
1362697	1817	1836	18296	18315	CCTAACGAGGTGTAAGGCCA	23	1318
1362709	1507	1526	17986	18005	GACCAAAGACATTCTTCTC	37	1319
1362724	1955	1974	18434	18453	CTGCTCCTCAGGCCAGTCTG	17	1320
1362733	2421	2440	18900	18919	TAAAATCATTTCCTTAGC	54	1321
1362752	2654	2673	19133	19152	TCAATTA AAAACCAATCAGAC	53	1322
1362774	1644	1663	18123	18142	AGGCAGATTGGGCAAACGC	15	1323
1362795	2033	2052	18512	18531	ACATGCTATCCAAAGAGTTA	47	1324
1362797	1310	1329	17789	17808	TATGAAGCAAAATGACTAAA	82	1325
1362805	2515	2534	18994	19013	GATGACTGGTGCATTCTGTT	16	212
1362819	3073	3092	19552	19571	CACTTTGTAAGATAAGTTTC	28	1326
1362873	1390	1409	17869	17888	AATTAGAGCCTCCATTCCCT	49	1327
1362890	2448	2467	18927	18946	TTAACACACCAAGATAACAT	56	1328
1362897	1268	1287	17747	17766	TCCAAAGAGAGACCTTAATC	72	1329
1362905	N/A	N/A	10135	10154	GTTCTCAGAAAACATTCCAG	39	1330
1362974	N/A	N/A	13446	13465	CCTGCATTAAACAGGTAGACA	83	1331
1363045	2915	2934	19394	19413	TTTGTATGTTATTAAATCA	80	1332
1363049	N/A	N/A	16458	16477	CCTTCTGCTTTTCAGAATA	60	1333
1363107	N/A	N/A	11316	11335	GACTTTATACAAAGTCAGCA	71	1334
1363117	N/A	N/A	4961	4980	ATTGCAAATTGATCTCTGTG	37	1335
1363118	2065	2084	18544	18563	CCAGAGTACACAATAATTA	19	1336
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	13	279
1363130	1756	1775	18235	18254	TGTAAGTAAGGTTGGCTGAG	52	1337
1363175	1455	1474	17934	17953	CCATCAGTGGAAGTACCCTT	26	1338
1363198	1202	1221	17681	17700	GCCAGTTGGTGGCAAAGGCA	37	1339
1363205	N/A	N/A	16761	16780	GGCTATAGCAAGTCATGTTT	30	1340
1363268	3034	3053	19513	19532	TGTGTTAAAATTGCAATTCT	27	1341
1363329	N/A	N/A	4250	4269	GACACATGACCACATCCATC	52	1342
1363374	2091	2110	18570	18589	GCACCATTGTGAAGATATGA	21	1343
1363399	1230	1249	17709	17728	CTTGTTACACTCATCAAGTA	44	1344
1363404	804	823	14863	14882	TGTTGAAGTAAATGTACACA	65	1345
1363407	1068	1087	17547	17566	GGACGGCAAAGTTGTAAGTG	26	1346
1363414	2601	2620	19080	19099	AGGAAAAGACTGAAATCTGG	34	1347
1363435	1859	1878	18338	18357	AGAAGGGAGTGAGAAGATGC	45	1348
1363442	1897	1916	18376	18395	TGGAAACCACAGGGTTGTCA	34	1349
1363458	2249	2268	18728	18747	AAACAGTCATAATCAAAGAA	66	1350
1363470	2779	2798	19258	19277	GAAAACAAGTATCAAGTGTC	32	1351
1363484	3008	3027	19487	19506	GAAATGAAGGAAACACTTTC	70	1352
1363499	2877	2896	19356	19375	GGATTACTTCACTGTCCCTT	19	1353
1363533	1990	2009	18469	18488	CCATCTCAGGTTACACCATT	25	1354
1363549	N/A	N/A	15852	15871	AAAACCTATGAATGCCTCTG	60	1355
1363564	N/A	N/A	12423	12442	TTGGCTTTCAGCATGTGAGA	46	1356
1363585	1338	1357	17817	17836	GCATTTCCCATTTCTAGCAG	35	1357

1363591	2281	2300	18760	18779	TGATGCTTAATGTCCAATTT	14	1358
1363662	N/A	N/A	7267	7286	ACAATAGTAGCCATACCTTG	80	1359
1363673	2119	2138	18598	18617	ACTGAATGGATAATACCCCA	18	1360
1363683	2336	2355	18815	18834	GAATACTTGTAGAAAATCCC	28	1361
1363750	1685	1704	18164	18183	GTGAAAGATCCTTGCTTTGA	82	1362
1363765	2552	2571	19031	19050	CTGTCCTTTTTCTGGAAGC	25	1363
1363778	2146	2165	18625	18644	ATCAAGACCTTCAAATCACC	51	1364
1363788	2395	2414	18874	18893	GAACGATCAGATTACTCAA	21	1365
1363819	N/A	N/A	8391	8410	AAGTCTAATCAATCTGTGAT	70	1366
1363822	1540	1559	18019	18038	GAGAATATATTTGGCCCCCTA	47	1367
1363912	N/A	N/A	16985	17004	AAATCACTTCACCTTCAGT	102	1368
1363916	2475	2494	18954	18973	AAATAACCTTTATGTTAAAC	81	1369
1363943	N/A	N/A	13994	14013	GGATACCAACAGATGGCTTA	53	1370
1363990	N/A	N/A	15538	15557	ATGGTATTAGCTACTCCCTT	26	1371
1364069	2368	2387	18847	18866	TCAAATTCACCAAATCTGTT	30	1372
1364107	2219	2238	18698	18717	GACATTTCTGATGCAACCCC	15	1373
1364183	N/A	N/A	5709	5728	CCATCATATGTACCTGGCCC	48	1374
1364216	2816	2835	19295	19314	TCTATGCAGCCTGGAAGCTT	35	1375
1364220	N/A	N/A	6271	6290	GGTTACCAGGGTAACAGCCA	39	1376
1364228	N/A	N/A	11799	11818	GAGTCTTTAATTTCTGAGG	50	1377
1364238	N/A	N/A	9418	9437	TCACCAGATCATAGCCTTTC	43	1378
1364250	N/A	N/A	7654	7673	ACTTATATACCACATTCAAG	88	1379
1364256	1579	1598	18058	18077	AATAGAGAGACCAGAATGAA	85	1380
1364271	N/A	N/A	8838	8857	CTCTCAAGAGACATTCTCAC	70	1381

Table 19

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362435	1578	1597	18057	18076	ATAGAGAGACCAGAATGAAT	81	1382
1362461	2683	2702	19162	19181	ACAAAAGAACTGTAGTACAA	36	1383
1362474	N/A	N/A	9141	9160	AGCAGAAGTGAAGAATCTCA	55	1384
1362478	N/A	N/A	16950	16969	TCTGCACAATGAGCACACTA	41	1385
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	15	201
1362493	N/A	N/A	5264	5283	ATTTACAGTTGTTATAGATC	44	1386
1362512	2117	2136	18596	18615	TGAATGGATAATACCCCATG	33	1387
1362532	1896	1915	18375	18394	GGAAACCACAGGGTTGTCAT	26	1388
1362541	N/A	N/A	4131	4150	ATCTAACTGAATGTTAAGGA	41	1389
1362544	1755	1774	18234	18253	GTAAGTAAGGTTGGCTGAGT	32	1390
1362553	3072	3091	19551	19570	ACTTTGTAAGATAAGTTTCT	39	1391

1362555	N/A	N/A	10134	10153	TTCTCAGAAAACATTCCAGA	62	1392
1362562	2734	2753	19213	19232	TAAATATTGCTGAAACCACT	36	1393
1362583	N/A	N/A	7260	7279	TAGCCATACCTTGTTCCCTCA	39	1394
1362619	2064	2083	18543	18562	CAGAGTACACAATAATTAA	45	1395
1362640	803	822	14862	14881	GTTGAAGTAAATGTACACAG	62	1396
1362655	1228	1247	17707	17726	TGTTACACTCATCAAGTAAG	32	1397
1362689	2280	2299	18759	18778	GATGCTTAATGTCCAATTTT	17	1398
1362702	N/A	N/A	4959	4978	TGCAAATTGATCTCTGTGGA	29	1399
1362716	2367	2386	18846	18865	CAAATTCACCAAATCTGTTT	56	1400
1362732	N/A	N/A	8835	8854	TCAAGAGACATTCTCACATT	82	1401
1362736	2032	2051	18511	18530	CATGCTATCCAAAGAGTTAT	41	1402
1362742	N/A	N/A	16690	16709	AACCGTAATTTATGACTGCA	26	1403
1362789	2600	2619	19079	19098	GGAAAAGACTGAAATCTGGG	24	1404
1362800	2653	2672	19132	19151	CAATTAAAACCAATCAGACT	74	1405
1362811	1506	1525	17985	18004	ACCAAAGACATTCTTCTCT	45	1406
1362832	2420	2439	18899	18918	AAAATCATTTTCCATTAGCT	32	1407
1362883	1684	1703	18163	18182	TGAAAGATCCTTGCTTTGAC	88	1408
1362910	N/A	N/A	13993	14012	GATACCAACAGATGGCTTAG	52	1409
1362930	2311	2330	18790	18809	ATTCAACTAGCCAATTTTTA	66	1410
1362944	N/A	N/A	5706	5725	TCATATGTACCTGGCCCAAG	83	1411
1362958	N/A	N/A	9417	9436	CACCAGATCATAGCCTTTCT	37	1412
1362977	1816	1835	18295	18314	CTAACGAGGTGTAAGGCCAG	44	1413
1362981	N/A	N/A	16455	16474	TCTTGCCTTTCAGAATAGCT	37	1414
1362991	N/A	N/A	7650	7669	ATATACCACATTCAAGTGCT	69	1415
1362992	N/A	N/A	6270	6289	GTTACCAGGGTAACAGCCAC	41	1416
1363040	2335	2354	18814	18833	AATACTTGTAGAAAATCCCA	30	1417
1363042	N/A	N/A	8362	8381	TCCAACCTTTAAGCCCTTCTC	51	1418
1363078	1538	1557	18017	18036	GAATATATTTGGCCCCTATA	91	1419
1363085	1267	1286	17746	17765	CCAAAGAGAGACCTTAATCA	57	1420
1363096	2172	2191	18651	18670	ATGAAATGTGCATCATTCTA	44	1421
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	17	279
1363128	1989	2008	18468	18487	CATCTCAGGTTACACCATTA	37	1422
1363191	1628	1647	18107	18126	ACGCTCTTATTGTTTTTCTG	15	1423
1363208	2248	2267	18727	18746	AACAGTCATAATCAAAGAAT	60	1424
1363228	3007	3026	19486	19505	AAATGAAGGAAACACTTTCA	61	1425
1363301	1417	1436	17896	17915	TGATCCTCAGGAGATGCTTG	37	1426
1363313	N/A	N/A	6755	6774	ACTATATTTCCCCTCCCACC	89	1427
1363370	1309	1328	17788	17807	ATGAAGCAAAATGACTAAAA	70	1428
1363423	1067	1086	17546	17565	GACGGCAAAGTTGTAAGTGG	34	1429
1363433	1200	1219	17679	17698	CAGTTGGTGGCAAAGGCAAA	42	1430
1363544	1167	1186	17646	17665	AGACGCAGCATTGTAGGCTG	13	1431
1363573	N/A	N/A	13445	13464	CTGCATTAACAGGTAGACAA	83	1432
1363576	1337	1356	17816	17835	CATTTCCCATTTCTAGCAGG	54	1433

1363643	1454	1473	17933	17952	CATCAGTGGAAGTACCCTTT	49	1434
1363678	3033	3052	19512	19531	GTGTTAAAATTGCAATTCTA	19	1435
1363684	N/A	N/A	15510	15529	ACCCAAATAACCCACTCACC	91†	1436
1363692	1858	1877	18337	18356	GAAGGGAGTGAGAAGATGCT	42	1437
1363697	2218	2237	18697	18716	ACATTTCTGATGCAACCCCA	34	1438
1363705	2393	2412	18872	18891	ACGATCAGATTACTCAAATT	24	1439
1363763	2815	2834	19294	19313	CTATGCAGCCTGGAAGCTTA	28	1440
1363824	N/A	N/A	5897	5916	GGCTCAGACAACTTCTAAAG	39	1441
1363833	N/A	N/A	15851	15870	AAACCTATGAATGCCTCTGT	69	1442
1363834	2090	2109	18569	18588	CACCATTGTGAAGATATGAC	23	1443
1363868	N/A	N/A	10837	10856	GCTATTTTTGAATAAGCAGG	41	1444
1363949	2145	2164	18624	18643	TCAAGACCTTCAAATCACCT	49	1445
1363984	2513	2532	18992	19011	TGACTGGTGCATTCTGTTAT	30	1446
1363988	2474	2493	18953	18972	AATAACCTTTATGTTAAACC	54	1447
1364051	N/A	N/A	17220	17239	GAAGTGAACAATATTTGGGC	57	1448
1364055	N/A	N/A	11315	11334	ACTTTATACAAAGTCAGCAA	67	1449
1364090	N/A	N/A	12420	12439	GCTTTCAGCATGTGAGATTG	42	1450
1364094	1383	1402	17862	17881	GCCTCCATTCTTTGTGACT	41	1451
1364095	2778	2797	19257	19276	AAAACAAGTATCAAGTGTCT	31	1452
1364197	1951	1970	18430	18449	TCCTCAGGCCAGTCTGTTCT	28	1453
1364198	N/A	N/A	11796	11815	TCTTTAATTCCTGAGGAAG	92	1454
1364201	2549	2568	19028	19047	TCCTTTTTCCTGGAAGCTTA	21	1455
1364239	2447	2466	18926	18945	TAACACACCAAGATAACATT	44	1456
1364257	2876	2895	19355	19374	GATTACTTCACTGTCCTTTA	17	1457
1364258	2913	2932	19392	19411	TGTTATGTTATTAAATCAAA	72	1458

Table 20

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362436	2912	2931	19391	19410	GTTATGTTATTAAATCAAAA	73	1459
1362487	N/A	N/A	11309	11328	TACAAAGTCAGCAAAGCATG	110	1460
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	21	201
1362506	802	821	14861	14880	TTGAAGTAAATGTACACAGG	97	1461
1362542	2365	2384	18844	18863	AATTCACCAAATCTGTTTCT	57	1462
1362575	2276	2295	18755	18774	CTTAATGTCCAATTTTCTTA	35	1463
1362581	N/A	N/A	13443	13462	GCATTAACAGGTAGACAAAC	103	1464
1362618	1988	2007	18467	18486	ATCTCAGGTTACACCATTAG	60	1465
1362639	3071	3090	19550	19569	CTTTGTAAGATAAGTTTCTA	56	1466
1362688	N/A	N/A	4924	4943	GCTACATTTGATAGGGAATA	26	1467
1362705	2419	2438	18898	18917	AAATCATTTTCCATTAGCTA	48	1468

1362781	N/A	N/A	5888	5907	AAC TTCTAAAGTTCCTTCCA	57	1469
1362783	N/A	N/A	6729	6748	CCAGGGTTGAGGTTGTTATT	74	1470
1362859	2652	2671	19131	19150	AATTAAAACCAATCAGACTT	75	1471
1362867	N/A	N/A	4094	4113	GTGCCAAAACACGACTCATT	28	1472
1362868	N/A	N/A	8361	8380	CCAAC TTTAAGCCCTTCTCA	67	1473
1362888	2116	2135	18595	18614	GAATGGATAATACCCCATGA	34	1474
1362914	2446	2465	18925	18944	AACACACCAAGATAACATTG	34	1475
1362926	1626	1645	18105	18124	GCTCTTATTGTTTTCTGAC	18	1476
1362948	1227	1246	17706	17725	GTTACACTCATCAAGTAAGA	19	1477
1362968	2392	2411	18871	18890	CGATCAGATTACTCAAATTG	47	1478
1363041	N/A	N/A	11765	11784	TAGACCTAATATTTCAACT	69	1479
1363062	3032	3051	19511	19530	TGTTAAAATTGCAATTCTAT	49	1480
1363099	N/A	N/A	12413	12432	GCATGTGAGATTGACCCAGA	54	1481
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	11	279
1363122	N/A	N/A	13990	14009	ACCAACAGATGGCTTAGAAA	66	1482
1363150	N/A	N/A	16688	16707	CCGTAATTTATGACTGCAAA	31	1483
1363155	N/A	N/A	10123	10142	CATTCCAGAAATTGATCTTC	60	1484
1363190	2777	2796	19256	19275	AAACAAGTATCAAGTGTCTT	27	1485
1363202	N/A	N/A	8826	8845	ATTCTCACATTTCCAGTCTA	87	1486
1363318	2247	2266	18726	18745	ACAGTCATAATCAAAGAATT	45	1487
1363358	1266	1285	17745	17764	CAAAGAGAGACCTTAATCAC	70	1488
1363385	2334	2353	18813	18832	ATACTTGTAGAAAATCCCAA	34	1489
1363387	1537	1556	18016	18035	AATATATTTGGCCCTATAG	88	1490
1363390	1451	1470	17930	17949	CAGTGGAAGTACCCTTTGAG	53	1491
1363412	1308	1327	17787	17806	TGAAGCAAAATGACTAAAAG	102	1492
1363498	2310	2329	18789	18808	TTCAACTAGCCAATTTTAA	69	1493
1363514	2473	2492	18952	18971	ATAACCTTTATGTTAAACCT	44	1494
1363520	1683	1702	18162	18181	GAAAGATCCTTGCTTTGACC	65	1495
1363530	2546	2565	19025	19044	TTTTTCCTGGAAGCTTACCA	41	1496
1363532	1334	1353	17813	17832	TTCCCATTTCTAGCAGGAAC	48	1497
1363541	1196	1215	17675	17694	TGGTGGCAAAGGCAAAGAGT	47	1498
1363557	1382	1401	17861	17880	CCTCCATTCCTTTGTGACTT	21	1499
1363596	N/A	N/A	17217	17236	GTGAACAATATTTGGGCTTT	23	1500
1363599	2731	2750	19210	19229	ATATTGCTGAAACCACTTTG	53	1501
1363602	2812	2831	19291	19310	TGCAGCCTGGAAGCTTATCT	18	1502
1363621	3006	3025	19485	19504	AATGAAGGAAACACTTTTACAG	69	1503
1363628	2872	2891	19351	19370	ACTTCACTGTCCTTTATCTT	24	1504
1363653	2030	2049	18509	18528	TGCTATCCAAAGAGTTATCT	30	1505
1363671	1895	1914	18374	18393	GAAACCACAGGGTTGTCATG	38	1506
1363700	1754	1773	18233	18252	TAAGTAAGGTTGGCTGAGTT	63	1507
1363725	1164	1183	17643	17662	CGCAGCATTGTAGGCTGTGT	52	120
1363741	N/A	N/A	16948	16967	TGCACAATGAGCACACTACA	55	1508
1363757	N/A	N/A	15509	15528	CCCAAATAACCCACTCACCT	75†	1509

