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(54) Title: MODIFIED COMPOUNDS AND USES THEREOF

(57) Abstract: The present disclosure provides oligomeric compound comprising a modified oligonucleotide having a central region comprising one or more modifications. In certain embodiments, the present disclosure provides oligomeric compounds having an improved therapeutic index or an increased maximum tolerated dose.

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MODIFIED COMPOUNDS AND USES THEREOF

Sequence Listing

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled CORE0148WOSEQ_ST25.txt created February 8, 2019 which is 368 kb in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field

The present disclosure provides oligomeric compounds comprising a modified oligonucleotide having a central region comprising one or more modifications. In certain embodiments, the present disclosure provides oligomeric compounds having an improved therapeutic index or an increased maximum tolerated dose.

Background

The principle behind antisense technology is that an antisense compound hybridizes to a target nucleic acid and modulates the amount, activity, and/or function of the target nucleic acid. For example, in certain instances, antisense compounds result in altered transcription or translation of a target. Such modulation of expression can be achieved by, for example, target RNA degradation or occupancy-based inhibition. An example of modulation of RNA target function by degradation is RNase H-based degradation of the target RNA upon hybridization with a DNA-like antisense compound. Another example of modulation of gene expression by target degradation is RNA interference (RNAi). RNAi refers to antisense-mediated gene silencing through a mechanism that utilizes the RNA-induced silencing complex (RISC). An additional example of modulation of RNA target function is by an occupancy-based mechanism such as is employed naturally by microRNA. MicroRNAs are small non-coding RNAs that regulate the expression of protein-coding RNAs. The binding of an antisense compound to a microRNA prevents that microRNA from binding to its messenger RNA targets, and thus interferes with the function of the microRNA. MicroRNA mimics can enhance native microRNA function. Certain antisense compounds alter splicing of pre-mRNA. Regardless of the specific mechanism, sequence-specificity makes antisense compounds attractive as tools for target validation and gene functionalization, as well as therapeutics to selectively modulate the expression of genes involved in the pathogenesis of disease.

Antisense technology is an effective means for modulating the expression of one or more specific gene products and can therefore prove to be uniquely useful in a number of therapeutic, diagnostic, and research applications. Chemically modified nucleosides may be incorporated into antisense compounds to enhance one or more properties, such as nuclease resistance, pharmacokinetics, or affinity for a target nucleic acid.

Summary

The present disclosure provides oligomeric compounds and methods of using oligomeric compounds that comprise a modified oligonucleotide consisting of 14-23 linked nucleosides, wherein the modified oligonucleotide comprises a gapmer consisting of a 5'-region, a central region, and a 3'-region wherein:

5 the 5'-region consists of 2-5 linked modified nucleosides, wherein each nucleoside of the 5'-region comprises a 2'-modified furanosyl sugar moiety;

the 3'-region consists of 1-5 linked modified nucleosides, wherein each nucleoside of the 3'-region comprises a 2'-modified furanosyl sugar moiety;

10 the central region consists of 7-10 linked nucleosides, where each nucleoside of the central region comprises a sugar moiety selected from an unmodified 2'- β -D-deoxyribosyl sugar moiety and a modified sugar moiety; wherein

the 3'- and 5'-most nucleosides of the central region each comprise a sugar moiety independently selected from a 2'-deoxyfuranosyl sugar moiety or a sugar surrogate; and wherein

the central region comprises:

15 at least one altered nucleotide, comprising a modified internucleoside linkage other than phosphorothioate and/or a modified nucleobase other than 5-methylcytosine and/or a modified sugar moiety; and

at least 6 nucleosides each comprising an unmodified 2'- β -D-deoxyribosyl sugar moiety.

20 In certain embodiments, oligomeric compounds are provided comprising a single conjugate group linked to the 5'-end. In certain embodiments, oligomeric compounds are provided comprising a single conjugate group linked to the 3'-end.

In certain embodiments, the oligomeric compounds provided herein have an increased maximum tolerated dose when administered to an animal compared to an otherwise identical oligomeric compound except that the otherwise identical oligomeric compound lacks the altered nucleotide in the central region.

25 In certain embodiments, the oligomeric compounds provided herein have an increased therapeutic index compared to an otherwise identical oligomeric compound except that the otherwise identical oligomeric compound lacks the altered nucleotide in the central region.

30 In certain embodiments, methods of inhibiting target RNA are provided comprising contacting one or more cells, a tissue or an animal with an oligomeric compound as provided herein wherein said oligomeric compound is complementary to a target RNA.

In certain embodiments, the cells are in a human. In certain embodiments, the target RNA is human RNA. In certain embodiments, the target is human mRNA. In certain embodiments, the target RNA is cleaved, thereby inhibiting its function.

35 In certain embodiments, in vitro methods of inhibiting gene expression are provided comprising contacting one or more cells or a tissue with an oligomeric compound as provided herein.

In certain embodiments, oligomeric compounds are provided for use in an in vivo method of inhibiting gene expression wherein the method comprises contacting one or more cells, a tissue or an animal with an oligomeric compound as provided herein.

In certain embodiments, oligomeric compounds are provided for use in medical therapy.

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Brief Description of the Drawings

Figure 1 is a SDS-PAGE gel showing the proteins eluted from a biotin-capture experiment with increasing concentrations of unlabeled modified oligonucleotides 508031, 895154, 895155, and 895156.

Figure 2 is a SDS-PAGE gel showing the proteins eluted from a biotin-capture experiment with decreasing concentrations of unlabeled modified oligonucleotides 464917, 465977, 483706, and 820685. Figure 2B shows aligned western blots for a variety of proteins at decreasing elution concentrations of 464917, 465977, 483706, and 820685.

Figure 3 is a SDS-PAGE gel showing the proteins eluted from a biotin-capture experiment with decreasing concentrations of unlabeled modified oligonucleotides 464917, 465178, 464932, and 465131.

Figure 4 is a SDS-PAGE gel showing the proteins eluted from a biotin-capture experiment with unlabeled modified oligonucleotides containing 2x MOP linkages in the central region.

Figure 5A is a SDS-PAGE gel showing proteins eluted from biotin-capture experiments with unlabeled modified oligonucleotides 464917 and 549148. Figure 5B shows aligned western blots for a variety of proteins at increasing elution concentrations of 464917 and 549148.

Detailed Description

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the embodiments, as claimed. 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.

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 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.

It is understood that the sequence set forth in each SEQ ID NO contained herein is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. 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(H) sugar moiety and a thymine base could be described as a DNA having a modified sugar (2'-OH in place of one 2'-H of DNA) or as an RNA having a modified base (thymine (methylated uracil) in place of an 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.

As used herein, “2'-deoxyfuranosyl sugar moiety” or “2'-deoxyfuranosyl sugar” means a furanosyl sugar moiety having two hydrogens at the 2'-position. 2'-deoxyfuranosyl sugar moieties may be unmodified or modified and may be substituted at positions other than the 2'-position or unsubstituted. A β-D-2'-deoxyribose sugar moiety or 2'-β-D-deoxyribose sugar moiety in the context of an oligonucleotide is an unsubstituted, unmodified 2'-deoxyfuranosyl and is found in naturally occurring deoxyribonucleic acids (DNA).