1363773	2503	2522	18982	19001	ATTCTGTTATGTGATCTATA	27	1510
1363785	N/A	N/A	16449	16468	CTTTCAGAATAGCTGTACCC	82	1511
1363787	N/A	N/A	7649	7668	TATACCACATTCAAGTGCTG	84	1512
1363790	1815	1834	18294	18313	TAACGAGGTGTAAGGCCAGA	55	1513
1363796	2063	2082	18542	18561	AGAGTACACAACCTAATTAAC	47	1514
1363820	2682	2701	19161	19180	CAAAAGAACTGTAGTACAAA	85	1515
1363837	N/A	N/A	7253	7272	ACCTTGTTCTCCTCAGGTCAGT	49	1516
1363844	N/A	N/A	15848	15867	CCTATGAATGCCTCTGTGCA	67	1517
1363878	1066	1085	17545	17564	ACGGCAAAGTTGTAAAGTGGC	27	1518
1363905	N/A	N/A	6262	6281	GGTAACAGCCACTGTTCTCA	64	1519
1363913	1857	1876	18336	18355	AAGGGAGTGAGAAGATGCTG	51	1520
1363919	2599	2618	19078	19097	GAAAAGACTGAAATCTGGGA	44	1521
1363924	N/A	N/A	5263	5282	TTTACAGTTGTTATAGATCT	53	1522
1363954	1505	1524	17984	18003	CCAAAGACATTCCTTCTCTG	44	1523
1363970	N/A	N/A	10836	10855	CTATTTTGAATAAGCAGGT	51	1524
1363995	2089	2108	18568	18587	ACCATTGTGAAGATATGACA	28	1525
1364005	N/A	N/A	5664	5683	GGACCCAATGTGCATCCTCA	60	1526
1364026	2171	2190	18650	18669	TGAAATGTGCATCATTTCTAA	63	1527
1364074	N/A	N/A	9397	9416	TTTTACATCCATTTTCTCTC	58	1528
1364125	1947	1966	18426	18445	CAGGCCAGTCTGTTCTCATG	14	1529
1364164	1415	1434	17894	17913	ATCCTCAGGAGATGCTTGAA	59	1530
1364207	2212	2231	18691	18710	CTGATGCAACCCCAAATAAG	49	1531
1364215	1577	1596	18056	18075	TAGAGAGACCAGAATGAATT	67	1532
1364233	N/A	N/A	9140	9159	GCAGAAGTGAAGAATCTCAG	62	1533
1364253	2144	2163	18623	18642	CAAGACCTTCAAATCACCTA	26	1534

Table 21

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362456	N/A	N/A	7246	7265	TCCTCAGGTCAGTCTCCAC	54	1535
1362459	1449	1468	17928	17947	GTGGAAGTACCCTTTGAGAA	43	1536
1362489	2115	2134	18594	18613	AATGGATAATACCCCATGAA	55	1537
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	29	201
1362519	1942	1961	18421	18440	CAGTCTGTTCTCATGTAAGC	20	1538
1362529	2143	2162	18622	18641	AAGACCTTCAAATCACCTAC	41	1539
1362536	N/A	N/A	5887	5906	ACTTCTAAAGTTCCTTCCAA	96	1540
1362570	N/A	N/A	6719	6738	GGTTGTTATTACTCAGATCG	69	1541
1362591	1160	1179	17639	17658	GCATTGTAGGCTGTGTGGTT	18	1542
1362611	1379	1398	17858	17877	CCATTCCTTTGTGACTTGCA	25	1543

1362620	1987	2006	18466	18485	TCTCAGGTTACACCATTAGC	49	1544
1362645	2088	2107	18567	18586	CCATTGTGAAGATATGACAG	73	1545
1362685	2868	2887	19347	19366	CACTGTCCTTTATCTTGATT	30	1546
1362722	3070	3089	19549	19568	TTTGTAAGATAAGTTTCTAA	61	1547
1362723	1813	1832	18292	18311	ACGAGGTGTAAGGCCAGATG	24	1548
1362729	1195	1214	17674	17693	GGTGGCAAAGGCAAAGAGTT	45	1549
1362730	2598	2617	19077	19096	AAAAGACTGAAATCTGGGAG	59	1550
1362771	1414	1433	17893	17912	TCCTCAGGAGATGCTTGAAA	66	1551
1362778	801	820	14860	14879	TGAAGTAAATGTACACAGGC	89	1552
1362780	N/A	N/A	7646	7665	ACCACATTCAAGTGCTGGAA	66	1553
1362784	2029	2048	18508	18527	GCTATCCAAAGAGTTATCTA	21	1554
1362785	1225	1244	17704	17723	TACACTCATCAAGTAAGAAG	53	1555
1362788	1064	1083	17543	17562	GGCAAAGTTGTAAGTGGCAG	31	1556
1362830	2062	2081	18541	18560	GAGTACACAACCTAATTAACA	34	1557
1362855	2472	2491	18951	18970	TAACCTTTATGTTAAACCTA	50	1558
1362912	N/A	N/A	15503	15522	TAACCCACTCACCTCAGCTG	104†	1559
1362952	N/A	N/A	16447	16466	TTCAGAATAGCTGTACCCAC	82	1560
1362956	N/A	N/A	8311	8330	TCAACAGAACCAATGTGACT	85	1561
1362969	N/A	N/A	5255	5274	TGTTATAGATCTTGCCCATT	54	1562
1363048	2309	2328	18788	18807	TCAACTAGCCAATTTTAAAT	52	1563
1363056	N/A	N/A	9128	9147	AATCTCAGTCAGTCTGTCCA	69	1564
1363089	1894	1913	18373	18392	AAACCACAGGGTTGTCTATGG	60	1565
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	22	279
1363173	2911	2930	19390	19409	TTATGTTATTAAATCAAAAC	106	1566
1363222	2729	2748	19208	19227	ATTGCTGAAACCACTTTGGG	49	1567
1363232	2811	2830	19290	19309	GCAGCCTGGAAGCTTATCTT	20	1568
1363254	1753	1772	18232	18251	AAGTAAGGTTGGCTGAGTTA	81	1569
1363265	1856	1875	18335	18354	AGGGAGTGAGAAGATGCTGA	36	1570
1363278	2545	2564	19024	19043	TTTTCTGGAAGCTTACCAA	49	1571
1363299	N/A	N/A	9393	9412	ACATCCATTTTTCCTCTATT	62	1572
1363341	N/A	N/A	17216	17235	TGAACAATATTTGGGCTTTG	66	1573
1363348	2445	2464	18924	18943	ACACACCAAGATAACATTGC	43	1574
1363381	1307	1326	17786	17805	GAAGCAAAATGACTAAAAGA	81	1575
1363384	N/A	N/A	8822	8841	TCACATTTCCAGTCTAAGTA	83	1576
1363426	1504	1523	17983	18002	CAAAGACATTCCTTCTCTGT	99	1577
1363447	2275	2294	18754	18773	TTAATGTCCAATTTTCCTAG	67	1578
1363494	N/A	N/A	4086	4105	ACACGACTCATTTAAACCAT	60	1579
1363508	N/A	N/A	5547	5566	TCCTCAGGGATTTTCATCCCC	104	1580
1363552	1536	1555	18015	18034	ATATATTTGGCCCCTATAGA	88	1581
1363554	2651	2670	19130	19149	ATTAAAACCAATCAGACTTTT	88	1582
1363555	2681	2700	19160	19179	AAAAGAAGTGTAGTACAAAT	83	1583
1363567	2391	2410	18870	18889	GATCAGATTACTCAAATTGA	32	1584
1363582	2170	2189	18649	18668	GAAATGTGCATCATTCTAAA	50	1585

1363593	N/A	N/A	12410	12429	TGTGAGATTGACCCAGAATC	80	1586
1363606	N/A	N/A	16947	16966	GCACAATGAGCACACTACAT	62	1587
1363618	N/A	N/A	11294	11313	GCATGAAACATCTTTCTGGC	50	1588
1363664	2499	2518	18978	18997	TGTTATGTGATCTATATCAG	46	1589
1363699	N/A	N/A	15847	15866	CTATGAATGCCTCTGTGCAC	69	1590
1363707	3005	3024	19484	19503	ATGAAGGAAACACTTTCAGT	60	1591
1363710	N/A	N/A	13379	13398	ACATAAGTGAGGTATACACC	79	1592
1363753	1332	1351	17811	17830	CCCATTCTAGCAGGAACCA	35	1593
1363777	N/A	N/A	10122	10141	ATTCCAGAAATTGATCTTCC	76	1594
1363808	1265	1284	17744	17763	AAAGAGAGACCTTAATCACT	100	1595
1363827	N/A	N/A	16687	16706	CGTAATTTATGACTGCAAAG	45	1596
1363877	2776	2795	19255	19274	AACAAGTATCAAGTGCTTT	31	1597
1363894	2246	2265	18725	18744	CAGTCATAATCAAAGAATTA	62	1598
1363981	N/A	N/A	6261	6280	GTAACAGCCACTGTTCTCAG	85	1599
1363987	2417	2436	18896	18915	ATCATTTTCCATTAGCTAGA	25	1600
1364001	1576	1595	18055	18074	AGAGAGACCAGAATGAATTC	82	1601
1364011	N/A	N/A	13962	13981	TTGTACAAAGCATCCCACAA	63	1602
1364050	1680	1699	18159	18178	AGATCCTTGCTTTGACCCCC	48	1603
1364088	N/A	N/A	4897	4916	CAACTGAGTCTCATTTTCATT	81	1604
1364099	1624	1643	18103	18122	TCTTATTGTTTTTCTGACAT	32	1605
1364102	3031	3050	19510	19529	GTAAAAATTGCAATTCTATA	59	1606
1364103	2333	2352	18812	18831	TACTTGTAAGAAAATCCCAAT	27	1607
1364133	2211	2230	18690	18709	TGATGCAACCCCAAATAAGT	44	1608
1364144	N/A	N/A	10829	10848	TGAATAAGCAGGTTGTGACA	65	1609
1364195	2364	2383	18843	18862	ATTCACCAAATCTGTTTCTG	34	1610
1364200	N/A	N/A	11764	11783	AGACCTAATATTTTCAACTA	78	1611

Table 22

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362439	N/A	N/A	4053	4072	CCCAAAGTTGGAAATTCTCT	74	1612
1362441	1622	1641	18101	18120	TTATTGTTTTTCTGACATTC	34	1613
1362471	2114	2133	18593	18612	ATGGATAATACCCCATGAAA	77	1614
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	27	201
1362525	1448	1467	17927	17946	TGGAAGTACCCCTTTGAGAAG	65	1615
1362535	1939	1958	18418	18437	TCTGTTCTCATGTAAGCTAG	19	1616
1362554	2244	2263	18723	18742	GTCATAATCAAAGAATTATT	33	1617
1362598	800	819	14859	14878	GAAGTAAATGTACACAGGCA	89	1618
1362643	2910	2929	19389	19408	TATGTTATTAAATCAAAACA	112	1619

1362679	1264	1283	17743	17762	AAGAGAGACCTTAATCACTG	49	1620
1362693	N/A	N/A	11762	11781	ACCTAATATTTTCAACTAAC	69	1621
1362708	1893	1912	18372	18391	AACCACAGGGTTGTCATGGT	26	1622
1362739	1331	1350	17810	17829	CCATTTCTAGCAGGAACCAG	50	1623
1362787	N/A	N/A	16937	16956	CACACTACATTACAGGGCA	52	1624
1362828	2471	2490	18950	18969	AACCTTTATGTTAAACCTAA	37	1625
1362841	2308	2327	18787	18806	CAACTAGCCAATTTTAATA	52	1626
1362851	2142	2161	18621	18640	AGACCTTCAAATCACCTACG	31	1627
1362865	1676	1695	18155	18174	CCTTGCTTTGACCCCTTCT	56	1628
1362871	2597	2616	19076	19095	AAAGACTGAAATCTGGGAGC	31	1629
1362896	N/A	N/A	5546	5565	CCTCAGGGATTTCATCCCCT	100	1630
1362898	1063	1082	17542	17561	GCAAAGTTGTAAGTGGCAGC	52	1631
1362921	2332	2351	18811	18830	ACTTGTAGAAAAATCCCAATA	40	1632
1362949	3030	3049	19509	19528	TTAAAAATTGCAATTCTATAT	104	1633
1362954	N/A	N/A	15502	15521	AACCCACTCACCTCAGCTGT	104†	1634
1363001	N/A	N/A	16413	16432	ATTTACTTGCCAAGATCATT	95	1635
1363010	N/A	N/A	15830	15849	CACAGCCCATTTTCTTGATA	55	1636
1363021	3069	3088	19548	19567	TTGTAAGATAAGTTTCTAAA	76	1637
1363028	N/A	N/A	17213	17232	ACAATATTTGGGCTTTGCCA	62	1638
1363044	N/A	N/A	7242	7261	CAGGTCAGTCTCCCACCATT	59	1639
1363067	N/A	N/A	13953	13972	GCATCCCACAAAACTCATGC	37	1640
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	15	279
1363125	N/A	N/A	5218	5237	TTATTGTTACTTGATTCTCA	61	1641
1363162	2028	2047	18507	18526	CTATCCAAAGAGTTATCTAT	44	1642
1363180	2168	2187	18647	18666	AATGTGCATCATTCTAAAAC	65	1643
1363181	N/A	N/A	6258	6277	ACAGCCACTGTTCTCAGACG	68	1644
1363246	1159	1178	17638	17657	CATTGTAGGCTGTGTGGTTA	72	1645
1363316	2498	2517	18977	18996	GTTATGTGATCTATATCAGG	31	1646
1363317	3004	3023	19483	19502	TGAAGGAAACACTTTCAGTT	56	1647
1363321	N/A	N/A	8306	8325	AGAACCAATGTGACTTACAC	95	1648
1363339	1854	1873	18333	18352	GGAGTGAGAAGATGCTGACA	56	1649
1363353	N/A	N/A	16678	16697	TGACTGCAAAGTACTTGGA	62	1650
1363371	2775	2794	19254	19273	ACAAGTATCAAGTGCTTTT	36	1651
1363372	2544	2563	19023	19042	TTTCCTGGAAGCTTACCAAC	51	1652
1363373	N/A	N/A	10828	10847	GAATAAGCAGGTTGTGACAG	68	1653
1363392	1378	1397	17857	17876	CATTCCTTTGTGACTTGCAG	25	1654
1363417	N/A	N/A	11292	11311	ATGAAACATCTTTCTGGCAC	76	1655
1363478	2710	2729	19189	19208	GGGAAAAGAACAACACAAC	56	1656
1363483	2860	2879	19339	19358	TTTATCTTGATTGGTTTCTT	51	1657
1363522	2444	2463	18923	18942	CACACCAAGATAACATTGCT	44	1658
1363535	1306	1325	17785	17804	AAGCAAAATGACTAAAAGAG	91	1659
1363547	2679	2698	19158	19177	AAGAACTGTAGTACAAATCT	50	1660
1363633	2808	2827	19287	19306	GCCTGGAAGCTTATCTTGTA	22	1661

1363637	N/A	N/A	4872	4891	TGTGTTTAAGCTGCTATCTT	47	1662
1363649	2363	2382	18842	18861	TTCACCAAATCTGTTTCTGC	25	1663
1363659	2274	2293	18753	18772	TAATGTCCAATTTTCCTAGT	56	1664
1363702	N/A	N/A	9389	9408	CCATTTTTCCTCTATTTTCT	74	1665
1363738	1224	1243	17703	17722	ACACTCATCAAGTAAGAAGA	32	1666
1363813	1413	1432	17892	17911	CCTCAGGAGATGCTTGAAAA	46	1667
1363860	2061	2080	18540	18559	AGTACACAACATAATTAACAG	48	1668
1363869	N/A	N/A	9124	9143	TCAGTCAGTCTGTCCAAGCA	62	1669
1363870	2415	2434	18894	18913	CATTTTCCATTAGCTAGAAA	40	1670
1363873	2390	2409	18869	18888	ATCAGATTACTCAAATTGAG	37	1671
1363884	1812	1831	18291	18310	CGAGGTGTAAGGCCAGATGC	32	1672
1363909	1503	1522	17982	18001	AAAGACATTCCTTCTCTGTA	86	1673
1363974	N/A	N/A	10121	10140	TTCCAGAAATTGATCTTCCT	71	1674
1363985	N/A	N/A	5884	5903	TCTAAAGTTCCTTCCAATCC	86	1675
1364019	1534	1553	18013	18032	ATATTTGGCCCTATAGATG	77	1676
1364029	1194	1213	17673	17692	GTGGCAAAGGCAAAGAGTTA	63	1677
1364030	N/A	N/A	12407	12426	GAGATTGACCCAGAATCCCT	52	1678
1364036	2650	2669	19129	19148	TTAAAACCAATCAGACTTTT	74	1679
1364072	N/A	N/A	13378	13397	CATAAGTGAGGTATACACCA	64	1680
1364077	N/A	N/A	6717	6736	TTGTTATTACTCAGATCGCT	64	1681
1364152	N/A	N/A	8820	8839	ACATTTCCAGTCTAAGTACA	87	1682
1364157	2087	2106	18566	18585	CATTGTGAAGATATGACAGA	55	1683
1364180	1986	2005	18465	18484	CTCAGGTTACACCATTAGCC	29	210
1364206	1575	1594	18054	18073	GAGAGACCAGAATGAATTCC	33	1684
1364209	N/A	N/A	7645	7664	CCACATTCAAGTGCTGGAAA	61	1685
1364221	2210	2229	18689	18708	GATGCAACCCCAAATAAGTA	48	1686
1364270	1751	1770	18230	18249	GTAAGGTTGGCTGAGTTAGG	39	1687

Table 23

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362463	N/A	N/A	16936	16955	ACACTACATTCACAGGGCAC	57	1688
1362472	N/A	N/A	10789	10808	TTGTATTAATTACTTAGGCT	98	1689
1362488	N/A	N/A	12406	12425	AGATTGACCCAGAATCCTTA	53	1690
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	18	201
1362497	1151	1170	17630	17649	GCTGTGTGGTTAGAGCCTCG	23	42
1362530	N/A	N/A	6255	6274	GCCACTGTTCTCAGACGACA	37	1691
1362589	N/A	N/A	7584	7603	GGATAGTCAAATCATGTGGA	55	1692
1362600	2497	2516	18976	18995	TTATGTGATCTATATCAGGA	40	1693