As used herein, “2'-modified” in reference to a furanosyl sugar moiety or nucleoside comprising a furanosyl sugar moiety means the furanosyl sugar moiety comprises a substituent other than H or OH at the 2'-position of the furanosyl sugar moiety. 2'-modified furanosyl sugar moieties include non-bicyclic and bicyclic sugar moieties and may comprise, but are not required to comprise, additional substituents at other positions of the furanosyl sugar moiety.

As used herein, “2'-ribo-F” indicates a 2'-fluororibose.

As used herein, “2'-substituted” in reference to a furanosyl sugar moiety or nucleoside comprising a furanosyl sugar moiety means the furanosyl sugar moiety or nucleoside comprising the furanosyl sugar moiety comprises a substituent other than H or OH at the 2'-position and is a non-bicyclic furanosyl sugar moiety. 2'-substituted furanosyl sugar moieties do not comprise additional substituents at other positions of the furanosyl

sugar moiety other than a nucleobase and/or internucleoside linkage(s) when in the context of an oligonucleotide.

As used herein, "4'-modified" in reference to a furanosyl sugar moiety or nucleoside comprising a furanosyl sugar moiety means the furanosyl sugar moiety comprises a substituent other than H at the 4'-position of the furanosyl sugar moiety. 4'-modified furanosyl sugar moieties include non-bicyclic and bicyclic sugar moieties and may but are not required to comprise additional substituents at other positions of the furanosyl sugar moiety.

As used herein, "4'-substituted" in reference to a furanosyl sugar moiety or nucleoside comprising a furanosyl sugar moiety means the furanosyl sugar moiety or nucleoside comprising the furanosyl sugar moiety comprises a substituent other than H at the 4'-position and is a non-bicyclic furanosyl sugar moiety. 4'-substituted furanosyl sugar moieties do not comprise additional substituents at other positions of the furanosyl sugar moiety other than a nucleobase and/or internucleoside linkage(s) when in the context of an oligonucleotide.

As used herein, "5'-modified" in reference to a furanosyl sugar moiety or nucleoside comprising a furanosyl sugar moiety means the furanosyl sugar moiety comprises a substituent other than H at the 5'-position of the furanosyl sugar moiety. 5'-modified furanosyl sugar moieties may but are not required to comprise additional substituents at other positions of the furanosyl sugar moiety.

As used herein, "5'-substituted" in reference to a furanosyl sugar moiety or nucleoside comprising a furanosyl sugar moiety means the furanosyl sugar moiety or nucleoside comprising the furanosyl sugar moiety comprises a substituent other than H at the 5'-position and is a non-bicyclic furanosyl sugar moiety. 5'-substituted furanosyl sugar moieties do not comprise additional substituents at other positions of the furanosyl sugar moiety other than a nucleobase and/or internucleoside linkage(s) when in the context of an oligonucleotide.

As used herein, "administration" or "administering" refers to routes of introducing a compound or composition provided herein to a subject to perform its intended function. Examples of routes of administration that can be used include, but are not limited to, administration by inhalation, subcutaneous injection, intrathecal injection, and oral administration.

As used herein, "administered concomitantly" or "co-administration" means administration of two or more compounds in any manner in which the pharmacological effects of both are manifest in the patient. Concomitant administration does not require that both compounds be administered in a single pharmaceutical composition, in the same dosage form, by the same route of administration, or at the same time. The effects of both compounds need not manifest themselves at the same time. The effects need only be overlapping for a period of time and need not be coextensive. Concomitant administration or co-administration encompasses administration in parallel, sequentially, separate, or simultaneous administration.

As used herein, “ALT” means alanine aminotransferase. As used herein, “AST” means aspartate transaminase. In certain embodiments, plasma levels of ALT and AST in a subject are measured in units per liter. As used herein, “units per liter” in the context of plasma ALT or plasma AST levels means international units per liter, the standard units for measurement of plasma ALT or plasma AST levels used by those of
5 ordinary skill in the medical arts.

As used herein, “animal” refers to a human or non-human animal, including, but not limited to, mice, rats, rabbits, dogs, cats, pigs, and non-human primates, including, but not limited to, monkeys and chimpanzees.

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
10 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 a compound comprising an antisense oligonucleotide and optionally one or more additional features, such as a conjugate group or terminal group.

As used herein, “antisense oligonucleotide” means an oligonucleotide having a nucleobase sequence
15 that is at least partially complementary to a target nucleic acid.

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

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

As used herein, a “central nervous system target” is a target RNA that is expressed in the central nervous system.

As used herein, “cEt” or “constrained ethyl” means a bicyclic sugar moiety, wherein the first ring of the bicyclic sugar moiety is a ribosyl sugar moiety, the second ring of the bicyclic sugar is formed via a bridge
30 connecting the 4'-carbon and the 2'-carbon, the bridge has the formula 4'-CH(CH₃)-O-2', and the methyl group of the bridge is in the *S* configuration. A cEt bicyclic sugar moiety is in the β-D configuration.

As used herein, a “cEt nucleoside” or “cEt nucleotide” is a nucleoside or nucleotide comprising a cEt.

As used herein, “complementary” in reference to an oligonucleotide means that at least 70% of the nucleobases of such oligonucleotide or one or more regions thereof and the nucleobases of another nucleic acid
35 or one or more regions 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. Complementary nucleobases are nucleobase pairs 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 nucleic acids need not
5 have nucleobase complementarity at each nucleoside. Rather, some mismatches are tolerated. As used herein, “fully complementary” or “100% complementary” in reference to oligonucleotides means that such oligonucleotides are complementary to another oligonucleotide or nucleic acid at each nucleoside of the oligonucleotide.

As used herein, “conjugate group” means a group of atoms that is directly or indirectly attached to an
10 oligonucleotide. Conjugate groups may comprise a conjugate moiety and a conjugate linker that attaches the conjugate moiety to the oligonucleotide.

As used herein, “conjugate linker” means 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
15 a conjugate linker.

As used herein, “contiguous” or “adjacent” in the context of an oligonucleotide refers to nucleosides, nucleobases, sugar moieties, or internucleoside linkages that are immediately adjacent to each other independent of the other moieties of the oligonucleotide. For example, “contiguous nucleobases” means nucleobases that are immediately adjacent to each other in a sequence. Moieties that are “directly linked” are
20 immediately adjacent to each other and not separated by any other type of moiety.

As used herein, “cytotoxic” or “cytotoxicity” in the context of an effect of an oligomeric compound or a parent oligomeric compound on cultured cells means an at least 2-fold increase in caspase activation following administration of 10 μM or less of the oligomeric compound or parent oligomeric compound to the cultured cells relative to cells cultured under the same conditions but that are not administered the oligomeric
25 compound or parent oligomeric compound. In certain embodiments, cytotoxicity is measured using a standard in vitro cytotoxicity assay.

As used herein, “double-stranded antisense compound” means an antisense compound comprising two oligomeric compounds that are complementary to each other and form a duplex, and wherein one of the two said oligomeric compounds comprises an antisense oligonucleotide.

As used herein, “effective amount” means the amount of compound sufficient to effectuate a desired physiological outcome in a subject in need of the compound. The effective amount may vary among subjects depending on the health and physical condition of the subject to be treated, the taxonomic group of the subjects to be treated, the formulation of the composition, assessment of the subject’s medical condition, and other relevant factors.

As used herein, “efficacy” means the ability to produce a desired effect.

As used herein, “expression” includes all the functions by which a gene’s coded information is converted into structures present and operating in a cell. Such structures include, but are not limited to, the products of transcription and translation. As used herein, “modulation of expression” means any change in amount or activity of a product of transcription or translation of a gene. Such a change may be an increase or a reduction of any amount relative to the expression level prior to the modulation.

As used herein, “gapmer” means an oligonucleotide having a central region comprising a plurality of nucleosides that support RNase H cleavage positioned between a 5’-region and a 3’-region. Herein, the nucleosides of the 5’-region and 3’-region each comprise a 2’-modified furanosyl sugar moiety, and the 3’- and 5’-most nucleosides of the central region each comprise a sugar moiety independently selected from a 2’-deoxyfuranosyl sugar moiety or a sugar surrogate. The positions of the central region refer to the order of the nucleosides of the central region and are counted starting from the 5’-end of the central region. Thus, the 5’-most nucleoside of the central region is at position 1 of the central region. The “central region” may be referred to as a “gap”, and the “5’-region” and “3’-region” may be referred to as “wings”.

As used herein, “hepatotoxic” in the context of a mouse means a plasma ALT level that is above 300 units per liter. Hepatotoxicity of an oligomeric compound or parent oligomeric compound that is administered to a mouse is determined by measuring the plasma ALT level of the mouse 24 hours to 2 weeks following at least one dose of 1-150 mg/kg of the compound.

As used herein, “hepatotoxic” in the context of a human means a plasma ALT level that is above 150 units per liter. Hepatotoxicity of an oligomeric compound or parent oligomeric compound that is administered to a human is determined by measuring the plasma ALT level of the human 24 hours to 2 weeks following at least one dose of 10-300 mg of the compound.

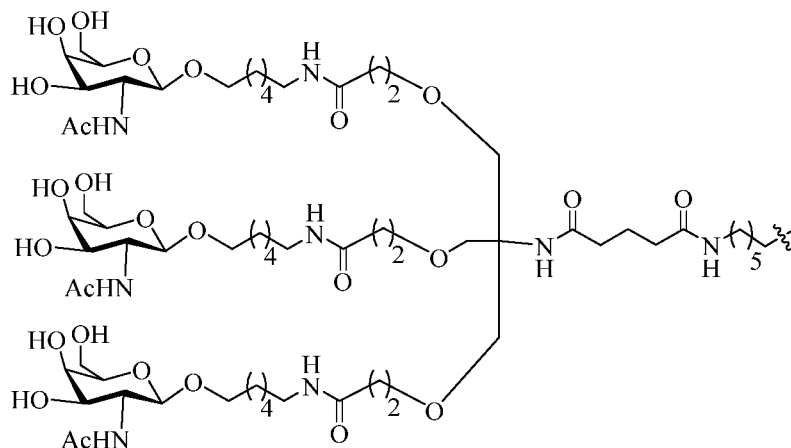
As used herein, “hybridization” means the pairing or annealing of complementary oligonucleotides and/or nucleic acids. While not limited to a particular mechanism, the most common mechanism of hybridization involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleobases.

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

As used herein, the terms “internucleoside linkage” means a group or bond that forms a covalent linkage between adjacent nucleosides in an oligonucleotide. As used herein “modified internucleoside linkage” means any internucleoside linkage other than a naturally occurring, phosphodiester internucleoside linkage. “Phosphorothioate linkage” means a modified internucleoside linkage in which one of the non-bridging oxygen atoms of a phosphodiester is replaced with a sulfur atom. Modified internucleoside linkages may or may not contain a phosphorus atom. A “neutral internucleoside linkage” is a modified internucleoside linkage that does not have a negatively charged phosphate in a buffered aqueous solution at pH=7.0.

As used herein, “abasic nucleoside” means a sugar moiety in an oligonucleotide or oligomeric compound that is not directly connected to a nucleobase. In certain embodiments, an abasic nucleoside is adjacent to one or two nucleosides in an oligonucleotide.

As used herein, “LICA-1” is a conjugate group that is represented by the formula:



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 sugar” or “non-bicyclic sugar moiety” means a sugar moiety that comprises fewer than 2 rings. Substituents of modified, non-bicyclic sugar moieties do not form a bridge between two atoms of the sugar moiety to form a second ring.

As used herein, “linked nucleosides” are nucleosides that are connected in a continuous sequence (*i.e.* no additional nucleosides are present between those that are linked).

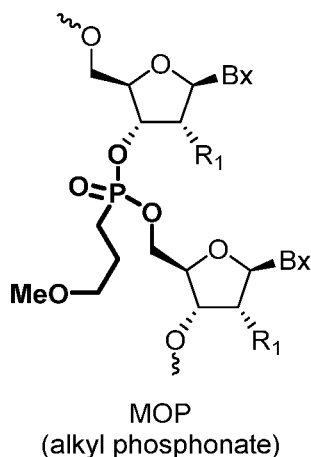
As used herein, “liver target” is a target RNA expressed in the liver wherein modulation of the expression of the target RNA in the liver is desired for therapeutic benefit. In certain embodiments, a liver target is expressed in tissues other than the liver as well as in the liver. As used herein, modulation of the expression of a target RNA that is “not a liver target” is desired in a tissue that is not the liver for therapeutic benefit. In certain embodiments, a target RNA that is not a liver target is expressed in the liver and is modulated by an oligomeric compound in therapy.

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 oligomeric compound are aligned.

As used herein, “modulating” refers to changing or adjusting a feature in a cell, tissue, organ or organism.

As used herein, “MOE” means methoxyethyl. “2’-MOE” or “2’-O-methoxyethyl” means a 2’-OCH₂CH₂OCH₃ group at the 2’-position of a furanosyl ring. In certain embodiments, the 2’-OCH₂CH₂OCH₃ group is in place of the 2’-OH group of a ribosyl ring or in place of a 2’-H in a 2’-deoxyribosyl ring.

As used herein, “MOP” or “methoxypropyl internucleoside linkage” means the alkyl phosphonate internucleoside bond shown below:



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

As used herein, “naturally occurring” means found in nature.