1362607	2596	2615	19075	19094	AAGACTGAAATCTGGGAGCT	35	1694
1362631	3068	3087	19547	19566	TGTAAGATAAGTTTCTAAAA	70	1695
1362633	N/A	N/A	5883	5902	CTAAAGTTCCTTCCAATCCC	73	1696
1362637	2060	2079	18539	18558	GTACACAATAATTAACAGA	31	1697
1362648	1412	1431	17891	17910	CTCAGGAGATGCTTGAAAAAT	72	1698
1362663	3003	3022	19482	19501	GAAGGAAACACTTTCAGTTG	50	1699
1362675	2086	2105	18565	18584	ATTGTGAAGATATGACAGAG	46	1700
1362710	1811	1830	18290	18309	GAGGTGTAAGGCCAGATGCC	44	1701
1362712	2362	2381	18841	18860	TCACCAAATCTGTTTCTGCA	22	1702
1362746	2773	2792	19252	19271	AAGTATCAAGTGTCTTTTGTG	41	1703
1362764	2678	2697	19157	19176	AGAACTGTAGTACAAATCTT	50	1704
1362815	1984	2003	18463	18482	CAGGTACACCATTAGCCAC	44	1705
1362886	2389	2408	18868	18887	TCAGATTACTCAAATTGAGA	38	1706
1362889	1892	1911	18371	18390	ACCACAGGGTTGTCATGGTA	45	1707
1362918	3029	3048	19508	19527	TAAAATTGCAATTCTATATC	114	1708
1362960	797	816	14856	14875	GTAAATGTACACAGGCACAG	50	1709
1362971	N/A	N/A	16677	16696	GACTGCAAAGTACTTGCCAA	39	1710
1362988	N/A	N/A	9337	9356	GCTCCACTACAGCTCAAAGC	56	1711
1363026	1935	1954	18414	18433	TTCTCATGTAAGCTAGTTTC	33	1712
1363034	1675	1694	18154	18173	CTTGCTTTGACCCCTTCTC	70	1713
1363112	1330	1349	17809	17828	CATTTCTAGCAGGAACCAGC	59	1714
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	20	279
1363195	N/A	N/A	4052	4071	CCAAAGTTGGAAATTCTCTT	63	1715
1363345	N/A	N/A	13374	13393	AGTGAGGTATACACCAGAGC	40	1716
1363393	1744	1763	18223	18242	TGGCTGAGTTAGGGCTTCAG	23	1717
1363394	N/A	N/A	11753	11772	TTTCAACTAACAATTCAGGC	52	1718
1363397	2414	2433	18893	18912	ATTTTCCATTAGCTAGAAAG	47	1719
1363401	1501	1520	17980	17999	AGACATTCCTTCTCTGTACC	50	1720
1363409	2443	2462	18922	18941	ACACCAAGATAACATTGCTA	35	1721
1363413	N/A	N/A	15756	15775	TCTATCTTTACCTAAAGCTA	58	1722
1363503	2908	2927	19387	19406	TGTTATTAAATCAAAACAAA	89	1723
1363511	2709	2728	19188	19207	GGAAAAGAACAACACAACCTC	56	1724
1363563	N/A	N/A	15333	15352	ATCTCTAATTATCCTGGCTG	70	1725
1363571	N/A	N/A	11290	11309	GAAACATCTTTCTGGCACTA	54	1726
1363603	2141	2160	18620	18639	GACCTTCAAATCACCTACGA	37	289
1363619	2470	2489	18949	18968	ACCTTTATGTTAAACCTAAC	46	1727
1363691	1620	1639	18099	18118	ATTGTTTTTCTGACATTCTT	38	1728
1363696	1574	1593	18053	18072	AGAGACCAGAATGAATTCCA	18	1729
1363708	2243	2262	18722	18741	TCATAATCAAAGAATTATTC	75	1730
1363747	2272	2291	18751	18770	ATGTCCAATTTTCTAGTTT	28	1731
1363792	1533	1552	18012	18031	TATTTGGCCCCTATAGATGG	90	1732
1363795	1374	1393	17853	17872	CCTTTGTGACTTGCAGTTGG	35	1733
1363815	2113	2132	18592	18611	TGGATAATACCCCATGAAAT	40	1734

1363818	2307	2326	18786	18805	AACTAGCCAATTTTAAATAT	52	1735
1363842	1192	1211	17671	17690	GGCAAAGGCAAAGAGTTAAG	28	1736
1363850	1262	1281	17741	17760	GAGAGACCTTAATCACTGCA	24	1737
1363863	N/A	N/A	17212	17231	CAATATTTGGGCTTTGCCAC	60	1738
1363881	2331	2350	18810	18829	CTTGTAAGAAAATCCCAATAG	45	1739
1363890	2167	2186	18646	18665	ATGTGCATCATTCTAAAACA	41	1740
1363914	1447	1466	17926	17945	GGAAGTACCCTTTGAGAAGA	64	1741
1363938	N/A	N/A	16410	16429	TACTTGCCAAGATCATTCAA	98	1742
1363948	N/A	N/A	5214	5233	TGTTACTTGATTCTCACAAC	45	1743
1363960	2649	2668	19128	19147	TAAAACCAATCAGACTTTTT	65	1744
1363967	1223	1242	17702	17721	CACTCATCAAGTAAGAAGAG	53	1745
1363978	2856	2875	19335	19354	TCTTGATTGGTTTCTTACAA	27	1746
1364013	N/A	N/A	4871	4890	GTGTTAAGCTGCTATCTTT	38	1747
1364022	N/A	N/A	5527	5546	TGAGGAAGTAATATTCAACA	86	1748
1364025	N/A	N/A	10093	10112	ACAGGTTAAGATACTAGATT	59	1749
1364034	1062	1081	17541	17560	CAAAGTTGTAAGTGGCAGCA	38	1750
1364045	2805	2824	19284	19303	TGGAAGCTTATCTTGTATAC	43	1751
1364062	N/A	N/A	8815	8834	TCCAGTCTAAGTACAGACTG	98	1752
1364064	N/A	N/A	13950	13969	TCCCACAAAACATGCTTT	40	1753
1364092	N/A	N/A	6532	6551	GCTGCACTTGATTATTTTAG	47	1754
1364121	2543	2562	19022	19041	TTCCTGGAAGCTTACCAACT	40	1755
1364137	1853	1872	18332	18351	GAGTGAGAAGATGCTGACAA	48	1756
1364142	1305	1324	17784	17803	AGCAAAATGACTAAAAGAGG	56	1757
1364151	2208	2227	18687	18706	TGCAACCCCAAATAAGTAAT	33	1758
1364176	2027	2046	18506	18525	TATCCAAAGAGTTATCTATC	53	1759
1364219	N/A	N/A	9114	9133	TGTCCAAGCAAGAATCAGAT	69	1760
1364234	N/A	N/A	8297	8316	GTGACTTACACAGATCCAGG	51	1761
1364236	N/A	N/A	7230	7249	CCACCATTTCTCTCTCTC	53	1762

Table 24

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362462	N/A	N/A	10090	10109	GGTTAAGATACTAGATTCAG	76	1763
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	30	201
1362495	N/A	N/A	13949	13968	CCCACAAAACATGCTTTC	52	1764
1362520	2085	2104	18564	18583	TTGTGAAGATATGACAGAGG	37	1765
1362601	N/A	N/A	5841	5860	TACTGCAATTGTTGAACAGC	90	1766
1362666	1260	1279	17739	17758	GAGACCTTAATCACTGCAAG	43	1767
1362672	1329	1348	17808	17827	ATTTCTAGCAGGAACCAGCT	49	1768

1362674	1191	1210	17670	17689	GCAAAGGCAAAGAGTTAAGA	66	1769
1362818	1891	1910	18370	18389	CCACAGGGTTGTCATGGTAG	44	1770
1362870	N/A	N/A	5490	5509	TCTGTTTTTAATGCACAACC	66	1771
1362892	2495	2514	18974	18993	ATGTGATCTATATCAGGAGA	28	1772
1362907	2242	2261	18721	18740	CATAATCAAAGAATTATTCT	85	1773
1362917	2271	2290	18750	18769	TGTCCAATTTTCCTAGTTTA	34	1774
1362920	N/A	N/A	16935	16954	CACTACATTCACAGGGCACT	60	1775
1362935	795	814	14854	14873	AAATGTACACAGGCACAGCA	72	1776
1362941	2306	2325	18785	18804	ACTAGCCAATTTTAAATATC	53	1777
1362947	2899	2918	19378	19397	ATCAAAACAAAACACAAGGT	57	1778
1362970	1148	1167	17627	17646	GTGTGGTTAGAGCCTCGCTA	23	197
1363006	N/A	N/A	11241	11260	GTGTCTTAAAGTGCTAAGAG	37	1779
1363014	3028	3047	19507	19526	AAAATTGCAATTCTATATCA	64	1780
1363015	2677	2696	19156	19175	GAAGTGTAAGTACAAATCTTT	51	1781
1363017	1573	1592	18052	18071	GAGACCAGAATGAATTCCAT	33	1782
1363057	N/A	N/A	15306	15325	GGATTCTACCAACAATCAGG	66	1783
1363065	N/A	N/A	9336	9355	CTCCACTACAGCTCAAAGCA	73	1784
1363072	N/A	N/A	8760	8779	TAATAACATTTCTCAATGCA	87	1785
1363076	2360	2379	18839	18858	ACCAAATCTGTTTCTGCAAA	28	1786
1363088	2026	2045	18505	18524	ATCCAAAGAGTTATCTATCC	45	1787
1363098	2853	2872	19332	19351	TGATTGGTTTCTTACAAAAC	49	1788
1363102	N/A	N/A	17196	17215	CCACATCAATATGTCCGAGT	19	253
1363120	N/A	N/A	7184	7203	GGAACCTTATTCTCTTCCTT	37	1789
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	17	279
1363133	2442	2461	18921	18940	CACCAAGATAACATTGCTAA	39	1790
1363152	2166	2185	18645	18664	TGTGCATCATTCTAAAACAA	30	1791
1363203	2140	2159	18619	18638	ACCTTCAAATCACCTACGAT	57	1792
1363266	2112	2131	18591	18610	GGATAATACCCCATGAAATG	28	1793
1363269	1810	1829	18289	18308	AGGTGTAAGGCCAGATGCCC	39	1794
1363275	N/A	N/A	4800	4819	ACAAAGACCCTTGTGCTCTG	81	1795
1363282	2759	2778	19238	19257	TTTTTGTAAGCTCTTACAT	62	1796
1363297	N/A	N/A	15752	15771	TCTTTACCTAAAGCTACAAA	91	1797
1363304	2059	2078	18538	18557	TACACAACATAATTAACAGAA	75	1798
1363315	2804	2823	19283	19302	GGAAGCTTATCTTGTATACT	21	1799
1363360	1499	1518	17978	17997	ACATTCTTCTCTGTACCTG	38	1800
1363378	N/A	N/A	11752	11771	TTCAACTAACAATTCAGGCA	42	1801
1363400	1982	2001	18461	18480	GGTTACACCATTAGCCACCA	25	1802
1363403	1304	1323	17783	17802	GCAAAATGACTAAAAGAGGT	61	1803
1363456	2595	2614	19074	19093	AGACTGAAATCTGGGAGCTA	49	1804
1363459	1222	1241	17701	17720	ACTCATCAAGTAAGAAGAGG	29	1805
1363463	1444	1463	17923	17942	AGTACCCTTTGAGAAGAAAT	48	1806
1363517	2207	2226	18686	18705	GCAACCCCAAATAAGTAATA	23	1807
1363526	N/A	N/A	16675	16694	CTGCAAAGTACTTGGCAACA	34	1808

1363537	N/A	N/A	8295	8314	GACTTACACAGATCCAGGTT	67	1809
1363587	2468	2487	18947	18966	CTTTATGTTAAACCTAACTC	45	1810
1363625	1060	1079	17539	17558	AAGTTGTAAGTGGCAGCAAT	92	1811
1363667	3067	3086	19546	19565	GTAAGATAAGTTTCTAAAAG	71	1812
1363670	1527	1546	18006	18025	GCCCCATAGATGGCAAGAG	53	1813
1363672	1674	1693	18153	18172	TTGCTTTGACCCCCTTCTCC	74	1814
1363701	1743	1762	18222	18241	GGCTGAGTTAGGGCTTCAGT	21	1815
1363712	N/A	N/A	6244	6263	CAGACGACAACAGGCTTGCA	88	1816
1363713	2413	2432	18892	18911	TTTTCCATTAGCTAGAAAGA	50	1817
1363731	3002	3021	19481	19500	AAGGAAACACTTTCAGTTGA	62	1818
1363772	N/A	N/A	16409	16428	ACTTGCCAAGATCATTCAA	86	1819
1363830	2388	2407	18867	18886	CAGATTACTCAAATTGAGAT	39	1820
1363838	1933	1952	18412	18431	CTCATGTAAGCTAGTTTCCT	27	1821
1363849	N/A	N/A	7581	7600	TAGTCAAATCATGTGGACAA	52	1822
1363861	2330	2349	18809	18828	TTGTAGAAAATCCCAATAGA	51	1823
1363874	N/A	N/A	4001	4020	GCTAAAGTTTTTGAAACTTA	124	1824
1363918	N/A	N/A	13373	13392	GTGAGGTATACACCAGAGCG	55	1825
1363927	1411	1430	17890	17909	TCAGGAGATGCTTGAAAATT	62	1826
1363936	1852	1871	18331	18350	AGTGAGAAGATGCTGACAAC	40	1827
1363955	2648	2667	19127	19146	AAAACCAATCAGACTTTTTT	53	1828
1363962	N/A	N/A	5213	5232	GTTACTTGATTCTCACAACC	29	1829
1364037	N/A	N/A	12401	12420	GACCCAGAATCCTTACTTTG	64	1830
1364058	1370	1389	17849	17868	TGTGACTTGCAGTTGGGAAG	47	1831
1364097	1618	1637	18097	18116	TGTTTTTCTGACATTCTTTT	34	1832
1364173	N/A	N/A	9112	9131	TCCAAGCAAGAATCAGATTT	77	1833
1364203	N/A	N/A	10788	10807	TGTATTAATTACTTAGGCTT	74	1834
1364226	2708	2727	19187	19206	GAAAAGAACAACACAACCTCT	60	1835
1364259	N/A	N/A	6527	6546	ACTTGATTATTTTAGTCAGT	44	1836
1364267	2542	2561	19021	19040	TCCTGGAAGCTTACCAACTG	42	1837

Table 25

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
805563	1058	1077	17537	17556	GTTGTAAGTGGCAGCAATCA	55	1838
1362438	2647	2666	19126	19145	AAACCAATCAGACTTTTTTTT	54	1839
1362452	N/A	N/A	13369	13388	GGTATACACCAGAGCGAGCA	67	1840
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	16	201
1362494	1890	1909	18369	18388	CACAGGGTTGTCATGGTAGC	58	1841
1362523	2139	2158	18618	18637	CCTTCAAATCACCTACGATG	50	1842
1362563	N/A	N/A	5488	5507	TGTTTTTAATGCACAACCTA	114	1843

1362572	N/A	N/A	6524	6543	TGATTATTTTAGTCAGTGTC	73	1844
1362608	2387	2406	18866	18885	AGATTACTCAAATTGAGATT	72	1845
1362628	2898	2917	19377	19396	TCAAAACAAAACACAAGGTA	65	1846
1362698	265	284	3975	3994	TCTTTGGGACTCTGACTCCA	100	1847
1362713	2164	2183	18643	18662	TGCATCATTCTAAAACAAAT	48	1848
1362728	N/A	N/A	15742	15761	AAGCTACAAACTTCTCTTTT	91	1849
1362749	1147	1166	17626	17645	TGTGGTTAGAGCCTCGCTAT	34	1850
1362759	2706	2725	19185	19204	AAAGAACAACACAACCTCTTT	71	1851
1362786	N/A	N/A	7067	7086	TTAATCAATCAGTACTTGCT	107	1852
1362793	1410	1429	17889	17908	CAGGAGATGCTTGAAAATTC	54	1853
1362798	2676	2695	19155	19174	AACTGTAGTACAAATCTTTC	65	1854
1362807	N/A	N/A	10089	10108	GTTAAGATACTAGATTACAGC	101	1855
1362813	2852	2871	19331	19350	GATTGGTTTCTTACAAAACA	19	1856
1362824	1981	2000	18460	18479	GTTACACCATTAGCCACCAG	79	1857
1362847	1608	1627	18087	18106	ACATTCTTTTTTCTTCTATC	56	1858
1362861	2539	2558	19018	19037	TGGAAGCTTACCAACTGAAT	81	1859
1362876	1851	1870	18330	18349	GTGAGAAGATGCTGACAACA	35	1860
1362929	N/A	N/A	16934	16953	ACTACATTCACAGGGCACTG	68	1861
1362931	N/A	N/A	15305	15324	GATTCTACCAACAATCAGGA	134	1862
1362989	2441	2460	18920	18939	ACCAAGATAACATTGCTAAG	57	1863
1363047	N/A	N/A	8758	8777	ATAACATTTCTCAATGCAAC	61	1864
1363054	N/A	N/A	13905	13924	GGAACCTTTGAAAGGTGAGG	46	1865
1363087	N/A	N/A	6243	6262	AGACGACAACAGGCTTGACAG	88	1866
1363111	N/A	N/A	12395	12414	GAATCCTTACTTTGTTTCAT	65	1867
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	34	279
1363149	1806	1825	18285	18304	GTAAGGCCAGATGCCCCCTT	56	1868
1363164	N/A	N/A	14681	14700	AAACCAGGTTCCAGGGCTCT	61	1869
1363241	1328	1347	17807	17826	TTTCTAGCAGGAACCAGCTA	67	1870
1363260	1742	1761	18221	18240	GCTGAGTTAGGGCTTCAGTA	45	1871
1363277	1221	1240	17700	17719	CTCATCAAGTAAGAAGAGGG	34	1872
1363324	2329	2348	18808	18827	TGTAGAAAATCCCAATAGAT	60	1873
1363325	2241	2260	18720	18739	ATAATCAAAGAATTATTCTC	76	1874
1363335	1443	1462	17922	17941	GTACCCTTTGAGAAGAAATT	53	1875
1363369	N/A	N/A	4796	4815	AGACCCTTGTGCTCTGCACA	43	1876
1363379	N/A	N/A	11751	11770	TCAACTAACAATTCAGGCAG	72	1877
1363418	N/A	N/A	9103	9122	GAATCAGATTTTAGATTCTA	118	1878
1363430	1491	1510	17970	17989	TCTCTGTACCTGAGCATCTT	37	1879
1363465	2206	2225	18685	18704	CAACCCCAAATAAGTAATAA	66	1880
1363538	1572	1591	18051	18070	AGACCAGAATGAATTCCATT	44	1881
1363588	2758	2777	19237	19256	TTTTGTAAAGCTCTTACATC	74	1882
1363594	2467	2486	18946	18965	TTTATGTTAAACCTAACTCT	87	1883
1363658	N/A	N/A	10771	10790	CTTGATTTTTGTATTCAAG	73	1884
1363745	1526	1545	18005	18024	CCCCTATAGATGGCAAGAGG	83	1885

1363769	2305	2324	18784	18803	CTAGCCAATTTTAAATATCA	35	1886
1363780	1190	1209	17669	17688	CAAAGGCAAAGAGTTAAGAT	77	1887
1363791	2412	2431	18891	18910	TTCCATTAGCTAGAAAGAA	46	1888
1363801	3000	3019	19479	19498	GGAAACACTTTCAGTTGATT	21	1889
1363802	2803	2822	19282	19301	GAAGCTTATCTTGTAATCTG	26	1890
1363807	2359	2378	18838	18857	CCAAATCTGTTTCTGCAAAAG	52	1891
1363828	N/A	N/A	5211	5230	TACTTGATTCTCACAACCCCT	83	1892
1363839	3027	3046	19506	19525	AAATTGCAATTCTATATCAG	100	1893
1363867	1673	1692	18152	18171	TGCTTTGACCCCTTCTCCC	76	1894
1363893	N/A	N/A	16673	16692	GCAAAGTACTTGGCAACATT	50	1895
1363911	N/A	N/A	5840	5859	ACTGCAATTGTTGAACAGCA	58	1896
1363923	N/A	N/A	9335	9354	TCCACTACAGCTCAAAGCAA	82	1897
1363942	2111	2130	18590	18609	GATAATACCCCATGAAATGA	82	1898
1363963	N/A	N/A	17177	17196	TGACTTAGAGTCATAGGGTG	81	1899
1364033	N/A	N/A	16326	16345	AGGTCATTTGGAAGTGCAGG	59†	1900
1364040	2493	2512	18972	18991	GTGATCTATATCAGGAGAAA	44	1901
1364068	1302	1321	17781	17800	AAAATGACTAAAAGAGGTAC	106	1902
1364075	N/A	N/A	7579	7598	GTCAAATCATGTGGACAAGG	72	1903
1364096	2025	2044	18504	18523	TCCAAAGAGTTATCTATCCT	43	1904
1364108	3066	3085	19545	19564	TAAGATAAGTTTCTAAAAGT	93	1905
1364110	2594	2613	19073	19092	GACTGAAATCTGGGAGCTAT	38	1906
1364149	N/A	N/A	11158	11177	GCACACAAGAAGTCACAGGC	41	1907
1364154	2269	2288	18748	18767	TCCAATTTTCTAGTTTAAA	59	1908
1364167	2058	2077	18537	18556	ACACAATAATTAACAGAAA	103	1909
1364184	N/A	N/A	8294	8313	ACTTACACAGATCCAGGTTT	98	1910
1364186	2084	2103	18563	18582	TGTGAAGATATGACAGAGGC	59	1911
1364212	1369	1388	17848	17867	GTGACTTGACAGTTGGGAAGT	47	1912
1364222	1259	1278	17738	17757	AGACCTTAATCACTGCAAGA	60	1913
1364266	1932	1951	18411	18430	TCATGTAAGCTAGTTTCCTT	46	1914