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 capable of pairing with at least one unmodified nucleobase. A universal base is a nucleobase that can pair with any one of the five unmodified nucleobases. 5-methylcytosine (mC) is one example of a modified nucleobase.

As used herein, “nucleobase sequence” means the order of contiguous nucleobases in a nucleic acid or oligonucleotide independent of any sugar moiety or internucleoside linkage modification.

As used herein, “nucleoside” means a moiety 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.

As used herein, “oligomeric compound” means a compound consisting of an oligonucleotide and optionally one or more additional features, such as a conjugate group or terminal group.

As used herein, “oligonucleotide” means a strand of linked nucleosides connected via internucleoside linkages, wherein each nucleoside and internucleoside linkage may be modified or unmodified. Unless otherwise indicated, oligonucleotides consist of 8-50 linked nucleosides. As used herein, “modified oligonucleotide” means an oligonucleotide, wherein at least one nucleoside or internucleoside linkage is modified. As used herein, “unmodified oligonucleotide” means an oligonucleotide that does not comprise any nucleoside modifications or internucleoside modifications.

As used herein, “parent oligomeric compound” in the context of an oligomeric compound comprising at least one modification in the central region other than phosphorothioate or 5-methylcytosine means an oligomeric compound that is identical to the oligomeric compound comprising the at least one modification in the central region except that the parent oligomeric compound does not comprise at least one modified internucleoside linkage other than phosphorothioate and/or at least one modified nucleoside comprising a modified nucleobase other than 5-methylcytosine and/or a modified sugar moiety. A parent oligomeric compound and its counterpart oligomeric compound comprising at least one modification in the central region have identical nucleobase sequences or differ in nucleobase sequence only due to inclusion of a modified nucleobase other than 5-methylcytosine in the oligomeric compound comprising at least one modification in the central region.

As used herein, “pharmaceutically acceptable carrier or diluent” means any substance suitable for use in administering to an animal. Certain such carriers enable pharmaceutical compositions to be formulated as, for example, liquids, powders, or suspensions that can be aerosolized or otherwise dispersed for inhalation by a subject. In certain embodiments, a pharmaceutically acceptable carrier or diluent is sterile water; sterile saline; or sterile buffer solution.

As used herein “pharmaceutically acceptable salts” means physiologically and pharmaceutically acceptable salts of compounds, such as oligomeric compounds, *i.e.*, salts that retain the desired biological activity of the 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 antisense compound and an aqueous solution.

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 oligonucleotides that act through RNase H.

As used herein, the term “single-stranded” in reference to an antisense compound means such a compound consisting of one oligomeric compound that is not paired with a second oligomeric compound to form a duplex. “Self-complementary” in reference to an oligonucleotide means an oligonucleotide that at least partially hybridizes to itself. A compound consisting of one oligomeric compound, wherein the oligonucleotide of the oligomeric compound is self-complementary, is a single-stranded compound. A single-stranded antisense or oligomeric compound may be capable of binding to a complementary oligomeric compound to form a duplex, in which case the compound would no longer be single-stranded.

As used herein, “standard cell assay” means any of the assays described in Examples 1-9, and

reasonable variations thereof.

As used herein, “standard in vitro activity assay” means a procedure, as described in Example 1 herein, wherein expression is measured by RT-PCR in cultured cells expressing the target RNA following administration of an oligomeric compound to the cultured cells.

5 As used herein, “standard in vitro cytotoxicity assay” means a procedure, as described in Example 8 herein, wherein activation of caspases 3 and 7 is measured in cultured 3T3-L1 cells following administration of an oligomeric compound to the cells.

As used herein, “standard in vivo experiment” means the procedure described in Example 10 and reasonable variations thereof.

10 As used herein, “stereorandom” in the context of a compound or moiety comprising a chiral center means the chiral center has a random stereochemical configuration. For example, in a population of molecules of identical formula 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
15 a chiral center is considered random when it is the result of a synthetic method that is not designed to control the stereochemical configuration.

As used herein, “subject” means a human or non-human animal selected for treatment or therapy.

As used herein, “sugar moiety” means an unmodified sugar moiety or a modified sugar moiety. As used herein, “unmodified sugar moiety” means a β -D-ribosyl moiety, as found in naturally occurring RNA, or
20 a β -D-2'-deoxyribosyl sugar moiety as found in naturally occurring DNA. As used herein, “modified sugar moiety” or “modified sugar” means a sugar surrogate or a furanosyl sugar moiety other than a β -D-ribosyl or a β -D-2'-deoxyribosyl. Modified furanosyl sugar moieties may be modified or substituted at a certain position(s) of the sugar moiety, or unsubstituted, and they may or may not have a stereoconfiguration other than β -D-ribosyl. Modified furanosyl sugar moieties include bicyclic sugars and non-bicyclic sugars. As used herein,
25 “sugar surrogate” means a modified sugar moiety that does not comprise a furanosyl or tetrahydrofuranyl ring (is not a “furanosyl sugar moiety”) and 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 nucleic acids.

30 As used herein, “susceptible” in the context of a disease, disorder, condition, or symptom such as degeneration, damage, or elevated apoptosis means that a subject has a higher risk than the average risk for the general population for the disease, disorder, condition, or symptom.

As used herein, “target nucleic acid,” “target RNA,” “target RNA transcript” and “nucleic acid target” mean a nucleic acid that an oligomeric compound, such as an antisense compound, is designed to affect. In
35 certain embodiments, an oligomeric compound comprises an oligonucleotide having a nucleobase sequence

that is complementary to more than one RNA, only one of which is the target RNA of the oligomeric compound. In certain embodiments, the target RNA is an RNA present in the species to which an oligomeric compound is administered. As used herein, a “liver target” is a target RNA that is expressed in the liver, and modulation of expression of the target RNA in the liver provides a therapeutic effect. As used herein a “central nervous system target” is a target RNA that is expressed in the central nervous system, and modulation of expression of the target RNA in the central nervous system provides a therapeutic effect.

The present disclosure provides certain individual cellular, tissue, or organ targets. For example, a “macrophage target” or a “liver target.” For each such individual target, modulation of the expression of the target RNA in the individual cellular, tissue, or organ target is desired for therapeutic benefit. In certain embodiments, modulation of the target RNA in an individual cellular, tissue, or organ target provides a therapeutic effect. In certain embodiments, a cellular, tissue, or organ target is expressed in tissues other than in a particular type of cell, tissue, or organ as well as being expressed in a particular type of cell, tissue, or organ. For example, certain target RNAs may be expressed in both a macrophage and a hepatocyte.

As used herein, “therapeutically effective amount” means an amount of a compound, pharmaceutical agent, or composition that provides a therapeutic benefit to a subject.

As used herein, “treat” refers to administering a compound or pharmaceutical composition to an animal in order to effect an alteration or improvement of a disease, disorder, or condition in the animal.

As used herein, “maximum tolerated dose” means the highest dose of a compound that does not cause unacceptable side effects. In certain embodiments, the maximum tolerated dose is the highest dose of a modified oligonucleotide that does not cause an ALT elevation of three times the upper limit of normal as measured by a standard assay, e.g. the assay of Example 12 or Example 1. In certain embodiments, the maximum tolerated dose is the highest dose of a modified oligonucleotide that does not cause caspase elevation of greater than 30,000 RLU as measured by a standard assay, e.g. the assay of Example 13, Example 8, or Example 4.

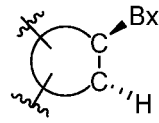
As used herein, “DNA isomer” means a nucleoside that comprises a modified sugar moiety that is a stereoisomer of β -D-2'-deoxyribosyl. As used herein, a “DNA isomer” does not include β -D-2'-deoxyribosyl nucleosides. Seven such isomers of 2'- β -D-deoxyxylosyl exist: 2'- β -D-deoxyxylosyl (β -D-XNA), 2'- α -D-deoxyribosyl (α -D-DNA), 2'- α -L-deoxyribosyl (α -L-DNA), 2'- β -L-deoxyribosyl (β -L-DNA), 2'- α -D-deoxyxylosyl (α -L-XNA), 1, 2'- α -L-deoxyxylosyl (α -L-XNA), 2'- β -L-deoxyxylosyl (β -L-XNA). In certain embodiments, a DNA isomer is 2'- α -D-deoxyribosyl, 2'- α -L-deoxyribosyl, 2'- β -L-deoxyribosyl, or 2'- β -D-deoxyxylosyl sugar moiety. As used herein, “DNA isomer” does not include any nonfuranosyl sugar moieties.

As used herein, “DNA nucleoside” means a nucleoside comprising a 2'-H(H) β -D-2'-deoxyribosyl sugar moiety, as found in naturally-occurring DNA. A “DNA nucleoside” may comprise a modified

nucleobase or a uracil nucleobase. A DNA nucleoside may be linked to adjacent nucleosides through unmodified phosphodiester internucleoside linkages or through modified internucleoside linkages.

As used herein, a “2’-modified DNA isomer” means a nucleoside that comprises a modified sugar moiety that is selected from 2’-β-D-deoxyxylosyl (β-D-XNA), 2’-α-D-deoxyribosyl (α-D-DNA), 2’-α-L-deoxyribosyl (α-L-DNA), 2’-β-L-deoxyribosyl (β-L-DNA), 2’-α-D-deoxyxylosyl (α-L-XNA), 1, 2’-α-L-deoxyxylosyl (α-L-XNA), 2’-β-L-deoxyxylosyl (β-L-XNA), and that further comprises a 2’-substituent. In certain embodiments, the 2’-substituent is fluoro, alkoxy, or C₁-C₁₀ alkyl.

As used herein, “DNA mimic” means a nucleoside other than a DNA nucleoside wherein the nucleobase is directly linked to a carbon atom of a ring bound to a second carbon atom within the ring, wherein the second carbon atom comprises a bond to at least one hydrogen atom, wherein the nucleobase and at least one hydrogen atom are trans to one another relative to the bond between the two carbon atoms. In

certain embodiments, a DNA mimic comprises a structure represented by the formula: , wherein Bx is a heterocyclic base moiety, the ring contains 5-7 members, and the ring is attached at two positions to a hydroxyl, a phosphate, an internucleoside linking group, or a conjugate linker.

As used herein, a “standard RNase H cleavage assay” is an assay wherein a heteroduplex of the modified oligonucleotide and a complementary strand of unmodified RNA are incubated with each other to form a heteroduplex, and are then incubated with RNase H1 for specified time points before being analyzed on a polyacrylamide gel.

As used herein, a modified nucleoside “supports RNase H cleavage” when incorporated into an oligonucleotide if RNase H cleavage of the complementary RNA is observed within two nucleobases of the modified nucleoside in a standard RNase H cleavage assay.

As used herein, “therapeutic index” means a comparison of the amount of a compound that causes a therapeutic effect to the amount that causes toxicity. Compounds having a high therapeutic index have strong efficacy and low toxicity. In certain embodiments, increasing the therapeutic index of a compound increases the amount of the compound that can be safely administered. In certain embodiments, therapeutic index is the ratio of the amount of modulation of a target nucleic acid by a modified oligonucleotide compared to ALT elevation, wherein the ALT elevation is measured by a standard assay, e.g. the assay of Example 12 or Example 1. In certain embodiments, therapeutic index is the ratio of the amount of modulation of a target nucleic acid by a modified oligonucleotide compared to caspase elevation, wherein the caspase elevation is measured by a standard assay, e.g. the assay of Example 13, Example 8, or Example 4.

As used herein, an “altered nucleotide” is a nucleotide that comprises one or more modifications relative to a nucleotide comprising a 2’-β-D-deoxyribosyl sugar moiety, a nucleobase selected from adenine (A), thymine (T), cytosine (C), 5-methyl cytosine (mC), uracil (U), or guanine (G), and a 5’ to 3’ internucleoside linkage selected from phosphodiester or stereorandom phosphorothioate. In certain embodiments, the altered

nucleotide is an altered nucleoside attached to a phosphorothioate or phosphodiester internucleoside linkage. In certain embodiments, the altered nucleotide comprises a 2'-modified sugar moiety, or is a "2'-altered nucleotide". In certain embodiments, the altered nucleotide comprises a modified internucleoside linking group, and is a "linkage-altered nucleotide". Herein, a linkage-altered nucleotide comprises an internucleoside
 5 linking group other than phosphodiester or phosphorothioate attached to the 3' carbon of the sugar moiety, or the equivalent position for a sugar surrogate. The nucleotide on the 5'-end of an internucleoside linking group other than phosphodiester or phosphorothioate is not an "altered nucleotide", as used herein.

Certain embodiments are described in the numbered embodiments below:

1. An oligomeric compound comprising a modified oligonucleotide consisting of 14-23 linked nucleosides,
 10 wherein the modified oligonucleotide comprises a gapmer consisting of a 5'-region, a central region, and a 3'-region wherein:
 - the 5'-region consists of 2-5 linked modified nucleosides, wherein each nucleoside of the 5'-region comprises a 2'-modified furanosyl sugar moiety;
 - the 3'-region consists of 1-5 linked modified nucleosides, wherein each nucleoside of the 3'-region
 15 comprises a 2'-modified furanosyl sugar moiety;
 - the central region consists of 7-10 linked nucleosides, where each nucleoside of the central region comprises a sugar moiety selected from an unmodified 2'-β-D-deoxyribosyl sugar moiety and a modified sugar moiety; wherein
 - the 3'- and 5'-most nucleosides of the central region each comprise a sugar moiety independently
 20 selected from a 2'-deoxyfuranosyl sugar moiety or a sugar surrogate; and wherein
 - the central region comprises:
 - at least one modified internucleoside linkage other than phosphorothioate and/or at least one modified nucleoside comprising a modified nucleobase other than 5-methylcytosine and/or a modified sugar moiety; and
 - 25 at least 6 nucleosides each comprising an unmodified 2'-β-D-deoxyribosyl sugar moiety.
2. The oligomeric compound of embodiment 1, wherein the 5'-region consists of 2-4 linked nucleosides.
3. The oligomeric compound of embodiment 1, wherein the 5'-region consists of 2 linked nucleosides.
4. The oligomeric compound of embodiment 1, wherein the 5'-region consists of 3 linked nucleosides.
5. The oligomeric compound of embodiment 1, wherein the 5'-region consists of 4 linked nucleosides.
- 30 6. The oligomeric compound of embodiment 1, wherein the 5'-region consists of 5 linked nucleosides.
7. The oligomeric compound of any of embodiments 1-6, wherein each nucleoside of the 5'-region comprises a 2'-modified ribosyl sugar moiety.
8. The oligomeric compound of any of embodiments 1-7, wherein at least one nucleoside of the 5'-region comprises a bicyclic furanosyl sugar moiety.