Table 26

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362434	2897	2916	19376	19395	CAAAAACAAAACACAAGGTAC	80	1915
1362470	N/A	N/A	11750	11769	CAACTAACAATTCAGGCAGC	88	1916
1362480	N/A	N/A	13904	13923	GAACCTTTGAAAGGTGAGGC	77	1917
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	23	201
1362504	2304	2323	18783	18802	TAGCCAATTTTAAATATCAT	99	1918
1362537	2057	2076	18536	18555	CACAATAATTAACAGAAAA	122	1919

1362540	N/A	N/A	14679	14698	ACCAGGTTCCAGGGCTCTCC	39	1920
1362576	N/A	N/A	5836	5855	CAATTGTTGAACAGCAGTGCC	82	1921
1362579	1889	1908	18368	18387	ACAGGGTTGTCATGGTAGCT	36	1922
1362596	2591	2610	19070	19089	TGAAATCTGGGAGCTATTCA	102	1923
1362614	1220	1239	17699	17718	TCATCAAGTAAGAAGAGGGC	73	1924
1362627	2328	2347	18807	18826	GTAGAAAATCCCAATAGATT	49	1925
1362646	N/A	N/A	9334	9353	CCACTACAGCTCAAAGCAAG	117	1926
1362743	N/A	N/A	6241	6260	ACGACAACAGGCTTGCAGAC	91	1927
1362753	N/A	N/A	8290	8309	ACACAGATCCAGGTTTCATCA	80	1928
1362754	2411	2430	18890	18909	TTCCATTAGCTAGAAAAGAAC	54	1929
1362773	1741	1760	18220	18239	CTGAGTTAGGGCTTCAGTAG	39	1930
1362777	N/A	N/A	16291	16310	GAACTGTTTCTTGCAACAGC	98	1931
1362834	1850	1869	18329	18348	TGAGAAGATGCTGACAACAC	92	1932
1362848	2850	2869	19329	19348	TTGGTTTCTTACAAAACATT	57	1933
1362853	1258	1277	17737	17756	GACCTTAATCACTGCAAGAC	61	1934
1362862	N/A	N/A	17175	17194	ACTTAGAGTCATAGGGTGCT	38	1935
1362869	N/A	N/A	16672	16691	CAAAGTACTTGGCAACATTA	87	1936
1362882	1366	1385	17845	17864	ACTTGCAGTTGGGAAGTCAT	61	1937
1362904	2757	2776	19236	19255	TTTGTAAGCTCTTACATCT	39	1938
1362915	2163	2182	18642	18661	GCATCATTCTAAAACAAATC	36	1939
1362919	2024	2043	18503	18522	CCAAAGAGTTATCTATCCTG	50	1940
1362937	N/A	N/A	5210	5229	ACTTGATTCTCACAACCCTG	40	1941
1362959	N/A	N/A	7484	7503	TGTTTCTTATACTCCCCACT	66	1942
1362964	N/A	N/A	10086	10105	AAGATACTAGATTTCAGCCTA	111	1943
1362990	1301	1320	17780	17799	AAATGACTAAAAGAGGTACA	87	1944
1362998	2268	2287	18747	18766	CCAATTTCTCTAGTTTAAAA	63	1945
1363050	2357	2376	18836	18855	AAATCTGTTTCTGCAAAGGC	55	1946
1363070	1672	1691	18151	18170	GCTTTGACCCCTTCTCCCA	63	1947
1363119	2083	2102	18562	18581	GTGAAGATATGACAGAGGCC	49	1948
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	18	279
1363124	2386	2405	18865	18884	GATTACTCAAATTGAGATTC	40	1949
1363138	N/A	N/A	15302	15321	TCTACCAACAATCAGGATCC	84	1950
1363163	2798	2817	19277	19296	TTATCTTGTATACTGGTTTG	32	1951
1363218	N/A	N/A	16932	16951	TACATTACAGGGCACTGTA	89	1952
1363236	1602	1621	18081	18100	TTTTTTCTTCTATCTTCAGT	75	1953
1363238	247	266	3957	3976	CAATTGTAGCCGGCTGGCTA	99	1954
1363262	N/A	N/A	4784	4803	TCTGCACACATTACTCTGAG	79	1955
1363274	1327	1346	17806	17825	TTCTAGCAGGAACCAGCTAT	58	1956
1363284	2466	2485	18945	18964	TTATGTTAAACCTAACTCTT	98	1957
1363286	1804	1823	18283	18302	AAGGCCAGATGCCCCCTTCG	38	1958
1363302	1407	1426	17886	17905	GAGATGCTTGAAAATTCAAT	55	1959
1363352	2205	2224	18684	18703	AACCCCAAATAAGTAATAAA	48	1960
1363366	1189	1208	17668	17687	AAAGGCCAAAGAGTTAAGATG	98	1961

1363420	N/A	N/A	5454	5473	CTGACATTAGATAGGATTCC	107	1962
1363432	2999	3018	19478	19497	GAAACACTTTCAGTTGATTA	75	1963
1363461	N/A	N/A	11157	11176	CACACAAGAAGTCACAGGCT	82	1964
1363474	1146	1165	17625	17644	GTGGTTAGAGCCTCGCTATT	28	1965
1363477	1442	1461	17921	17940	TACCCTTTGAGAAGAAATTA	86	1966
1363515	2110	2129	18589	18608	ATAATACCCCATGAAATGAG	70	1967
1363627	2675	2694	19154	19173	ACTGTAGTACAAATCTTTCC	23	1968
1363657	3026	3045	19505	19524	AATTGCAATTCTATATCAGA	84	1969
1363690	2138	2157	18617	18636	CTTCAAATCACCTACGATGA	73	1970
1363724	1571	1590	18050	18069	GACCAGAATGAATTCCATTT	31	1971
1363739	N/A	N/A	11990	12009	TCAGCAATTCAAATAGCAAG	89	1972
1363743	1980	1999	18459	18478	TTACACCATTAGCCACCAGC	61	1973
1363774	N/A	N/A	6518	6537	TTTTAGTCAGTGTCTCCAGG	76	1974
1363845	1929	1948	18408	18427	TGTAAGCTAGTTTCCTTCTA	52	1975
1363880	2492	2511	18971	18990	TGATCTATATCAGGAGAAAA	75	1976
1363896	1525	1544	18004	18023	CCCTATAGATGGCAAGAGGA	74	1977
1363906	3065	3084	19544	19563	AAGATAAGTTTCTAAAAGTT	81	1978
1363910	N/A	N/A	7066	7085	TAATCAATCAGTACTTGCTG	77	1979
1363928	2240	2259	18719	18738	TAATCAAAGAATTATTCTCC	90	1980
1363941	2440	2459	18919	18938	CCAAGATAACATTGCTAAGT	44	1981
1363966	N/A	N/A	9099	9118	CAGATTTTAGATTCTAACTG	118	1982
1363986	2646	2665	19125	19144	AACCAATCAGACTTTTTTTT	67	1983
1364004	N/A	N/A	15711	15730	GGTTGGAAAGGAAGTCTTTC	65	1984
1364014	N/A	N/A	13368	13387	GTATACACCAGAGCGAGCAC	67	1985
1364053	2538	2557	19017	19036	GGAAGCTTACCAACTGAATA	75	1986
1364087	2705	2724	19184	19203	AAGAACAACACAACCTCTTA	85	1987
1364143	1487	1506	17966	17985	TGTACCTGAGCATCTTCTCT	37	1988
1364168	1057	1076	17536	17555	TTGTAAGTGGCAGCAATCAT	61	1989
1364194	N/A	N/A	10768	10787	GGATTTTGTATTCAAGCAT	99	1990
1364211	N/A	N/A	8755	8774	ACATTCTCAATGCAACTCA	60	1991

Table 27

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362457	2384	2403	18863	18882	TTACTCAAATTGAGATTCAA	48	1992
1362469	N/A	N/A	9235	9254	AAGCTATAAACAATTCAGTA	78	1993
1362475	1978	1997	18457	18476	ACACCATTAGCCACCAGCAA	53	1994
1362484	1144	1163	17623	17642	GGTTAGAGCCTCGCTATTAG	32	119
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	20	201
1362501	184	203	3894	3913	CTCTCCAGCCTCCTTCTTCG	76	1995

1362546	2356	2375	18835	18854	AATCTGTTTCTGCAAAGGCA	38	1996
1362552	2796	2815	19275	19294	ATCTTGATACTGGTTTGAA	47	1997
1362574	2847	2866	19326	19345	GTTTCTTACAAAACATTTTC	32	1998
1362592	N/A	N/A	16910	16929	ACTATCAGCAAGACCTGGGA	77	1999
1362594	2109	2128	18588	18607	TAATACCCCATGAAATGAGC	50	2000
1362616	1300	1319	17779	17798	AATGACTAAAAGAGGTACAT	61	2001
1362659	1786	1805	18265	18284	CGTCTACACAGATTCTACGC	28	2002
1362700	1927	1946	18406	18425	TAAGCTAGTTTCCTTCTATT	53	2003
1362719	2239	2258	18718	18737	AATCAAAGAATTATTCTCCA	40	2004
1362721	2439	2458	18918	18937	CAAGATAACATTGCTAAGTA	67	2005
1362751	N/A	N/A	13364	13383	ACACCAGAGCGAGCACCTTA	65	2006
1362768	2896	2915	19375	19394	AAAACAAAACACAAGGTACG	75	2007
1362808	2755	2774	19234	19253	TGTAAGCTCTTACATCTCC	31	2008
1362820	N/A	N/A	7404	7423	ATGATGTACACATTCCAATT	67	2009
1362842	3025	3044	19504	19523	ATTGCAATTCTATATCAGAA	28	2010
1362879	N/A	N/A	11156	11175	ACACAAGAAGTCACAGGCTC	65	2011
1362881	N/A	N/A	8272	8291	CAAGGGACTGTGTTGATCCT	67	2012
1362993	1056	1075	17535	17554	TGTAAGTGGCAGCAATCATG	36	2013
1363022	1569	1588	18048	18067	CCAGAATGAATTCATTTTG	25	2014
1363024	1441	1460	17920	17939	ACCCTTTGAGAAGAAATTAC	60	2015
1363053	1326	1345	17805	17824	TCTAGCAGGAACCAGCTATG	63	2016
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	29	279
1363171	2704	2723	19183	19202	AGAACAACACAACCTTTTAC	57	2017
1363186	2327	2346	18806	18825	TAGAAAATCCCAATAGATTC	52	2018
1363229	2204	2223	18683	18702	ACCCCAAATAAGTAATAAAC	39	2019
1363242	2162	2181	18641	18660	CATCATTCTAAAACAAATCA	52	2020
1363258	N/A	N/A	6500	6519	GGAAGACTAGGTGAACATGC	67	2021
1363327	N/A	N/A	8656	8675	GTTTATGTGAATTCAGTACA	54	2022
1363330	N/A	N/A	14525	14544	GCTTCAGAGGATGTTTTTGG	27	2023
1363365	2265	2284	18744	18763	ATTTTCCTAGTTTAAAAAAC	77	2024
1363368	1365	1384	17844	17863	CTTGCAGTTGGGAAGTCATC	64	2025
1363375	1740	1759	18219	18238	TGAGTTAGGGCTTCAGTAGT	50	2026
1363377	N/A	N/A	9016	9035	TGAGAAAAGATCCATTGGGC	70	2027
1363411	N/A	N/A	5453	5472	TGACATTAGATAGGATTCCT	88	2028
1363444	N/A	N/A	11749	11768	AACTAACAATTCAGGCAGCC	57	2029
1363468	2465	2484	18944	18963	TATGTTAAACCTAACTCTTA	77	2030
1363481	N/A	N/A	5835	5854	AATTGTTGAACAGCAGTGCA	97	2031
1363497	N/A	N/A	6239	6258	GACAACAGGCTTGACAGACAA	43	2032
1363502	1881	1900	18360	18379	GTCATGGTAGCTGTTATCAA	28	2033
1363505	N/A	N/A	15301	15320	CTACCAACAATCAGGATCCT	75	2034
1363512	2491	2510	18970	18989	GATCTATATCAGGAGAAAAT	50	2035
1363548	N/A	N/A	16255	16274	GTAAATCATGAATACAGCTT	43	2036
1363560	1671	1690	18150	18169	CTTTGACCCCTTCTCCAG	73	2037

1363572	1257	1276	17736	17755	ACCTTAATCACTGCAAGACT	58	2038
1363574	N/A	N/A	5150	5169	TGAGGAAGTGTTGATTCACT	100	2039
1363612	2590	2609	19069	19088	GAAATCTGGGAGCTATTCAG	46	2040
1363616	3064	3083	19543	19562	AGATAAGTTTCTAAAAGTTT	68	2041
1363617	N/A	N/A	16670	16689	AAGTACTTGGCAACATTACA	45	2042
1363624	2023	2042	18502	18521	CAAAGAGTTATCTATCTCTGT	83	2043
1363629	1406	1425	17885	17904	AGATGCTTGAAAATTCAATT	47	2044
1363695	1188	1207	17667	17686	AAGGCAAAGAGTTAAGATGG	63	2045
1363723	1486	1505	17965	17984	GTACCTGAGCATCTTTCCTT	29	2046
1363726	N/A	N/A	11989	12008	CAGCAATTCAAATAGCAAGC	39	2047
1363766	2410	2429	18889	18908	TCCATTAGCTAGAAAGAACG	45	2048
1363779	N/A	N/A	10767	10786	GATTTTTGTATTCAAGCATT	73	2049
1363793	2627	2646	19106	19125	TTTTTTAACCCTAAAGTTAAC	80	2050
1363821	N/A	N/A	13886	13905	GCTAAGCCAGCTGGGCACCA	61	2051
1363855	1849	1868	18328	18347	GAGAAGATGCTGACAACACC	47	2052
1363859	N/A	N/A	10085	10104	AGATACTAGATTGAGCCTAT	85	2053
1363925	2302	2321	18781	18800	GCCAAATTTTAAATATCATTT	36	2054
1363940	2674	2693	19153	19172	CTGTAGTACAAATCTTTCCT	28	2055
1363961	2082	2101	18561	18580	TGAAGATATGACAGAGGCCA	44	2056
1363977	2997	3016	19476	19495	AACACTTTCAGTTGATTAAC	59	2057
1363979	N/A	N/A	4782	4801	TGCACACATTACTCTGAGTA	72	2058
1363992	2137	2156	18616	18635	TTCAAATCACCTACGATGAC	76	2059
1364027	2056	2075	18535	18554	ACAACATAATTAACAGAAAAA	102	2060
1364080	1595	1614	18074	18093	TTCTATCTTCAGTGGTAATA	47	2061
1364172	N/A	N/A	15707	15726	GGAAAGGAAGTCTTCTATG	52	2062
1364199	1219	1238	17698	17717	CATCAAGTAAGAAGAGGGCC	61	2063
1364214	N/A	N/A	7063	7082	TCAATCAGTACTTGCTGAGC	51	2064
1364237	N/A	N/A	17174	17193	CTTAGAGTCATAGGGTGCTT	63	2065
1364254	1524	1543	18003	18022	CCTATAGATGGCAAGAGGAC	72	2066
1364268	2537	2556	19016	19035	GAAGCTTACCAACTGAATAG	43	2067

Table 28

Reduction of PLP1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SK-MEL-28 cells

Compound ID	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')	PLP1 (% UTC)	SEQ ID No.
1362440	2996	3015	19475	19494	ACACTTTCAGTTGATTAAC	35	2068
1362444	N/A	N/A	15299	15318	ACCAACAATCAGGATCCTCT	70	2069
1362455	2409	2428	18888	18907	CCATTAGCTAGAAAGAACGA	50	2070
1362490	1731	1750	18210	18229	GCTTCAGTAGTCCATCGCCA	13	201
1362502	1299	1318	17778	17797	ATGACTAAAAGAGGTACATA	84	2071

1362522	N/A	N/A	14521	14540	CAGAGGATGTTTTTGGGCAG	40	2072
1362585	2301	2320	18780	18799	CCAATTTTAAATATCATTG	67	2073
1362605	N/A	N/A	11987	12006	GCAATTCAAATAGCAAGCCA	31	2074
1362654	N/A	N/A	11128	11147	GCTGTGTTCCAAGTACTAGT	66	2075
1362667	N/A	N/A	7062	7081	CAATCAGTACTTGCTGAGCT	38	2076
1362668	N/A	N/A	10763	10782	TTTGTATTCAAGCATTCTC	70	2077
1362673	N/A	N/A	10084	10103	GATACTAGATTACAGCCTATA	72	2078
1362717	N/A	N/A	5120	5139	AGGTCACATAGTTCATAAGT	88	2079
1362727	1053	1072	17532	17551	AAGTGGCAGCAATCATGAAG	50	2080
1362734	1785	1804	18264	18283	GTCTACACAGATTCTACGCT	30	285
1362760	2795	2814	19274	19293	TCCTGTATACTGGTTTGAAA	55	2081
1362762	N/A	N/A	17170	17189	GAGTCATAGGGTGCTTGCTG	54	2082
1362772	N/A	N/A	16909	16928	CTATCAGCAAGACCTGGGAC	66	2083
1362790	1924	1943	18403	18422	GCTAGTTTCCTTCTATTCTC	15	2084
1362837	1364	1383	17843	17862	TTGCAGTTGGGAAGTCATCT	41	2085
1362845	2464	2483	18943	18962	ATGTTAAACCTAACTCTTAA	53	2086
1362891	N/A	N/A	6438	6457	GCATTCTTGCCATTTTGATG	51	2087
1362894	N/A	N/A	13759	13778	CCCAATTTTCCCCACCCCT	63	2088
1362901	2081	2100	18560	18579	GAAGATATGACAGAGGCCAG	36	2089
1362903	1977	1996	18456	18475	CACCATTAGCCACCAGCAAC	36	2090
1362927	1735	1754	18214	18233	TAGGGCTTCAGTAGTCCATC	12	2091
1362972	1405	1424	17884	17903	GATGCTTGAAAATTCAATTA	34	2092
1363094	2895	2914	19374	19393	AAACAAAACACAAGGTACGG	27	2093
1363121	1732	1751	18211	18230	GGCTTCAGTAGTCCATCGCC	25	279
1363132	2536	2555	19015	19034	AAGCTTACCAACTGAATAGC	47	2094
1363153	3023	3042	19502	19521	TGCAATTCTATATCAGAAAT	38	2095
1363156	N/A	N/A	15705	15724	AAAGGAAGTCTTTCTATGCA	60	2096
1363194	2108	2127	18587	18606	AATACCCCATGAAATGAGCA	33	2097
1363210	1256	1275	17735	17754	CCTTAATCACTGCAAGACTC	37	2098
1363226	2018	2037	18497	18516	AGTTATCTATCCTGTGTCTA	51	2099
1363233	2589	2608	19068	19087	AAATCTGGGAGCTATTCAGG	50	2100
1363235	2673	2692	19152	19171	TGTAGTACAAATCTTTCCTT	16	2101
1363249	2160	2179	18639	18658	TCATTCTAAAACAAATCAAG	80	2102
1363267	N/A	N/A	7403	7422	TGATGTACACATTCCAATTT	54	2103
1363310	1880	1899	18359	18378	TCATGGTAGCTGTTATCAAG	35	2104
1363312	1187	1206	17666	17685	AGGCAAAGAGTTAAGATGGG	40	2105
1363334	2845	2864	19324	19343	TTCTTACAAAACATTTTCCC	42	2106
1363336	N/A	N/A	8169	8188	GCTCCATGATGGAAATTCAG	68	2107
1363402	2625	2644	19104	19123	TTTTAACCCAAAGTTAACAA	64	2108
1363415	1141	1160	17620	17639	TAGAGCCTCGCTATTAGAGA	24	2109
1363471	N/A	N/A	9013	9032	GAAAAGATCCATTGGGCTCC	56	2110
1363485	2754	2773	19233	19252	GTAAAGCTCTTACATCTCCT	11	2111
1363540	2136	2155	18615	18634	TCAAATCACCTACGATGACT	71	2112

1363561	2203	2222	18682	18701	CCCCAAATAAGTAATAAACA	36	2113
1363562	N/A	N/A	5833	5852	TTGTTGAACAGCAGTGCCT	85	2114
1363600	N/A	N/A	6230	6249	CTTGCAGACAATGTTTGTCT	40	2115
1363615	1325	1344	17804	17823	CTAGCAGGAACCAGCTATGA	36	2116
1363669	N/A	N/A	5452	5471	GACATTAGATAGGATTCCTG	93	2117
1363689	2263	2282	18742	18761	TTTCCTAGTTTAAAAAACAG	72	2118
1363717	2055	2074	18534	18553	CAACTAATTAACAGAAAAAA	92	2119
1363719	1844	1863	18323	18342	GATGCTGACAACACCCTGTT	40	2120
1363740	2490	2509	18969	18988	ATCTATATCAGGAGAAAATA	68	2121
1363749	N/A	N/A	16665	16684	CTTGGCAACATTACATGTTC	38	2122
1363752	1218	1237	17697	17716	ATCAAGTAAGAAGAGGGCCA	50	2123
1363784	1440	1459	17919	17938	CCCTTTGAGAAGAAATTACT	48	2124
1363832	2437	2456	18916	18935	AGATAACATTGCTAAGTAAA	60	2125
1363853	2238	2257	18717	18736	ATCAAAGAATTATTCTCCAG	38	2126
1363862	1555	1574	18034	18053	ATTTTGTACACCAAAGAGAA	70	2127
1363898	N/A	N/A	9227	9246	AACAATTCAGTAATATCAGC	54	2128
1363908	1485	1504	17964	17983	TACCTGAGCATCTTTCCTTC	38	2129
1363926	N/A	N/A	13301	13320	CATGCTTTCACCTTATCTTT	47	2130
1363939	1523	1542	18002	18021	CTATAGATGGCAAGAGGACC	67	2131
1363944	N/A	N/A	16251	16270	ATCATGAATACAGCTTTCCTG	74	2132
1363973	2326	2345	18805	18824	AGAAAATCCCAATAGATTCA	37	2133
1363989	1594	1613	18073	18092	TCTATCTTCAGTGGAATAG	29	2134
1364057	N/A	N/A	11748	11767	ACTAACAATTCAGGCAGCCA	47	2135
1364076	3063	3082	19542	19561	GATAAGTTTCTAAAAGTTTA	56	2136
1364120	N/A	N/A	8651	8670	TGTGAATTCAGTACAAGAAT	62	2137
1364122	2351	2370	18830	18849	GTTTCTGCAAAGGCAGAATA	83	2138
1364127	2703	2722	19182	19201	GAACAACACAACCTCTTTACA	40	2139
1364148	N/A	N/A	4780	4799	CACACATTACTCTGAGTAGA	36	2140
1364190	1668	1687	18147	18166	TGACCCCTTCTCCAGCTG	49	2141
1364231	149	168	3859	3878	TCTCTGAGTATCTTTGTCCT	75	2142
1364241	2383	2402	18862	18881	TACTCAAATTGAGATTCAAA	54	2143

Example 3: Effect of modified oligonucleotides on human PLP1 RNA *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in SK-MEL-28 cells. Cultured SK-MEL-28 cells at a density of 20,000 cells per well were transfected using electroporation with

5 concentrations of modified oligonucleotides as specified in the tables below. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and PLP1 RNA levels were measured by quantitative real-time RTPCR. Human PLP1 primer probe set RTS35092 was used to measure RNA levels, as described above. PLP1 RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. The modified oligonucleotides were tested in a series of experiments using the same culture conditions, and the results for each experiment are presented in separate tables

below. Reduction of PLP1 RNA is presented in the tables below as percent PLP1 RNA relative to the amount in untreated control cells (% UTC).

The half maximal inhibitory concentration (IC₅₀) 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 tables below.

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Table 29

Dose-dependent reduction of human PLP1 RNA in SK-MEL-28 cells by modified oligonucleotides

Compound ID	PLP1 (% UTC)				IC ₅₀ (μM)
	556 nM	1667 nM	5000 nM	15000 nM	
1218118	89	66	35	22	3.3
1218157	69	45	21	15	1.4
1218162	74	54	28	18	2.0
1218165	73	51	23	9	1.6
1218166	79	55	41	21	2.7
1218178	83	56	34	18	2.6
1218179	55	24	12	10	< 0.6
1218181	57	41	23	15	0.8
1218186	67	44	23	25	1.3
1218190	80	55	34	20	2.5
1218193	67	38	20	9	1.1
1218209	60	33	19	6	0.8
1218221	79	56	32	13	2.3
1218222	71	44	32	21	1.7
1218225	70	45	23	7	1.4
1218226	78	53	29	17	2.1
1218229	70	44	21	9	1.4
1218233	82	61	31	13	2.5
1218354	71	43	22	18	1.4

Table 30

Dose-dependent reduction of human PLP1 RNA in SK-MEL-28 cells by modified oligonucleotides

Compound ID	PLP1 (% UTC)				IC ₅₀ (μM)
	556 nM	1667 nM	5000 nM	15000 nM	
1218163	61	31	13	7	0.8
1218168	69	46	26	18	1.5
1218175	64	36	22	14	1.0
1218180	72	52	25	15	1.8
1218188	72	45	29	24	1.7
1218191	75	51	26	13	1.8
1218192	75	47	23	11	1.7
1218203	74	50	22	7	1.6
1218204	50	57	31	31	1.0

1218208	63	34	17	10	0.9
1218209	61	33	27	10	0.8
1218215	75	47	17	5	1.5
1218216	68	47	36	18	1.7
1218219	61	31	19	8	0.8
1218220	85	65	37	16	3.0
1218223	60	34	23	10	0.8
1218228	67	44	22	13	1.3
1218355	75	46	21	9	1.6
1218387	62	33	21	19	0.8

Table 31

Dose-dependent reduction of human PLP1 RNA in SK-MEL-28 cells by modified oligonucleotides

Compound ID	PLP1 (% UTC)				IC ₅₀ (μM)
	94 nM	375 nM	1500 nM	6000 nM	
1362449	107	88	67	28	2.5
1362490	82	45	21	10	0.4
1362496	81	49	21	11	0.4
1362641	92	65	30	14	0.8
1362987	89	78	43	29	1.4
1363103	123	81	35	10	1.2
1363134	75	57	26	10	0.5
1363184	104	78	59	16	1.5
1363410	100	66	27	12	0.8
1363439	91	63	40	21	0.9
1363641	80	48	18	10	0.4
1363734	80	59	19	14	0.5
1363736	90	73	39	12	0.9
1363900	91	58	25	8	0.6
1363959	84	65	34	15	0.7
1364007	78	59	27	12	0.5
1364235	109	86	41	14	1.3

5

Table 32

Dose-dependent reduction of human PLP1 RNA in SK-MEL-28 cells by modified oligonucleotides

Compound ID	PLP1 (% UTC)				IC ₅₀ (μM)
	94 nM	375 nM	1500 nM	6000 nM	
1362468	90	67	24	6	0.6
1362490	83	41	13	5	0.3
1362500	106	83	43	10	1.2

1362900	115	78	30	6	1.0
1363141	99	63	31	13	0.8
1363257	118	82	40	12	1.2
1363493	139	93	48	9	1.5
1363550	72	54	21	5	0.4
1363565	88	52	29	14	0.6
1363644	103	91	36	12	1.2
1363758	84	49	16	5	0.4
1363983	74	71	30	9	0.6
1363993	78	60	36	10	0.6
1364066	103	78	34	8	1.0
1364073	107	82	56	17	1.5
1364246	125	70	17	11	0.9
1364248	80	62	30	9	0.6

Table 33

Dose-dependent reduction of human PLP1 RNA in SK-MEL-28 cells by modified oligonucleotides

Compound ID	PLP1 (% UTC)				IC ₅₀ (μM)
	94 nM	375 nM	1500 nM	6000 nM	
1362445	72	55	24	8	0.4
1362490	69	33	11	4	0.2
1362556	81	58	30	14	0.6
1362612	86	79	56	26	1.6
1362649	92	64	37	10	0.8
1362924	87	80	55	26	1.7
1362996	79	62	32	8	0.6
1363013	103	67	38	15	1.0
1363019	79	59	20	6	0.5
1363143	74	47	16	5	0.3
1363146	110	101	59	24	2.2
1363322	70	52	19	6	0.3
1363583	98	65	34	7	0.8
1364202	113	88	73	31	3.0

5

Table 34

Dose-dependent reduction of human PLP1 RNA in SK-MEL-28 cells by modified oligonucleotides

Compound ID	PLP1 (% UTC)				IC ₅₀ (μM)
	94 nM	375 nM	1500 nM	6000 nM	
1362458	95	67	37	20	1.0
1362490	76	41	21	7	0.3

1362680	91	50	28	7	0.6
1362817	94	76	31	13	0.9
1362856	77	57	34	8	0.5
1363012	90	74	48	17	1.1
1363101	76	45	26	10	0.4
1363255	102	77	39	8	1.0
1363287	99	69	39	13	0.9
1363351	103	74	40	11	1.0
1363398	85	66	45	18	0.9
1363640	96	82	54	23	1.6
1363685	86	67	43	10	0.8
1363762	77	57	23	7	0.5
1363883	103	60	23	18	0.8
1364182	86	64	35	8	0.7
1364208	77	57	30	16	0.5

Table 35

Dose-dependent reduction of human PLP1 RNA in SK-MEL-28 cells by modified oligonucleotides

Compound ID	PLP1 (% UTC)				IC ₅₀ (μM)
	94 nM	375 nM	1500 nM	6000 nM	
1362490	72	42	19	5	0.3
1362866	82	50	25	12	0.5
1362909	91	53	24	18	0.6
1363145	86	66	39	10	0.8
1363179	87	55	20	7	0.5
1363196	110	85	47	18	1.5
1363273	82	72	34	12	0.7
1363391	87	71	37	21	0.9
1363429	81	59	23	9	0.5
1363431	92	51	20	5	0.5
1363452	100	72	41	16	1.1
1363486	90	80	37	14	1.0
1363519	78	53	15	5	0.4
1363638	81	56	23	7	0.5
1363642	97	84	39	17	1.2
1363648	107	72	35	14	1.0
1363971	101	79	46	20	1.3
1364147	75	66	24	7	0.5

Table 36

Dose-dependent reduction of human PLP1 RNA in SK-MEL-28 cells by modified oligonucleotides

Compound ID	PLP1 (% UTC)				IC ₅₀ (μM)
	94 nM	375 nM	1500 nM	6000 nM	
1362473	93	73	28	8	0.8
1362490	80	48	15	6	0.4
1362517	78	42	12	3	0.3
1362602	80	68	20	8	0.5
1362689	90	61	28	8	0.6
1362724	112	78	46	12	1.2
1362774	93	70	41	11	0.9
1362805	94	85	38	11	1.0
1362928	84	69	26	10	0.7
1363191	91	48	18	6	0.5
1363544	87	50	17	4	0.4
1363591	74	50	19	6	0.4
1363673	89	70	32	13	0.8
1363889	81	38	12	4	0.3
1364107	84	55	23	9	0.5
1364116	78	56	15	6	0.4
1364257	83	62	16	15	0.5

Table 37

Dose-dependent reduction of human PLP1 RNA in SK-MEL-28 cells by modified oligonucleotides

Compound ID	PLP1 (% UTC)				IC ₅₀ (μM)
	94 nM	375 nM	1500 nM	6000 nM	
1362490	76	39	15	3	0.3
1362519	77	51	24	7	0.4
1362535	77	56	28	5	0.5
1362591	111	72	31	8	0.9
1362611	77	41	14	5	0.3
1362723	94	60	28	13	0.7
1362784	88	57	20	10	0.5
1362948	68	41	9	4	0.2
1363557	97	75	38	7	0.9
1363602	80	52	16	4	0.4
1363633	81	58	31	8	0.5
1363678	73	61	30	11	0.5
1364125	68	42	14	4	0.2
1363121	89	70	36	11	0.8

Table 38

Dose-dependent reduction of human PLP1 RNA in SK-MEL-28 cells by modified oligonucleotides

Compound ID	PLP1 (% UTC)				IC ₅₀ (μM)
	94 nM	375 nM	1500 nM	6000 nM	
1362490	86	54	18	8	0.5
1362497	110	86	50	18	1.5
1362712	77	46	21	13	0.4
1362892	91	86	56	30	2.2
1362970	91	61	26	10	0.7
1363102	91	85	45	20	1.3
1363392	77	53	26	14	0.5
1363393	74	72	37	13	0.7
1363517	97	81	36	18	1.1
1363696	77	52	26	13	0.5
1363701	89	75	49	21	1.2
1363850	102	76	36	13	1.0
1363121	76	48	22	8	0.4

5

Table 39

Dose-dependent reduction of human PLP1 RNA in SK-MEL-28 cells by modified oligonucleotides

Compound ID	PLP1 (% UTC)				IC ₅₀ (μM)
	94 nM	375 nM	1500 nM	6000 nM	
1362490	83	47	22	13	0.4
1362659	98	76	46	15	1.2
1362749	84	49	22	6	0.4
1362790	102	76	46	41	2.2
1362813	114	82	47	13	1.3
1362842	106	96	57	35	2.8
1362927	89	72	36	10	0.8
1363022	104	85	44	14	1.3
1363235	91	68	43	17	1.0
1363330	83	91	37	16	1.1
1363415	87	72	59	16	1.3
1363474	103	77	30	9	0.9
1363485	80	50	13	4	0.4
1363627	95	86	66	15	1.7
1363724	107	89	49	9	1.3
1363801	85	73	29	10	0.7
1363802	80	65	26	9	0.6
1363940	88	72	30	13	0.8

Example 4: Design of modified oligonucleotides complementary to human PLP1 nucleic acid

Modified oligonucleotides complementary to a human PLP1 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 tables 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.

The modified oligonucleotides in Table 40 are 6-10-4 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5’ to 3’): eeeeeeddddddddeeee; wherein each ‘d’ represents a 2’-β-D-deoxyribose sugar moiety, and each ‘e’ represents a 2’-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5’ to 3’): soooooosssssssoss; wherein each “s” represents a phosphorothioate internucleoside linkage, and each “o” represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 40

6-10-4 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human PLP1

Compound ID	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.
1523584	2225	2244	18704	18723	TCTCCAGACATTTCTGATGC	934
1523586	2227	2246	18706	18725	ATTCTCCAGACATTTCTGAT	2146
1523587	2228	2247	18707	18726	TATTCTCCAGACATTTCTGA	2147
1523588	2495	2514	18974	18993	ATGTGATCTATATCAGGAGA	1772
1523589	2496	2515	18975	18994	TATGTGATCTATATCAGGAG	2148
1523590	2497	2516	18976	18995	TTATGTGATCTATATCAGGA	1693
1523591	1996	2015	18475	18494	AGAGGGCCATCTCAGGTTAC	2149
1523592	1998	2017	18477	18496	CCAGAGGGCCATCTCAGGTT	993
1523593	1999	2018	18478	18497	ACCAGAGGGCCATCTCAGGT	881
1523594	3024	3043	19503	19522	TTGCAATTCTATATCAGAAA	2144
1523595	3025	3044	19504	19523	ATTGCAATTCTATATCAGAA	2010
1523596	2695	2714	19174	19193	CAACTCTTTACAACAAAAGA	630
1523597	2696	2715	19175	19194	ACAACTCTTTACAACAAAAG	556
1523598	2698	2717	19177	19196	ACACAACCTTTTACAACAAA	411
1523599	3028	3047	19507	19526	AAAATTGCAATTCTATATCA	1780
1523600	3029	3048	19508	19527	TAAAATTGCAATTCTATATC	1708
1523601	2667	2686	19146	19165	ACAAATCTTTCCTTCAATTA	682
1523602	2669	2688	19148	19167	GTACAAATCTTTCCTTCAAT	2150
1523603	2670	2689	19149	19168	AGTACAAATCTTTCCTTCAA	545
1523604	N/A	N/A	9198	9217	AGATGTTTCATCTCTTCACAA	2151

1523605	N/A	N/A	9199	9218	CAGATGTTTCATCTCTTCACA	1124
1523606	N/A	N/A	9200	9219	TCAGATGTTTCATCTCTTCAC	2152
1523607	N/A	N/A	9201	9220	ATCAGATGTTTCATCTCTTCA	2153
1523608	N/A	N/A	9202	9221	CATCAGATGTTTCATCTCTTC	2145
1523609	N/A	N/A	9203	9222	GCATCAGATGTTTCATCTCTT	1050
1523610	1382	1401	17861	17880	CCTCCATTTCCTTTGTGACTT	1499
1523611	1383	1402	17862	17881	GCCTCCATTTCCTTTGTGACT	1451
1523612	1384	1403	17863	17882	AGCCTCCATTTCCTTTGTGAC	2154
1523613	1385	1404	17864	17883	GAGCCTCCATTTCCTTTGTGA	2155

Example 5: Activity of modified oligonucleotides complementary to human PLP1 in transgenic mice

Modified oligonucleotides selected from the examples above were tested in a human BAC wild type *PLP1* transgenic mouse model. A bacterial artificial chromosome (BAC) subclone carrying the human *Plp1* gene, including down- and up-stream regulatory elements was identified. Full gene sequencing confirmed the presence of the human genomic region corresponding to current NCBI refseq assembly GRCh38.p13, ChrX sequence NC_000023.11 at position 103776506..103792619. The BAC subclone was introduced via pronuclear injection into the Taconic Biosciences C57BL/6N Tac ES cell line. Line C57BL/6NTac-Tg(PLP1)1483Tac-17235 was generated and used in these experiments. Human *Plp1* mRNA expression was found in the brain and spinal cord.

10 Treatment

The PLP1 transgenic mice were divided into groups of 2 mice each. Each mouse received a single intracerebroventricular (ICV) bolus of 100µg of modified oligonucleotide. A group of 3-5 mice received PBS as a negative control.

15 RNA analysis

Two weeks post treatment, mice were sacrificed and RNA was extracted from cortical brain tissue, spinal cord, and/or cerebellum for RTPCR analysis to measure the amount of PLP1 RNA using human primer probe set RTS48932 (forward sequence TGCACCAGTCATCAGCTATTC, designated herein as SEQ ID NO: 14; reverse sequence AGACTGAAATCTGGGAGCTATTC, designated herein as SEQ ID NO: 15; probe sequence AGGTCTCAAACCTTTCTGCCTGTCC designated herein as SEQ ID NO: 16). Results are presented as percent human PLP1 RNA relative to PBS control, normalized to mouse GAPDH. GAPDH was amplified using primer probe set mGapdh_LTS00102 (forward sequence GGCAAATTCACGGCACAGT, designated herein as SEQ ID NO: 17; reverse sequence GGGTCTCGCTCCTGGAAGAT, designated herein as SEQ ID NO: 18; probe sequence AAGGCCGAGAATGGGAAGCTTGTGATC, designated herein as SEQ ID NO: 19).

25 As shown in the tables below, treatment with modified oligonucleotides resulted in reduction of PLP1 RNA in comparison to the PBS control (% control).