9. The oligomeric compound of any of embodiments 1-8, wherein each nucleoside of the 5'-region comprises a bicyclic furanosyl sugar moiety.
10. The oligomeric compound of any of embodiments 1-8, wherein at least one nucleoside of the 5'-region comprises a non-bicyclic sugar moiety.
- 5 11. The oligomeric compound of embodiment 10, wherein the non-bicyclic sugar moiety of the at least one nucleoside of the 5'-region is a 2'-substituted ribosyl sugar moiety.
12. The oligomeric compound of any of embodiments 1-7 or 10-11, wherein each nucleoside of the 5'-region comprises a non-bicyclic sugar moiety.
13. The oligomeric compound of embodiment 12, wherein each nucleoside of the 5'-region comprises a 2'-
10 substituted ribosyl sugar moiety.
14. The oligomeric compound of any of embodiments 1-7, wherein each nucleoside of the 5'-region comprises a 2'-modified furanosyl sugar moiety independently selected from a bicyclic sugar moiety and a non-bicyclic sugar moiety, 2'-substituted ribosyl sugar moiety.
15. The oligomeric compound of any of embodiments 8-11 or 14, wherein each bicyclic sugar moiety of the
15 5'-region is selected from among cEt, LNA, and ENA.
16. The oligomeric compound of any of embodiments 10-14, wherein each nonbicyclic sugar moiety of the 5'-region has a 2'-substituent selected from among 2'-MOE, 2'-OMe, and 2'-NMA.
17. The oligomeric compound of any of embodiments 1-16, wherein none of the nucleosides of the 5'-region comprise a sugar moiety having a 2'-F substituent.
- 20 18. The oligomeric compound of any of embodiments 1-17, wherein each nucleobase of the 5'-region is independently selected from among thymine, uracil, guanine, cytosine, 5-methylcytosine, and adenine.
19. The oligomeric compound of any of embodiments 1-18, wherein each internucleoside linkage of the 5'-region is selected from among phosphodiester and phosphorothioate internucleoside linkages.
20. The oligomeric compound of any of embodiments 1-19, wherein the 3'-region consists of 2-4 linked
25 nucleosides.
21. The oligomeric compound of any of embodiments 1-19, wherein the 3'-region consists of 1 nucleoside.
22. The oligomeric compound of any of embodiments 1-19, wherein the 3'-region consists of 2 linked nucleosides.
23. The oligomeric compound of any of embodiments 1-19, wherein the 3'-region consists of 3 linked
30 nucleosides.
24. The oligomeric compound of any of embodiments 1-19, wherein the 3'-region consists of 4 linked nucleosides.
25. The oligomeric compound of any of embodiments 1-19, wherein the 3'-region consists of 5 linked nucleosides.

26. The oligomeric compound of any of embodiments 1-25, wherein each nucleoside of the 3'-region comprises a 2'-modified ribosyl sugar moiety.
27. The oligomeric compound of any of embodiments 1-26, wherein at least one nucleoside of the 3'-region comprises a bicyclic furanosyl sugar moiety.
- 5 28. The oligomeric compound of any of embodiments 1-27, wherein each nucleoside of the 3'-region comprises a bicyclic furanosyl sugar moiety.
29. The oligomeric compound of any of embodiments 1-27, wherein at least one nucleoside of the 3'-region comprises a non-bicyclic sugar moiety.
30. The oligomeric compound of embodiment 29, wherein the non-bicyclic sugar moiety of the at least one
10 nucleoside of the 3'-region is a 2'-substituted ribosyl sugar moiety.
31. The oligomeric compound of any of embodiments 1-26 or 29-30, wherein each nucleoside of the 3'-region comprises a non-bicyclic sugar moiety.
32. The oligomeric compound of embodiment 31, wherein each nucleoside of the 3'-region comprises a 2'-substituted ribosyl sugar moiety.
- 15 33. The oligomeric compound of any of embodiments 1-26, wherein each nucleoside of the 3'-region comprises a 2'-modified furanosyl sugar moiety independently selected from a bicyclic sugar moiety and a non-bicyclic sugar moiety, 2'-substituted ribosyl sugar moiety.
34. The oligomeric compound of any of embodiments 27-30 or 33, wherein each bicyclic sugar moiety of the 3'-region is selected from among cEt, LNA, and ENA.
- 20 35. The oligomeric compound of any of embodiments 29-33, wherein each nonbicyclic sugar moiety of the 3'-region has a 2'-substituent selected from among 2'-MOE, 2'-OMe, and 2'-NMA.
36. The oligomeric compound of any of embodiments 1-35, wherein none of the nucleosides of the 3'-region comprise a sugar moiety having a 2'-F substituent.
37. The oligomeric compound of any of embodiments 1-36, wherein each nucleobase of the 3'-region is
25 independently selected from among thymine, uracil, guanine, cytosine, 5-methylcytosine, and adenine.
38. The oligomeric compound of any of embodiments 1-37, wherein each internucleoside linkage of the 3'-region is selected from among phosphodiester and phosphorothioate internucleoside linkages.
39. The oligomeric compound of any of embodiments 1-38, wherein the central region consists of 7 linked nucleosides.
- 30 40. The oligomeric compound of any of embodiments 1-38, wherein the central region consists of 8 linked nucleosides.
41. The oligomeric compound of any of embodiments 1-38, wherein the central region consists of 9 linked nucleosides.
42. The oligomeric compound of any of embodiments 1-38, wherein the central region consists of 10 linked
35 nucleosides.