Table 41

Reduction of human PLP1 RNA in transgenic mice by modified oligonucleotides

Compound ID	PLP1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1362445	43	50
1362473	69	71
1362556	63	66
1362712	25	36

Table 42

Reduction of human PLP1 RNA in transgenic mice by modified oligonucleotides

Compound ID	PLP1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1362445	22	50
1362449	43	61
1362458	27	33
1362468	33	59

Table 43

Reduction of human PLP1 RNA in transgenic mice by modified oligonucleotides

Compound ID	PLP1 RNA (% control)				
	Spinal Cord	Cortex	Cerebellum	Brain Stem	Hippocampus
PBS	100	100	100	100	100
1362928	24	49	38	25	29
1363102	65	60	70	52	36
1363410	54	74	65	47	67
1363485	27	30	39	26	16
1363486	86	98	92	71	62
1363565	54	74	39	46	43

Table 44

Reduction of human PLP1 RNA in transgenic mice by modified oligonucleotides

Compound ID	PLP1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1362500	59	100
1362517	50	91

1362602	44	45
1362641	57	70
1362749	69	85
1362784	52	93
1362805	54	63
1362842	34	43
1362892	33	41
1362987	52	63
1362996	73	115

Table 45

Reduction of human PLP1 RNA in transgenic mice by modified oligonucleotides

Compound ID	PLP1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1362649	39	42
1363866	57	43
1363013	34	49
1363146	69	57

5

Table 46

Reduction of human PLP1 RNA in transgenic mice by modified oligonucleotides

Compound ID	PLP1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1363184	68	58
1363235	29	48
1363255	63	58
1363257	50	50
1363391	69	57
1363398	41	39
1363429	70	48
1363452	81	57
1363493	80	56
1363544	53	92
1363550	79	82
1363557	49	34
1363583	93	69

Table 47

Reduction of human PLP1 RNA in transgenic mice by modified oligonucleotides

Compound ID	PLP1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1362612	50	46
1363591	31	42
1363734	35	54
1363736	49	67
1363762	33	51
1363801	50	67
1363940	24	46
1363993	64	107
1364073	31	51
1364116	29	52
1364182	35	63
1523588	5	35
1523589	37	31
1523590	17	46
1523591	42	17
1523592	43	51
1523593	8	31
1523608	25	42

5

Table 48

Reduction of human PLP1 RNA in transgenic mice by modified oligonucleotides

Compound ID	PLP1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1523601	29	35
1523602	11	16
1523603	14	35
1523604	28	35
1523605	32	34
1523606	50	31
1523607	24	29
1523609	14	28
1523610	43	41
1523611	66	40
1523612	35	30

Table 49

Reduction of human PLP1 RNA in transgenic mice by modified oligonucleotides

Compound ID	PLP1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1363627	23	63
1523584	12	39
1523586	39	55
1523587	41	53
1523594	33	47
1523595	45	41
1523596	69	71
1523597	63	81
1523598	11	37
1523599	80	78
1523600	59	75
1523613	64	78

5

Example 6: Potency of modified oligonucleotides complementary to human PLP1 in transgenic mice

Modified oligonucleotides selected from the examples above were tested in a human BAC wild type *PLP1* transgenic mouse model (described herein above).

Treatment

10 The PLP1 transgenic mice were divided into groups of 4 mice each. Each mouse received a single intracerebroventricular (ICV) bolus of modified oligonucleotide at the doses indicated in the table below. A group of 4 mice received PBS as a negative control.

RNA analysis

15 Two weeks post treatment, mice were sacrificed and RNA was extracted from spinal cord and cortical brain tissue for RTPCR analysis to measure the amount of PLP1 RNA using human primer probe sets RTS48932 (described herein above) and RTS48933 (forward sequence CCCTAACTCAGCCAACCTTAC, designated herein as SEQ ID NO: 5; reverse sequence CACCCTGTTTCTCTCCCTAAC, designated herein as SEQ ID NO: 6; probe sequence AGGGAGCGTAGAATCTGTGTAGACGA, designated herein as SEQ ID NO: 7). Results are presented as percent
20 human PLP1 RNA relative to PBS control, normalized to mouse GAPDH. GAPDH was amplified using primer probe set mGapdh_LTS00102 (described herein above).

Dose response and tissue concentration response data were analyzed using Microsoft Excel (v14.4) and GraphPad Prism software (v 8.2.0, San Diego, CA). ED₅₀ values were calculated from log transformed dose and

individual animal Plp1 mRNA levels using custom equation Motulsky: Agonist vs response – Variable slope (four parameters) $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + (10^{\log \text{EC50} / X})^{\text{HillSlope}})$, with the following constraints: bottom > 0, top = 100, HillSlope < -1 and > -2.

As shown in the table below, treatment with modified oligonucleotides resulted in dose-responsive reduction of PLP1 RNA in comparison to the PBS control.

Table 50

Reduction of human PLP1 RNA in transgenic mice by modified oligonucleotides

Compound ID	Dose (μg)	PLP1 RNA (% control) RTS48932				PLP1 RNA (% control) RTS48933			
		Spinal Cord	ED ₅₀ (μg)	Cortex	ED ₅₀ (μg)	Spinal Cord	ED ₅₀ (μg)	Cortex	ED ₅₀ (μg)
PBS	N/A	100	N/A	100	N/A	100	N/A	100	N/A
1363235	10	101	86	92	65	102	82	96	60
	30	97		70		88		68	
	100	44		39		45		41	
	300	14		15		14		16	
1523605	10	91	35	84	35	93	44	86	37
	30	55		63		57		66	
	100	39		29		42		30	
	300	17		19		17		20	
1523608	10	92	33	91	76	97	37	92	73
	30	53		65		56		66	
	100	30		44		31		48	
	300	9		14		9		15	

Example 7: Dose-dependent inhibition of human PLP1 in SK-MEL-28 cells by modified oligonucleotides

Modified oligonucleotides selected from the examples above were tested at various doses in SK-MEL-28 cells (American Type Culture Collection). Cultured SK-MEL-28 cells at a density of 20,000 cells per well were transfected using electroporation with concentrations of modified oligonucleotides as specified in the tables below. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and PLP1 RNA levels were measured by quantitative real-time RTPCR. PLP1 RNA levels were measured by quantitative real-time RTPCR using human primer-probe set RTS35092, described in Example 1 above. PLP1 RNA levels were normalized to human GAPDH, amplified using primer probe set RTS104 (forward sequence GAAGGTGAAGGTCGGAGTC, designated herein as SEQ ID NO: 8; reverse sequence GAAGATGGTGATGGGATTTTC, designated herein as SEQ ID NO: 9; probe sequence CAAGCTTCCCGTTCTCAGCC, designated herein as SEQ ID NO: 10).

Reduction of PLP1 RNA is presented in the table below as percent PLP1 RNA relative to the amount in untreated control cells (% UTC). The half maximal inhibitory concentration (IC₅₀) of each modified oligonucleotide was calculated using GraphPad Prism 6 software and is also presented in the table below. IC₅₀ values were calculated from

dose and PLP1 RNA levels by least squares fit to equation: $\log(\text{inhibitor})$ vs. normalized response -- Variable slope,
 $Y=100/(1+10^{((\text{LogIC}_{50}-X)*\text{HillSlope}))})$.

Table 51

Dose-dependent reduction of human PLP1 RNA in SK-MEL-28 cells by modified oligonucleotides

Compound No.	PLP1 RNA (% UTC)										IC ₅₀ (μM)
	5.24 nM	13.11 nM	32.77 nM	81.92 nM	205 nM	512 nM	1280 nM	3200 nM	8000 nM	20000 nM	
1363235	109	102	104	101	91	77	56	47	21	11	2.14
1523601	110	103	100	102	99	94	83	57	34	15	4.46
1523605	105	101	106	101	92	87	76	52	40	18	4.19
1523608	103	95	97	95	92	84	68	45	29	22	3.01

5

CLAIMS:

1. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 85% complementary to an equal length portion of a PLP1 nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.
2. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 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 any of the nucleobase sequences of SEQ ID NOs: 20-2155, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.
3. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising 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, or at least 20 contiguous nucleobases complementary to:
 - an equal length portion of nucleobases 9198-9222 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 13702-13766 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 14037-14062 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 16761-16800 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 17558-17602 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 17615-17667 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 17853-17883 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 18097-18160 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 18206-18237 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 18237-18340 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 18350-18387 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 18412-18469 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 18461-18506 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 18539-18579 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 18697-18727 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 18755-18793 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 18797-18819 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 18839-18862 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 18974-19021 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 19028-19080 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 19146-19173 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 19228-19253 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 19347-19393 of SEQ ID NO: 2;

- an equal length portion of nucleobases 19500-19523 of SEQ ID NO: 2; or
an equal length portion of nucleobases 19512-19534 of SEQ ID NO: 2,
wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.
4. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising 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, or at least 18 contiguous nucleobases of a sequence selected from:
- SEQ ID NOs: 1050, 1124, 2145, 2151, 2152, 2153;
SEQ ID NOs: 36, 86, 114, 164, 191, 242, 269, 426, 523, 602, 691, 780;
SEQ ID NOs: 89, 167, 245, 322, 323;
SEQ ID NOs: 720, 808, 904, 937, 1058, 1097, 1184, 1278, 1340;
SEQ ID NOs: 40, 41, 117, 118, 195, 196, 273, 274, 588, 690;
SEQ ID NOs: 42, 43, 119, 120, 197, 198, 275, 276, 373, 460, 1431, 1542, 1645, 1850, 1965, 2109;
SEQ ID NOs: 1451, 1499, 1543, 1654, 1733, 2154, 2155,
SEQ ID NOs: 200, 420, 504, 620, 646, 709, 823, 980, 1029, 1149, 1196, 1253, 1323, 1423, 1476, 1605, 1613, 1728, 1832;
SEQ ID NOs: 45, 46, 123, 124, 201, 202, 279, 280, 538, 562, 2091;
SEQ ID NOs: 48, 49, 50, 51, 52, 53, 125, 126, 127, 128, 129, 130, 131, 203, 204, 205, 206, 207, 208, 281, 282, 283, 284, 285, 286, 414, 459, 485, 503, 579, 580, 693, 724, 840, 873, 911, 1034, 1081, 1125, 1159, 1318, 1413, 1513, 1548, 1672, 1701, 1794, 1868, 1958, 2002;
SEQ ID NOs: 209, 287, 335, 439, 506, 606, 659, 1922, 2033, 2104;
SEQ ID NOs: 784, 842, 869, 978, 1082, 1131, 1218, 1250, 1320, 1453, 1529, 1538, 1616, 1712, 1821;
SEQ ID NOs: 54, 55, 132, 133, 210, 288, 419, 499, 564, 665, 764, 800, 881, 993, 1059, 1200, 1295, 1354, 1422, 1465, 1544, 1705, 1802, 2149;
SEQ ID NOs: 338, 438, 525, 604, 658, 758, 813, 887, 977, 1043, 1108, 1199, 1258, 1336, 1395, 1514, 1557, 1668, 1697, 2089;
SEQ ID NOs: 875, 934, 1047, 1110, 1229, 1243, 1373, 1438, 2146, 2147;
SEQ ID NOs: 761, 798, 890, 946, 1022, 1120, 1198, 1293, 1358, 1398, 1463;
SEQ ID NOs: 56, 134, 683, 718;
SEQ ID NOs: 1610, 1663, 1702, 1786;
SEQ ID NOs: 212, 1060, 1090, 1181, 1277, 1446, 1510, 1589, 1646, 1693, 1772, 2148;
SEQ ID NOs: 57, 586, 666, 714, 812, 914, 951, 1052, 1138, 1162, 1248, 1363, 1455;
SEQ ID NOs: 385, 416, 545, 621, 682, 1968, 2055, 2101, 2150;
SEQ ID NOs: 363, 467, 541, 2008, 2111;
SEQ ID NOs: 58, 59, 136, 213, 214, 291, 292, 383, 417, 519, 612, 671, 730, 900, 986, 1019, 1136, 1353, 1457, 1504, 1546, 2093;
SEQ ID NOs: 398, 435, 2095, 2010, 2144; or
SEQ ID NOs: 1201, 1238, 1341, 1435,

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

5. The oligomeric compound of any of claims 1-4, wherein the modified oligonucleotide has a nucleobase sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to the nucleobase sequence of SEQ ID NO: 1 or SEQ ID NO: 2 when measured across the entire nucleobase sequence of the modified oligonucleotide.
6. The oligomeric compound of any of claims 1-5, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.
7. The oligomeric compound of claim 6, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.
8. The oligomeric compound of claim 7, wherein the bicyclic sugar moiety comprises a 4'-2' bridge, wherein the 4'-2' bridge is selected from -CH₂-O-; and -CH(CH₃)-O-.
9. The oligomeric compound of any of claims 6-8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.
10. The oligomeric compound of claim 9, wherein the non-bicyclic modified sugar moiety is a 2'-MOE sugar moiety or a 2'-OMe sugar moiety.
11. The oligomeric compound of any of claims 6-10, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.
12. The oligomeric compound of claim 11, wherein the sugar surrogate is any of morpholino, modified morpholino, PNA, THP, and F-HNA.
13. The oligomeric compound of any of claims 1-6 or 9-12, wherein the modified oligonucleotide does not comprise a bicyclic sugar moiety.
14. The oligomeric compound of any of claims 1-13, wherein the modified oligonucleotide is a gapmer.
15. The oligomeric compound of any of claims 1-14, wherein the modified oligonucleotide comprises:
 - a 5'-region consisting of 1-7 linked 5'-region nucleosides;
 - a central region consisting of 6-10 linked central region nucleosides; and
 - a 3'-region consisting of 1-7 linked 3'-region nucleosides; whereineach 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'-deoxyfuranosyl sugar moiety.
16. The oligomeric compound of claim 15, wherein the modified oligonucleotide comprises:
 - 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; whereineach of the 5'-region nucleosides and each of the 3'-region nucleosides is a 2'-MOE nucleoside, and each of the central region nucleosides is a 2'-β-D-deoxynucleoside.

17. The oligomeric compound of claim 15, wherein the modified oligonucleotide comprises:
 - a 5'-region consisting of 6 linked 5'-region nucleosides;
 - a central region consisting of 10 linked central region nucleosides; and
 - a 3'-region consisting of 4 linked 3'-region nucleosides; wherein
 each of the 5'-region nucleosides and each of the 3'-region nucleosides is a 2'-MOE nucleoside, and each of the central region nucleosides is a 2'-β-D-deoxynucleoside.
18. The oligomeric compound of any of claims 1-17, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.
19. The oligomeric compound of claim 18, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.
20. The oligomeric compound of claim 18 or claim 19, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.
21. The oligomeric compound of claim 18 or claim 20 wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.
22. The oligomeric compound of any of claims 18, 20, or 21, wherein each internucleoside linkage is either a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.
23. The oligomeric compound of claim 19, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.
24. The oligomeric compound of any of claims 1-18 or 20-22, wherein the modified oligonucleotide has an internucleoside linkage motif of sooooooooooooo or sooooooooooooo; wherein,
 - s = a phosphorothioate internucleoside linkage and o = a phosphodiester internucleoside linkage.
25. The oligomeric compound of any of claims 1-24, wherein the modified oligonucleotide comprises at least one modified nucleobase.
26. The oligomeric compound of claim 25, wherein the modified nucleobase is a 5-methyl cytosine.
27. The oligomeric compound of any of claims 1-26, wherein the modified oligonucleotide consists of 12-30, 12-22, 12-20, 14-18, 14-20, 15-17, 15-25, 16-18, 16-20, 17-20, 18-20 or 18-22 linked nucleosides.
28. The oligomeric compound of any of claims 1-26, wherein the modified oligonucleotide consists of 16, 17, 18, 19, or 20 linked nucleosides.
29. The oligomeric compound of claim 28, wherein the modified oligonucleotide consists of 20 linked nucleosides.
30. The oligomeric compound of claim 28, wherein the modified oligonucleotide consists of 18 linked nucleosides.
31. An oligomeric compound comprising a modified oligonucleotide according to any of the following chemical notations:

^mC_{es}^mC_{eo}^mC_{eo}A_{eo}A_{eo}T_{ds}A_{ds}G_{ds}A_{ds}T_{ds}T_{ds}^mC_{ds}A_{ds}A_{ds}^mC_{ds}T_{eo}A_{eo}G_{es}^mC_{es}^mC_e (SEQ ID NO: 134);

$A_{es}^m C_{eo} A_{eo}^m C_{eo} A_{ds}^m C_{ds} T_{ds}^m C_{ds} T_{ds} T_{ds} A_{ds}^m C_{ds} A_{ds} A_{eo}^m C_{eo} A_{es} A_{es} A_e$ (SEQ ID NO: 411);
 $T_{es}^m C_{eo} T_{eo}^m C_{eo}^m C_{eo} A_{ds} G_{ds} A_{ds}^m C_{ds} A_{ds} T_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds} G_{eo} A_{eo} T_{es} G_{es}^m C_e$ (SEQ ID NO: 934);
 $G_{es} T_{eo} G_{eo} T_{eo} G_{eo} T_{ds} T_{ds} A_{ds} A_{ds} A_{ds} A_{ds} T_{ds} T_{ds} G_{ds}^m C_{ds} A_{eo} A_{eo} T_{es} T_{es}^m C_e$ (SEQ ID NO: 1238);
 $A_{es} T_{eo} T_{eo} G_{eo}^m C_{eo} A_{ds} A_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds} A_{ds} T_{ds} A_{ds} T_{ds}^m C_{eo} A_{eo} G_{es} A_{es} A_e$ (SEQ ID NO: 2010);
 $A_{es} T_{eo} G_{eo} T_{eo} G_{eo} A_{ds} T_{ds}^m C_{ds} T_{ds} A_{ds} T_{ds} A_{ds} T_{ds}^m C_{ds} A_{ds} G_{eo} G_{eo} A_{es} G_{es} A_e$ (SEQ ID NO: 1772); or
 $A_{es}^m C_{eo}^m C_{eo} A_{eo} G_{eo} A_{ds} G_{ds} G_{ds} G_{ds}^m C_{ds}^m C_{ds} A_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{eo} A_{eo} G_{es} G_{es} T_e$ (SEQ ID NO: 881)
 $T_{es} G_{eo} T_{eo} A_{eo} G_{eo} T_{ds} A_{ds}^m C_{ds} A_{ds} A_{ds} A_{ds} T_{ds}^m C_{ds} T_{ds} T_{ds} T_{eo}^m C_{eo}^m C_{es} T_{es} T_e$ (SEQ ID NO: 2101);
 $G_{es}^m C_{eo} A_{eo} T_{eo}^m C_{eo} A_{ds} G_{ds} A_{ds} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} A_{ds} T_{ds}^m C_{eo} T_{eo}^m C_{es} T_{es} T_e$ (SEQ ID NO: 1050);
 $^m C_{es}^m C_{eo} T_{eo}^m C_{eo}^m C_{eo} A_{ds} T_{ds} T_{ds}^m C_{ds}^m C_{ds} T_{ds} T_{ds} T_{ds} G_{ds} T_{ds} G_{eo} A_{eo}^m C_{es} T_{es} T_e$ (SEQ ID NO: 1449),

wherein:

A = an adenine nucleobase,
 $^m C$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

32. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

$T_{es} G_{eo} T_{eo} A_{eo} G_{eo} T_{ds} A_{ds}^m C_{ds} A_{ds} A_{ds} A_{ds} T_{ds}^m C_{ds} T_{ds} T_{ds} T_{eo}^m C_{eo}^m C_{es} T_{es} T_e$ (SEQ ID NO: 2101), wherein:

A = an adenine nucleobase,
 $^m C$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

33. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

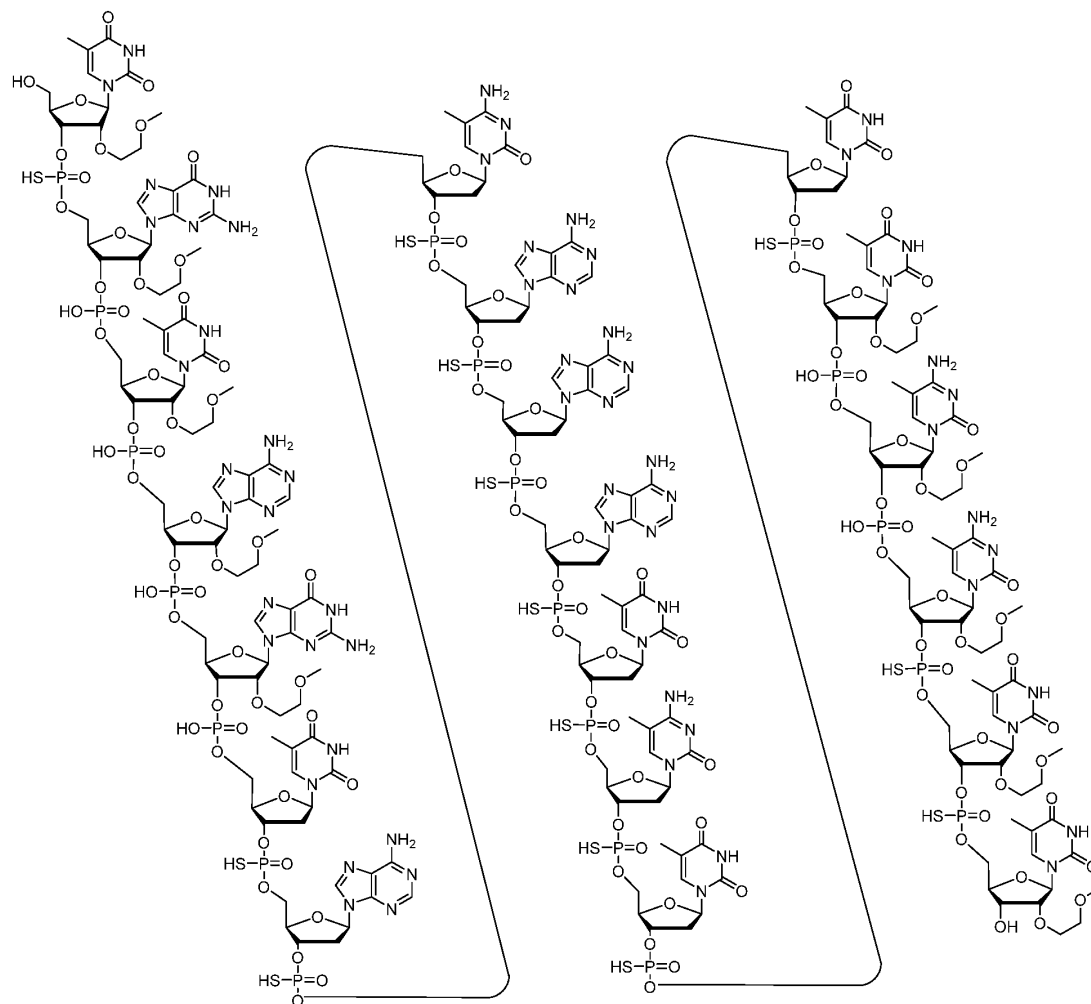
$A_{es}^m C_{eo} A_{eo} A_{eo} A_{eo} T_{eo}^m C_{ds} T_{ds} T_{ds} T_{ds}^m C_{ds}^m C_{ds} T_{ds} T_{ds}^m C_{ds} A_{ds} A_{eo} T_{es} T_{es} A_e$ (SEQ ID NO: 682), wherein:

A = an adenine nucleobase,
 $^m C$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

34. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:
 ${}^m\text{C}_{\text{es}}\text{A}_{\text{eo}}\text{G}_{\text{eo}}\text{A}_{\text{eo}}\text{T}_{\text{eo}}\text{G}_{\text{eo}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{es}}{}^m\text{C}_{\text{es}}\text{A}_{\text{e}}$ (SEQ ID NO: 1124), wherein:
 A = an adenine nucleobase,
 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribose sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.
35. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:
 ${}^m\text{C}_{\text{es}}\text{A}_{\text{eo}}\text{T}_{\text{eo}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{eo}}\text{G}_{\text{eo}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{eo}}\text{T}_{\text{es}}{}^m\text{C}_{\text{e}}$ (SEQ ID NO: 2145), wherein:
 A = an adenine nucleobase,
 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribose sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.
36. The oligomeric compound of any of claims 1-35 wherein the oligomeric compound is a singled-stranded oligomeric compound.
37. The oligomeric compound of any of claims 1-36, consisting of the modified oligonucleotide.
38. The oligomeric compound of any of claims 1-36, further comprising a conjugate group.
39. The oligomeric compound of claim 38, wherein the conjugate group comprises a conjugate moiety and a conjugate linker.
40. The oligomeric compound of claim 38, wherein the conjugate group comprises a GalNAc cluster comprising 1-3 GalNAc ligands.
41. The oligomeric compound of claim 38 or claim 39, wherein the conjugate linker consists of a single bond.
42. The oligomeric compound of and of claims 39 or claim 41, wherein the conjugate linker is cleavable.
43. The oligomeric compound of claim 39 or claim 42, wherein the conjugate linker comprises 1-3 linker-nucleosides.
44. The oligomeric compound of any of claims 38-43, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.

45. The oligomeric compound of any of claims 38-43, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.
46. The oligomeric compound of any of claims 1-36 or 38-45 further comprising a terminal group.
47. The oligomeric compound of any of claims 1-42 or 44-46, wherein the oligomeric compound does not comprise linker-nucleosides.
48. The oligomeric compound of any of claims 1-47, wherein the modified oligonucleotide of the oligomeric compound is a salt, and wherein the salt is a sodium salt or a potassium salt.
49. The oligomeric compound of any of claims 1-48, wherein the modified oligonucleotide is an RNAi compound.
50. An oligomeric duplex comprising an oligomeric compound of any of claims 1-35 or 37-49.
51. An antisense compound comprising or consisting of an oligomeric compound of any of claims 1-49 or an oligomeric duplex of claim 50.

52. A modified oligonucleotide according to the following chemical structure:

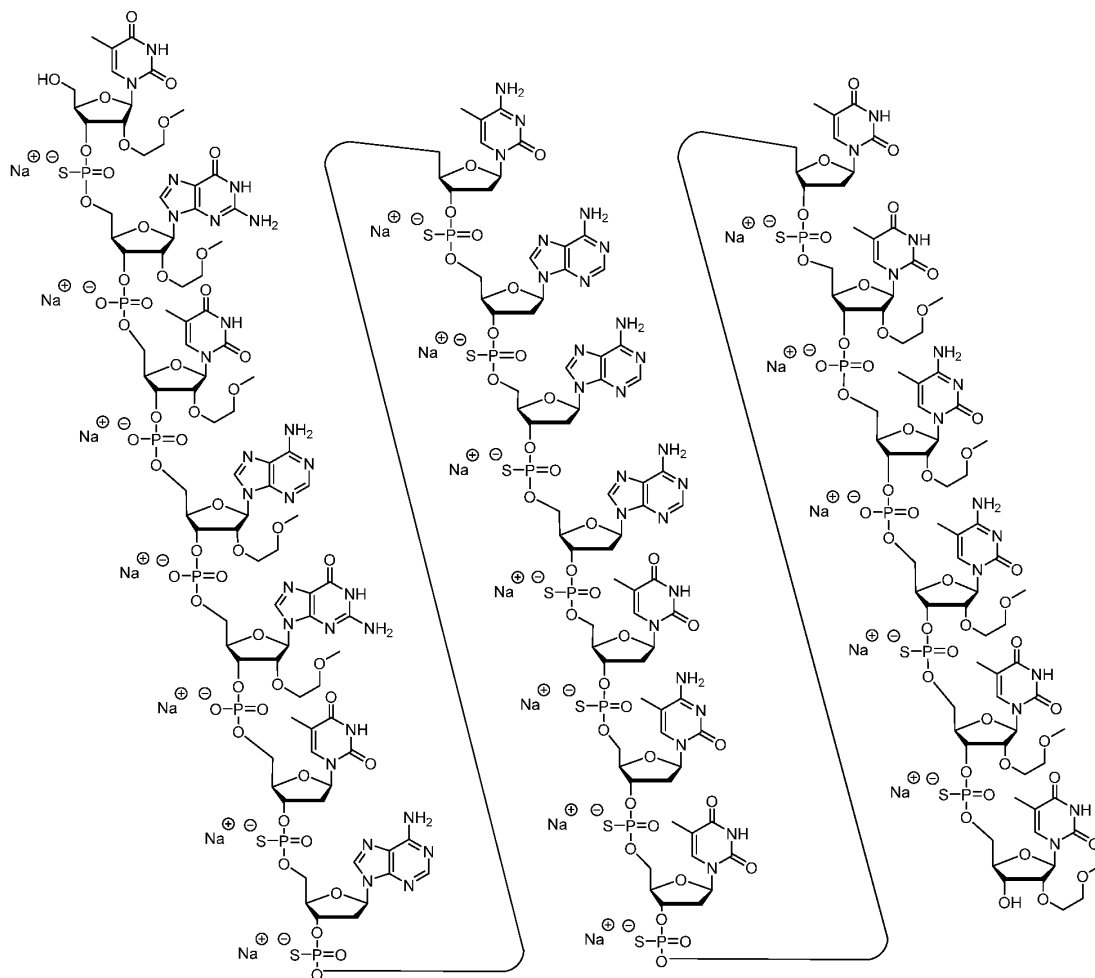


(SEQ ID NO: 2101)

or a salt thereof.

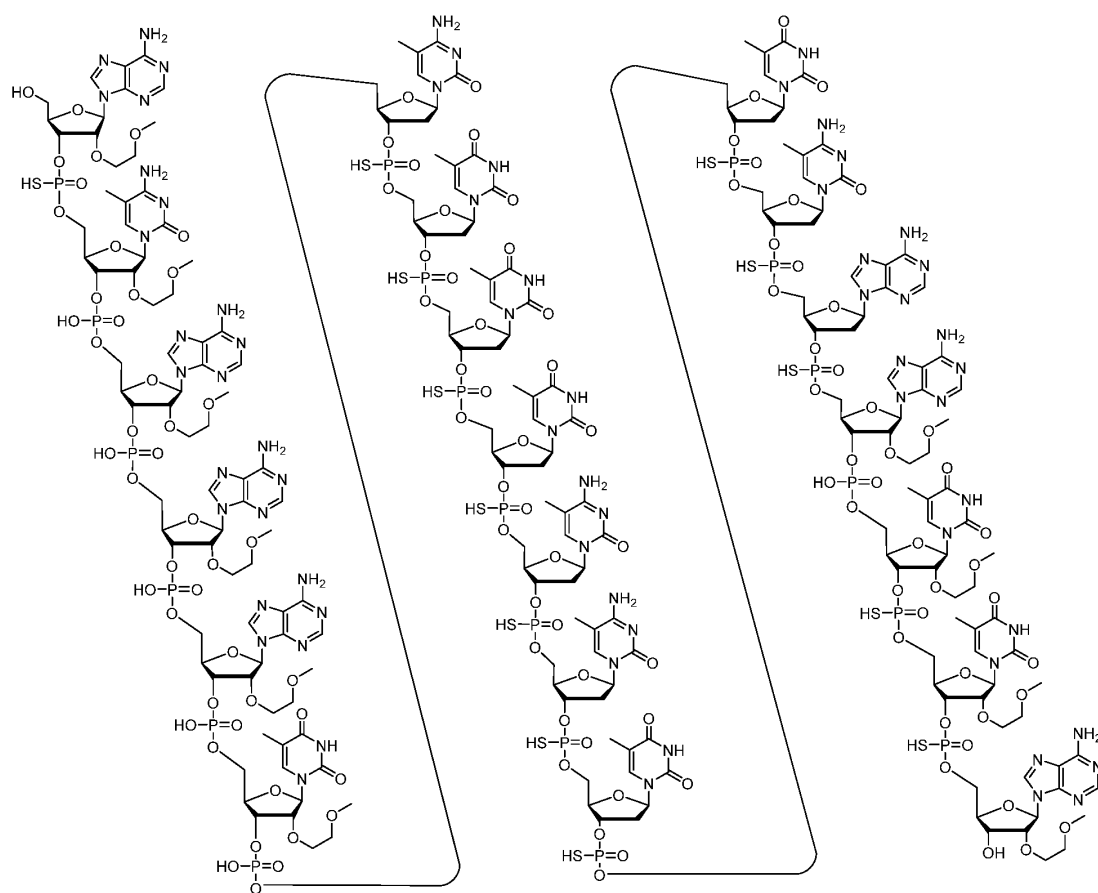
53. The modified oligonucleotide of claim 52, which is the sodium salt or the potassium salt.

54. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2101).

55. A modified oligonucleotide according to the following chemical structure:

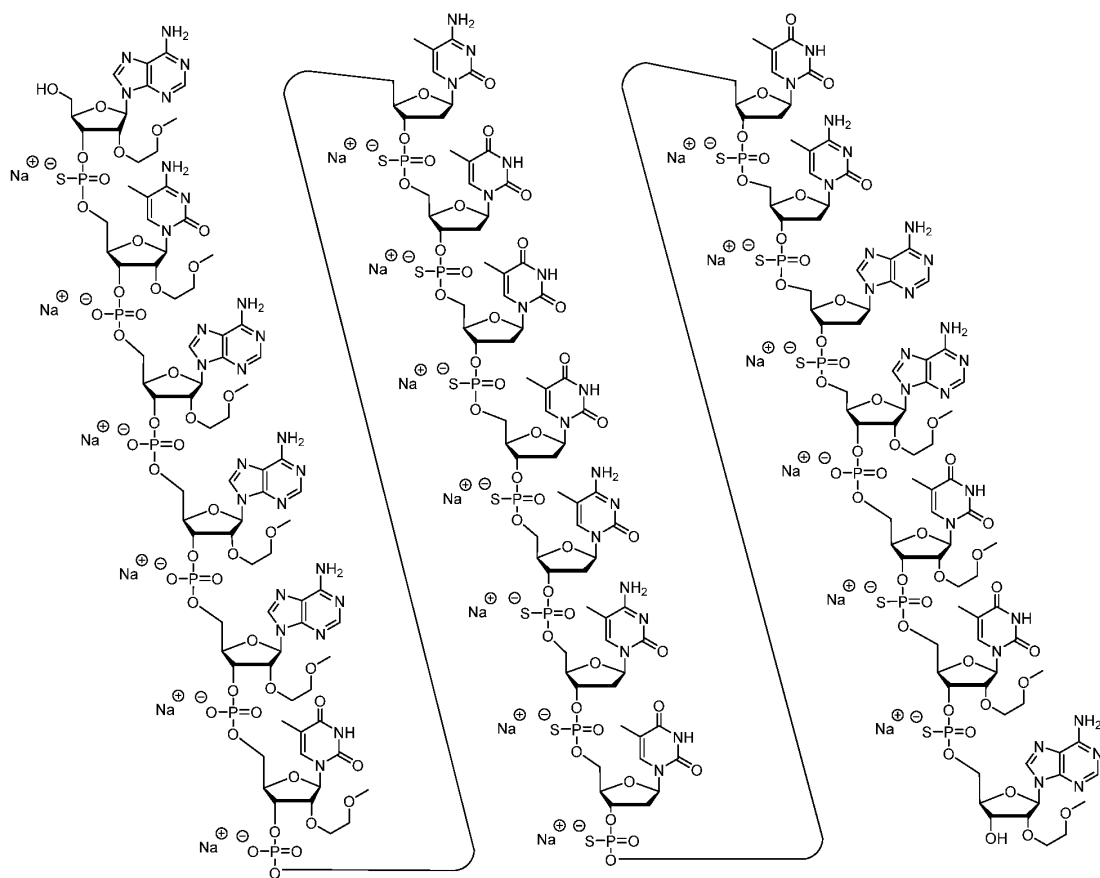


(SEQ ID NO: 682)

or a salt thereof.

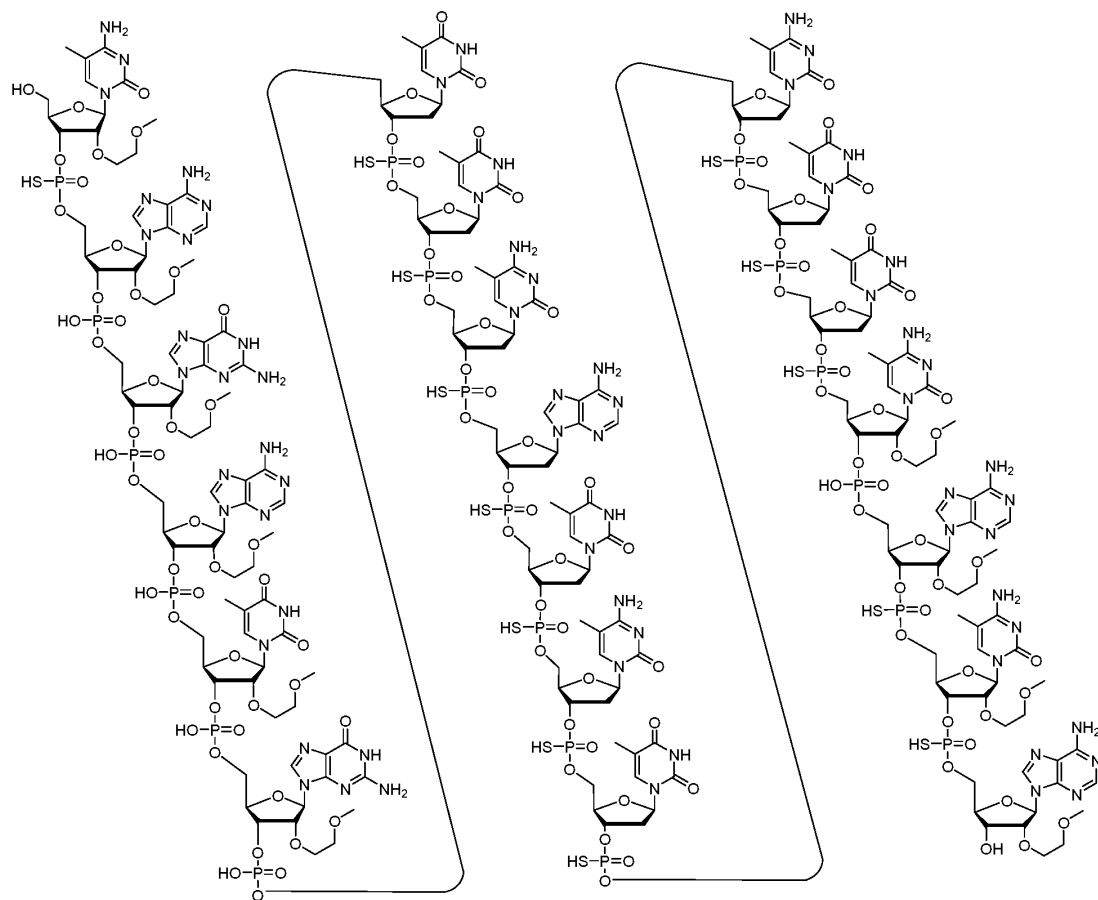
56. The modified oligonucleotide of claim 55, which is the sodium salt or the potassium salt.

57. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 682).

58. A modified oligonucleotide according to the following chemical structure:

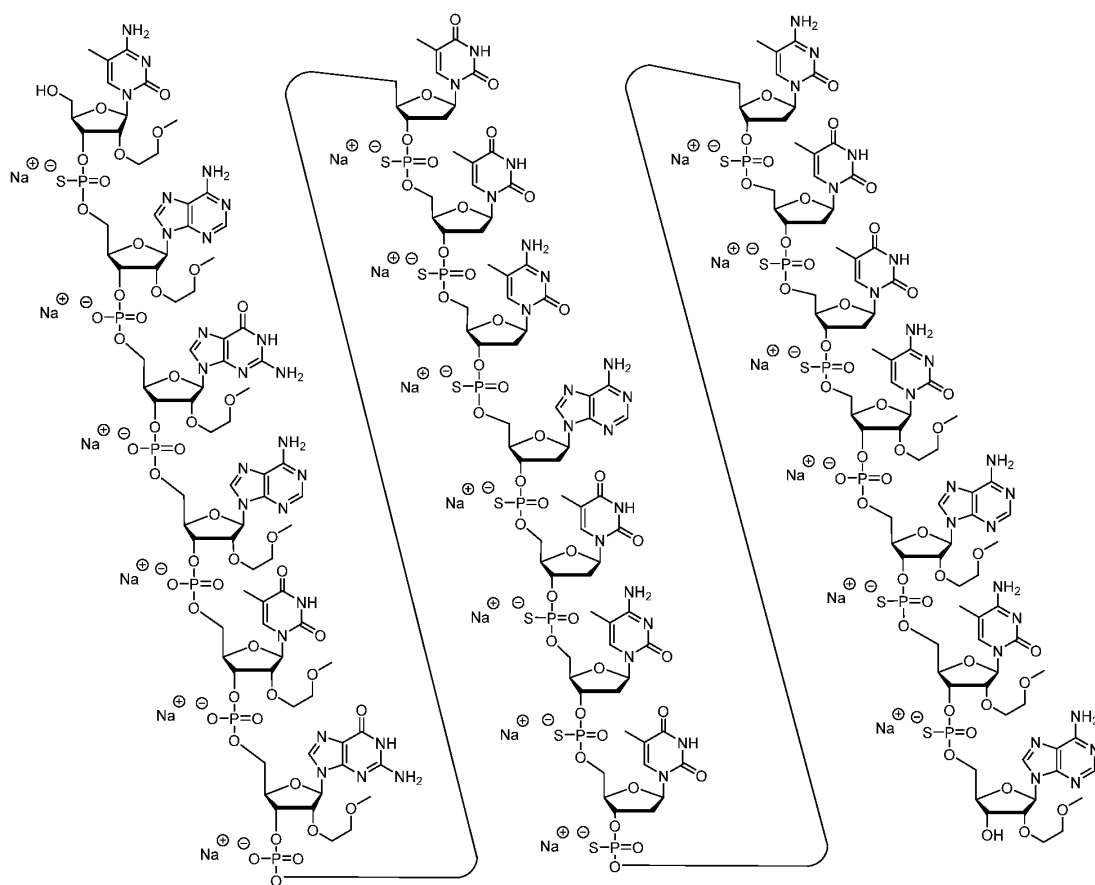


(SEQ ID NO: 1124)

or a salt thereof.

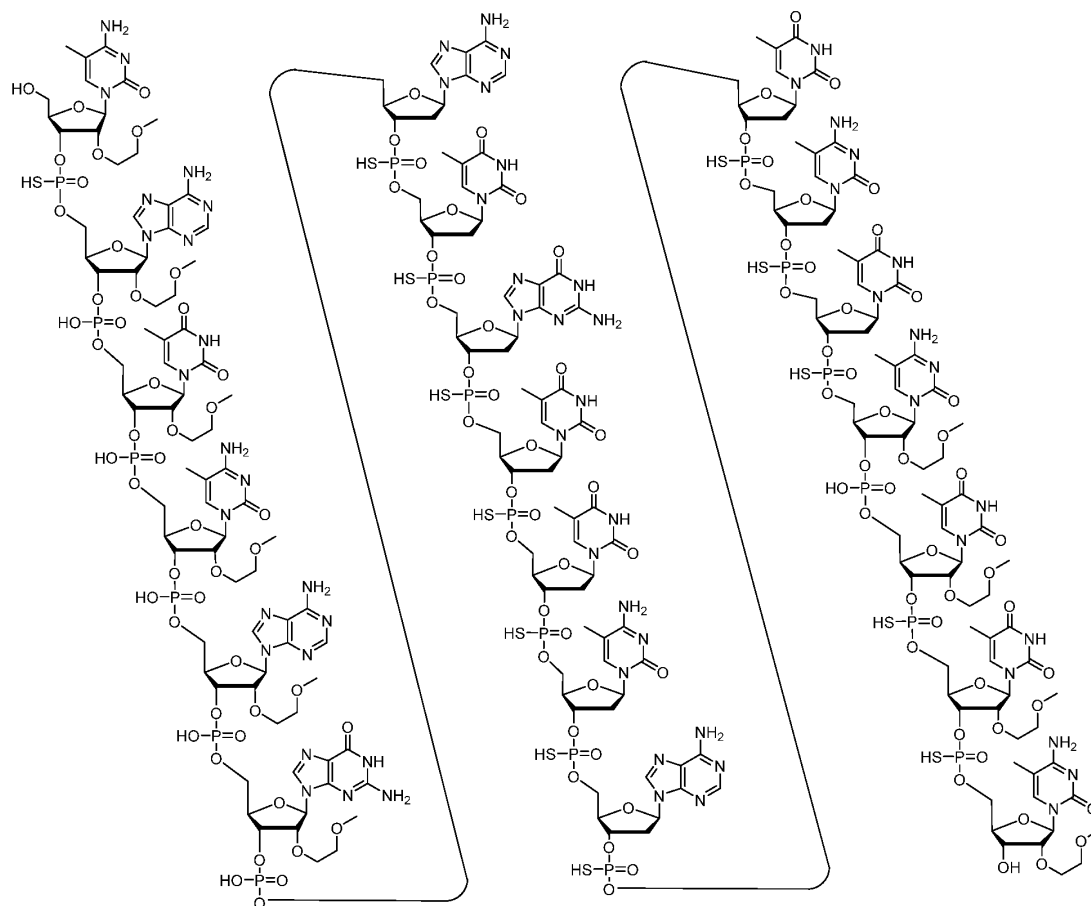
59. The modified oligonucleotide of claim 58, which is the sodium salt or the potassium salt.

60. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 1124).

61. A modified oligonucleotide according to the following chemical structure:

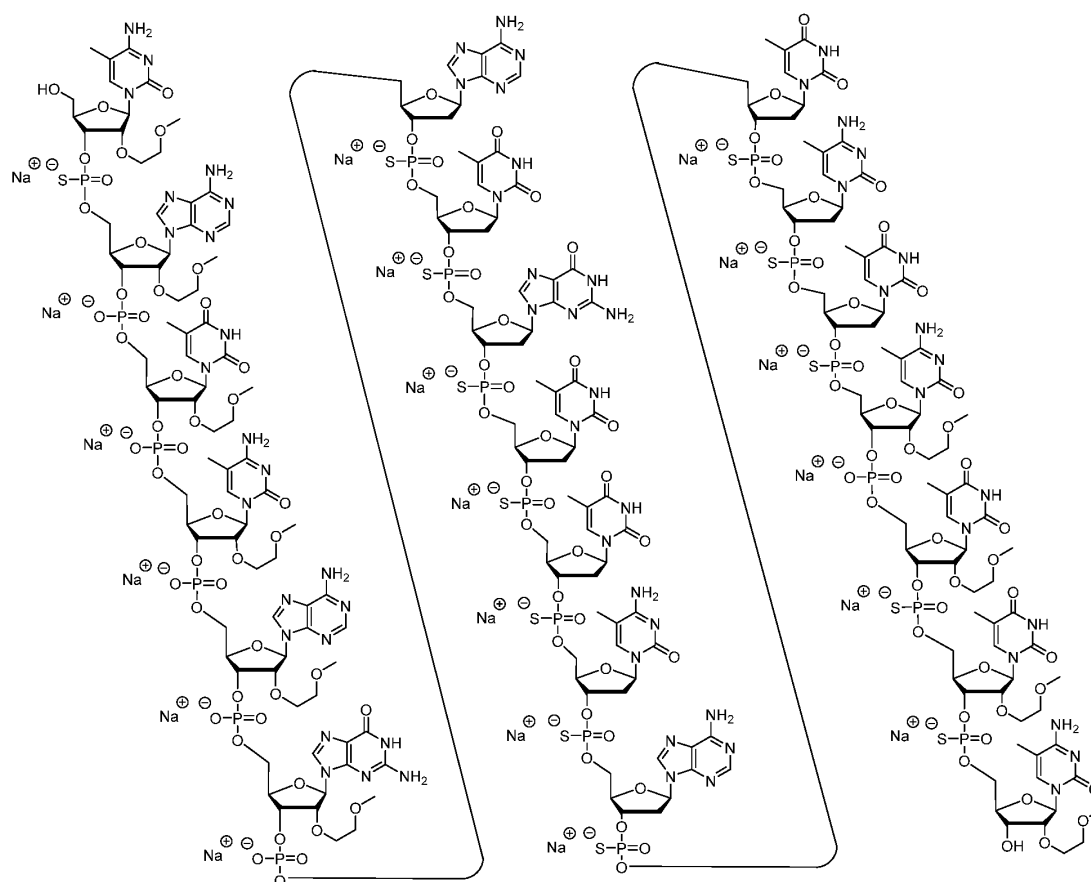


(SEQ ID NO: 2145)

or a salt thereof.

62. The modified oligonucleotide of claim 61, which is the sodium salt or the potassium salt.

63. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2145).

64. A pharmaceutical composition comprising the oligomeric compound of any of claims 1-49, the oligomeric duplex of claim 50, the antisense compound of claim 51, or the modified oligonucleotide of any of claims 52-63 and a pharmaceutically acceptable diluent or carrier.

65. The pharmaceutical composition of claim 64, comprising a pharmaceutically acceptable diluent and wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or phosphate-buffered saline (PBS).

66. The pharmaceutical composition of claim 65, wherein the pharmaceutical composition consists essentially of the oligomeric compound or the modified oligonucleotide and aCSF.

67. The pharmaceutical composition of claim 65, wherein the pharmaceutical composition consists essentially of the oligomeric compound or the modified oligonucleotide and PBS.

68. A pharmaceutical composition comprising a modified oligonucleotide of any of claims 52-63 and a pharmaceutically acceptable diluent.

69. The pharmaceutical composition of claim 68, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or phosphate-buffered saline (PBS).
70. The pharmaceutical composition of claim 69, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and aCSF.
71. The pharmaceutical composition of claim 69, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.
72. A pharmaceutical composition comprising an oligomeric compound of any of claims 32-35 and a pharmaceutically acceptable diluent.
73. The pharmaceutical composition of claim 72, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or phosphate-buffered saline (PBS).
74. The pharmaceutical composition of claim 73, wherein the pharmaceutical composition consists essentially of the oligomeric compound and aCSF.
75. The pharmaceutical composition of claim 73, wherein the pharmaceutical composition consists essentially of the oligomeric compound and PBS.
76. A chirally enriched population of modified oligonucleotides of any of claims 52-63, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.
77. The chirally enriched population of claim 76, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*Sp*) configuration.
78. The chirally enriched population of claim 76, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*Rp*) configuration.
79. The chirally enriched population of claim 76, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.
80. The chirally enriched population of claim 79, wherein the population is enriched for modified oligonucleotides having the (*Sp*) configuration at each phosphorothioate internucleoside linkage or for modified oligonucleotides having the (*Rp*) configuration at each phosphorothioate internucleoside linkage.
81. The chirally enriched population of claim 79, 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.
82. The chirally enriched population of claim 79, 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.

83. A population of modified oligonucleotides of any of claims 52-63, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.
84. A chirally enriched population of oligomeric compounds of any of claims 32-35, wherein the population is enriched for oligomeric compounds comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.
85. The chirally enriched population of claim 84, wherein the population is enriched for oligomeric compounds comprising at least one particular phosphorothioate internucleoside linkage having the (*Sp*) configuration.
86. The chirally enriched population of claim 84, wherein the population is enriched for oligomeric compounds comprising at least one particular phosphorothioate internucleoside linkage having the (*Rp*) configuration.
87. The chirally enriched population of claim 84, wherein the population is enriched for oligomeric compounds having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.
88. The chirally enriched population of claim 87, wherein the population is enriched for oligomeric compounds having the (*Sp*) configuration at each phosphorothioate internucleoside linkage or for modified oligonucleotides having the (*Rp*) configuration at each phosphorothioate internucleoside linkage.
89. The chirally enriched population of claim 87, wherein the population is enriched for oligomeric compounds having the (*Rp*) configuration at one particular phosphorothioate internucleoside linkage and the (*Sp*) configuration at each of the remaining phosphorothioate internucleoside linkages.
90. The chirally enriched population of claim 87, wherein the population is enriched for oligomeric compounds having at least 3 contiguous phosphorothioate internucleoside linkages in the *Sp*, *Sp*, and *Rp* configurations, in the 5' to 3' direction.
91. A population of oligomeric compounds of any of claims 32-35, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.
92. A pharmaceutical composition comprising the chirally enriched population of any of claims 76-82 or 84-90, the population of claim 83, or the population of claim 91 and a pharmaceutically acceptable diluent.
93. The pharmaceutical composition of claim 92, wherein the pharmaceutically acceptable diluent is artificial CSF (aCSF) or phosphate-buffered saline (PBS).
94. The pharmaceutical composition of claim 93, wherein the pharmaceutical composition consists essentially of the oligomeric compounds or the modified oligonucleotides and artificial CSF (aCSF).
95. The pharmaceutical composition of claim 93, wherein the pharmaceutical composition consists essentially of the oligomeric compounds or the modified oligonucleotides and PBS.
96. A method comprising administering to an animal the pharmaceutical composition of any of claims 64-75 or 92-95.

97. A method of treating a disease or disorder associated with PLP1, comprising administering to a subject having or at risk for developing a disease or disorder associated with PLP1 a therapeutically effective amount of a pharmaceutical composition according to any of claims 64-75 or 92-95, and thereby treating the disease or disorder associated with PLP1.
98. A method of reducing PLP1 protein in the CSF of a subject having or at risk for developing a disease or disorder associated with PLP1 a therapeutically effective amount of a pharmaceutical composition according any of claims 64-75 or 92-95, and thereby reducing PLP1 protein in the CSF.
99. The method of claim 97 or claim 98, wherein the disease or disorder associated with PLP1 is a neurodegenerative disease.
100. The method of any of claims 97-99, wherein the disease or disorder associated with PLP1 is a leukodystrophy.
101. The method of claim 100, wherein the leukodystrophy is PMD.
102. The method of claim 101, wherein the PMD is any of connatal PMD, classic PMD, transitional PMD.
103. The method of claim 101, wherein the PMD is caused by overexpression of PLP1 protein.
104. The method of claim 101, wherein the PMD is caused by multiple copies of the PLP1 gene.
105. The method of claim 101, wherein the PMD is caused by the expression of duplicate copies of the PLP1 gene.
106. The method of any of claims 100-105, wherein at least one symptom or hallmark of the leukodystrophy is ameliorated.
107. The method of claim 97 or claim 98, wherein the disease or disorder associated with PLP1 is SPG2.
108. The method of claim 107, wherein at least one symptom or hallmark of SPG2 is ameliorated.
109. The method of claim 106 or claim 108, wherein the symptom or hallmark is any of hypotonia, nystagmus, optic atrophy, respiratory distress, motor delays, cognitive dysfunction, speech dysfunction, spasticity, ataxia, seizures, choreiform movements, and death.
110. The method of any of claims 96-109 wherein administering the modified oligonucleotide reduces hypotonia, nystagmus, optic atrophy, respiratory distress, motor delays, cognitive dysfunction, speech dysfunction, spasticity, ataxia, seizures, or choreiform movements, or delays death in the subject.
111. The method of any of claims 96-110, wherein the pharmaceutical composition is administered to the central nervous system or systemically.
112. The method of claim 111, wherein the pharmaceutical composition is administered to the central nervous system and systemically.
113. The method of any of claims 96-110, wherein the pharmaceutical composition is administered any of intrathecally, systemically, subcutaneously, or intramuscularly.

114. A method of reducing PLP1 RNA in a cell comprising contacting the cell with an oligomeric compound of any of claims 1-49, an oligomeric duplex according to claim 50, an antisense compound according to claim 51, or a modified oligonucleotide of any of claims 52-63, and thereby reducing PLP1 RNA in the cell.
115. A method of reducing PLP1 protein in a cell comprising contacting the cell with an oligomeric compound of any of claims 1-49, an oligomeric duplex according to claim 50, an antisense compound according to claim 51, or a modified oligonucleotide of any of claims 52-63, and thereby reducing PLP1 protein in the cell.
116. The method of claim 114 or claim 115, wherein the cell is an oligodendrocyte or an oligodendrocyte progenitor cell.
117. The method of claim 114 or claim 115, wherein the cell is a Schwann cell or a Schwann cell progenitor.
118. The method of any of claims 114-117, wherein the cell is in an animal.
119. The method of claim 96 or claim 117, wherein the animal is human.
120. A method comprising administering to a subject a pharmaceutical composition of any of claims 68-71.
121. A method of treating a disease or disorder associated with PLP1, comprising administering to an subject having or at risk for developing a disease or disorder associated with PLP1 a therapeutically effective amount of a pharmaceutical composition according to any of claims 68-71 and thereby treating the disease or disorder associated with PLP1.
122. The method of claim 121, wherein the disease associated with PLP1 is a neurodegenerative disease.
123. The method of claim 122, wherein the neurodegenerative disease is a leukodystrophy.
124. The method of claim 123, wherein the leukodystrophy is PMD.
125. The method of claim 124, wherein the PMD is any of connatal PMD, classic PMD, transitional PMD.
126. The method of claim 124, wherein the PMD is caused by overexpression of PLP1 protein.
127. The method of claim 124, wherein the PMD is caused by multiple copies of the PLP1 gene.
128. The method of claim 124, wherein the PMD is caused by the expression of duplicate copies of the PLP1 gene.
129. The method of any of claims 122-128, wherein at least one symptom or hallmark of the neurodegenerative disease is ameliorated.
130. The method of claim 129, wherein the symptom or hallmark is any of hypotonia, nystagmus, optic atrophy, respiratory distress, motor delays, cognitive dysfunction, speech dysfunction, spasticity, ataxia, seizures, choreiform movements, and death.
131. The method of any of claims 121-130 wherein administering the pharmaceutical composition reduces hypotonia, nystagmus, optic atrophy, respiratory distress, motor delays, cognitive dysfunction, speech dysfunction, spasticity, ataxia, seizures, or choreiform movements, or delays death in the subject.
132. The method of any of claims 121-131, wherein the subject is human.

133. A method of reducing expression of PLP1 in a cell comprising contacting the cell with a modified oligonucleotide of any of claims 52-63.
134. The method of claim 134, wherein the cell is a human cell.
135. Use of an oligomeric compound any of claims 1-49, an oligomeric duplex according to claim 50, an antisense compound according to claim 51, or a modified oligonucleotide of any of claims 52-63 for reducing PLP1 expression in a cell.
136. The use of claim 135, wherein the level of PLP1 RNA in the cell is reduced.
137. The use of claim 135, wherein the level of PLP1 protein in the cell is reduced.
138. The use of any of claims 135-137, wherein the cell is an oligodendrocyte or an oligodendrocyte progenitor cell.
139. The use of any of claims 135-137, wherein the cell is a Schwann cell or a Schwann cell progenitor.