43. The oligomeric compound of any of embodiments 1-42, wherein each of the two internucleoside linkages connecting the central region to the 5'-region and 3'-region are independently selected from among phosphodiester and phosphorothioate internucleoside linkages.
44. The oligomeric compound of any of embodiments 1-43, wherein the modified oligonucleotide consists of
5 the gapmer.
45. The oligomeric compound of any of embodiments 1-43, comprising a conjugate group.
46. The oligomeric compound of any of embodiments 1-43 or 45, wherein the modified oligonucleotide comprises 1-3 linker nucleosides.
47. The oligomeric compound of embodiment 46, wherein the linker nucleosides are linked to the 5'-end or
10 the 3'-end of the gapmer.
48. The oligomeric compound of any of embodiments 45-47, wherein the conjugate group comprises GalNAc.
49. The oligomeric compound of any of embodiments 45-47, comprising LICA-1.
50. The oligomeric compound of any of embodiments 1-49, wherein the central region comprises one, and no more than one, modified sugar moiety.
- 15 51. The oligomeric compound of embodiment 50, wherein the each internucleoside linkage within the central region is selected from among phosphodiester and phosphorothioate internucleoside linkages.
52. The oligomeric compound of any of embodiments 50-51, wherein each nucleobase of the central region is independently selected from among thymine, uracil, guanine, cytosine, 5-methylcytosine, and adenine.
53. The oligomeric compound of any of embodiments 1-50 or 52, wherein the central region comprises one,
20 and no more than one, modified internucleoside linkage other than phosphorothioate.
54. The oligomeric compound of embodiment 53, wherein the modified internucleoside linkage other than phosphorothioate contains phosphorus.
55. The oligomeric compound of any of embodiments 53-54, wherein the modified internucleoside linkage other than phosphorothioate is a neutral internucleoside linkage.
- 25 56. The oligomeric compound of any of embodiments 1-50 or 52, wherein the central region comprises two, and no more than two, modified internucleoside linkages other than phosphorothioate.
57. The oligomeric compound of embodiment 56, wherein the two modified internucleoside linkages other than phosphorothioate each contain phosphorus.
58. The oligomeric compound of any of embodiments 56-57, wherein at least one of the modified
30 internucleoside linkages other than phosphorothioate is a neutral internucleoside linkage.
59. The oligomeric compound of any of embodiments 56-57, wherein the two modified internucleoside linkages other than phosphorothioate are neutral internucleoside linkages.
60. The oligomeric compound of any of embodiments 1-51 or 53-59, wherein the central region comprises one, and no more than one, modified nucleobase other than 5-methylcytosine.

61. The oligomeric compound of any of embodiments 1-60, wherein each of the unmodified sugar moieties of the central region are 2'- β -D-deoxyribosyl sugar moieties.
62. The oligomeric compound of any of embodiments 50-61, wherein the one modified sugar moiety of the central region is at one of positions 2-9 of the central region.
- 5 63. The oligomeric compound of any of embodiments 50-61, wherein the one modified sugar moiety of the central region is at one of positions 1-6 of the central region.
64. The oligomeric compound of any of embodiments 50-61, wherein the one modified sugar moiety of the central region is at one of positions 1-4 of the central region.
65. The oligomeric compound of any of embodiments 50-61, wherein the one modified sugar moiety of the central region is at one of positions 2-4 of the central region.
- 10 66. The oligomeric compound of any of embodiments 50-61, wherein the one modified sugar moiety of the central region is at one of positions 3-4 of the central region.
67. The oligomeric compound of any of embodiments 50-66, wherein the one modified sugar moiety of the central region is a sugar surrogate, a bicyclic furanosyl sugar moiety, a non-bicyclic 2'-modified furanosyl sugar moiety, a non-bicyclic 4'-modified furanosyl sugar moiety, a non-bicyclic 5'-modified furanosyl sugar moiety, or a modified 2'-deoxyfuranosyl sugar moiety.
- 15 68. The oligomeric compound of embodiment 67, wherein the one modified sugar moiety of the central region is a bicyclic ribosyl sugar moiety, a non-bicyclic 2'-modified ribosyl sugar moiety, a non-bicyclic 4'-modified 2'-deoxyribosyl sugar moiety, a non-bicyclic 5'-modified 2'-deoxyribosyl sugar moiety, or a modified 2'-deoxyfuranosyl sugar moiety.
- 20 69. The oligomeric compound of embodiment 68, wherein the one modified sugar moiety of the central region is a bicyclic ribosyl sugar moiety, a non-bicyclic 2'-substituted ribosyl sugar moiety, a non-bicyclic 4'-substituted 2'-deoxyribosyl sugar moiety, a non-bicyclic 5'-substituted 2'-deoxyribosyl sugar moiety, or a modified, unsubstituted 2'-deoxyfuranosyl sugar moiety.
- 25 70. The oligomeric compound of any of embodiments 67-69, wherein the one modified sugar moiety of the central region is a 2'-substituted ribosyl sugar moiety.
71. The oligomeric compound of embodiment 70, wherein the 2'-substituted ribosyl sugar moiety is a 2'-F, 2'-MOE, or 2'-O-methyl substituted sugar moiety.
72. The oligomeric compound of any of embodiments 67-69, wherein the one modified sugar moiety of the central region is a 4'-alkyl substituted 2'-deoxyribosyl sugar moiety.
- 30 73. The oligomeric compound of embodiment 72, wherein the 4'-alkyl substituted ribosyl sugar moiety is a 4'-methyl substituted 2'-deoxyribosyl sugar moiety.
74. The oligomeric compound of any of embodiments 67-69, wherein the one modified sugar moiety of the central region is a 5'-alkyl substituted 2'-deoxyribosyl sugar moiety.

75. The oligomeric compound of embodiment 74, wherein the 5'-alkyl substituted ribosyl sugar moiety is a 5'-methyl, 5'-ethyl, or 5'-allyl substituted 2'-deoxyribosyl sugar moiety.
76. The oligomeric compound of any of embodiments 67-69, wherein the one modified sugar moiety of the central region is a modified, unsubstituted 2'-deoxyfuranosyl sugar moiety.
- 5 77. The oligomeric compound of embodiment 76, wherein the modified, unsubstituted 2'-deoxyfuranosyl sugar moiety is an unsubstituted α -D-2'-deoxyribosyl, α -L-2'-deoxyribosyl, β -L-2'-deoxyribosyl, or β -D-2'-deoxyxylosyl sugar moiety.
78. The oligomeric compound of any of embodiments 67-69, wherein the one modified sugar moiety of the central region is a bicyclic ribosyl sugar moiety.
- 10 79. The oligomeric compound of embodiment 78, wherein the bicyclic ribosyl sugar moiety is cEt, LNA, or ENA.
80. The oligomeric compound of any of embodiments 67-69, wherein the one modified sugar moiety of the central region is a morpholino, cEt, 2'-F, 2'-O-Methyl, 2'-MOE, 4'-Methyl, 5'-Methyl, 5'-allyl, 5'-ethyl, β -L-2'-deoxyribosyl, α -D-2'-deoxyribosyl, β -D-2'-deoxyxylosyl, or α -L-2'-deoxyribosyl sugar moiety.
- 15 81. The oligomeric compound of embodiment 62, wherein the one modified sugar moiety of the central region is a 2'-O-Methyl substituted ribosyl, unsubstituted α -D-2'-deoxyribosyl, unsubstituted α -L-2'-deoxyribosyl, or unsubstituted β -L-2'-deoxyribosyl sugar moiety.
82. The oligomeric compound of embodiment 81, wherein the one modified sugar moiety of the central region is a 2'-O-Methyl substituted ribosyl or unsubstituted β -L-2'-deoxyribosyl sugar moiety.
- 20 83. The oligomeric compound of embodiment 63, wherein the one modified sugar moiety of the central region is a morpholino, 2'-O-Methyl substituted ribosyl, unsubstituted α -D-2'-deoxyribosyl, or unsubstituted β -L-2'-deoxyribosyl sugar moiety sugar moiety.
84. The oligomeric compound of embodiment 64, wherein the one modified sugar moiety of the central region is a morpholino, unsubstituted α -D-2'-deoxyribosyl, or unsubstituted β -L-2'-deoxyribosyl sugar moiety
- 25 sugar moiety.
85. The oligomeric compound of embodiment 65, wherein the one modified sugar moiety of the central region is a 2'-F substituted ribosyl, 2'-MOE substituted ribosyl, 2'-O-Methyl substituted ribosyl, 5'-(S)-Methyl substituted 2'-deoxyribosyl, 5'-allyl substituted 2'-deoxyribosyl, unsubstituted α -D-2'-deoxyribosyl, or cEt bicyclic sugar moiety.
- 30 86. The oligomeric compound of embodiment 85, wherein the one modified sugar moiety of the central region is a 2'-MOE substituted ribosyl, 2'-O-Methyl substituted ribosyl, or 5'-allyl substituted 2'-deoxyribosyl sugar moiety.
87. The oligomeric compound of embodiment 85 or 86, wherein the 5'-allyl substituted ribosyl sugar moiety is stereorandom at the 5'-position of the modified sugar moiety.

88. The oligomeric compound of embodiment 66, wherein the one modified sugar moiety of the central region is a 2'-F substituted ribosyl, 2'-MOE substituted ribosyl, 2'-O-Methyl substituted ribosyl, 4'-Methyl substituted 2'-deoxyribosyl, 5'-(*S*)-Methyl substituted 2'-deoxyribosyl, 5'-(*R*)-Methyl substituted 2'-deoxyribosyl, 5'-stereorandom Methyl substituted 2'-deoxyribosyl, 5'-(*S*)-Ethyl substituted 2'-deoxyribosyl, 5'-(*R*)-Ethyl substituted 2'-deoxyribosyl, 5'-stereorandom Ethyl 2'-deoxyribosyl, 5'-(*S*)-Allyl substituted 2'-deoxyribosyl, 5'-(*R*)-Allyl substituted 2'-deoxyribosyl, 5'-stereorandom allyl substituted 2'-deoxyribosyl, unsubstituted α -D-2'-deoxyribosyl, unsubstituted α -L-2'-deoxyribosyl, unsubstituted β -L-2'-deoxyribosyl, cEt, or morpholino sugar moiety.
89. The oligomeric compound of embodiment 88, wherein the one modified sugar moiety of the central region is a 2'-F substituted ribosyl, 2'-MOE substituted ribosyl, 2'-O-Methyl substituted ribosyl, 4'-Methyl substituted 2'-deoxyribosyl, 5'-(*R*)-Methyl substituted 2'-deoxyribosyl, 5'-(*S*)-Ethyl substituted 2'-deoxyribosyl, 5'-(*R*)-Ethyl substituted 2'-deoxyribosyl, 5'-(*S*)-Allyl substituted 2'-deoxyribosyl, 5'-(*R*)-Allyl substituted 2'-deoxyribosyl, 5'-stereorandom allyl substituted 2'-deoxyribosyl, unsubstituted β -L-2'-deoxyribosyl, cEt, or morpholino sugar moiety.
90. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is at position 1 of the central region.
91. The oligomeric compound of embodiment 90, wherein the one modified sugar moiety of the central region is a morpholino, unsubstituted β -L-2'-deoxyribosyl, or unsubstituted α -D-2'-deoxyribosyl sugar moiety.
92. The oligomeric compound of embodiment 90, wherein the one modified sugar moiety of the central region is a morpholino or unsubstituted α -D-2'-deoxyribosyl sugar moiety.
93. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is at position 2 of the central region.
94. The oligomeric compound of embodiment 93, wherein the one modified sugar moiety of the central region is a 2'-F substituted ribosyl, 2'-MOE substituted ribosyl, 2'-O-Methyl substituted ribosyl, 5'-(*S*)-Methyl substituted 2'-deoxyribosyl, 5'-Allyl substituted 2'-deoxyribosyl, unsubstituted α -D-2'-deoxyribosyl, or cEt sugar moiety.
95. The oligomeric compound of embodiment 93, wherein the one modified sugar moiety of the central region is a 2'-MOE substituted ribosyl, 2'-O-Methyl substituted ribosyl, 5'-(*S*)-Methyl substituted 2'-deoxyribosyl, 5'-Allyl substituted 2'-deoxyribosyl, or unsubstituted α -D-2'-deoxyribosyl sugar moiety.
96. The oligomeric compound of embodiment 94 or 95, wherein the 5'-allyl substituted 2'-deoxyribosyl sugar moiety is stereorandom at the 5'-position of the modified sugar moiety.
97. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is at position 3 of the central region.
98. The oligomeric compound of embodiment 97, wherein the one modified sugar moiety of the central region is a 2'-F substituted ribosyl, 2'-MOE substituted ribosyl, 2'-O-Methyl substituted ribosyl, 4'-Methyl

substituted 2'-deoxyribosyl, 5'-(*R*)-Methyl substituted 2'-deoxyribosyl, 5'-(*S*)-Methyl substituted 2'-deoxyribosyl, 5'-(*S*)-Ethyl substituted 2'-deoxyribosyl, 5'-(*R*)-Ethyl substituted 2'-deoxyribosyl, 5'-(*S*)-Allyl substituted 2'-deoxyribosyl, 5'-(*R*)-Allyl substituted 2'-deoxyribosyl, 5'-stereorandom allyl substituted 2'-deoxyribosyl, unsubstituted β -L-2'-deoxyribosyl, unsubstituted β -D-2'-deoxyxylosyl, unsubstituted α -L-2'-deoxyribosyl, unsubstituted α -D-2'-deoxyribosyl, cEt, or morpholino sugar moiety.

99. The oligomeric compound of embodiment 97, wherein the one modified sugar moiety of the central region is a 2'-F substituted ribosyl, 2'-MOE substituted ribosyl, 2'-O-Methyl substituted ribosyl, 4'-Methyl substituted 2'-deoxyribosyl, 5'-(*R*)-Methyl substituted 2'-deoxyribosyl, 5'-(*S*)-Ethyl substituted 2'-deoxyribosyl, 5'-(*R*)-Ethyl substituted 2'-deoxyribosyl, 5'-(*S*)-Allyl substituted 2'-deoxyribosyl, 5'-(*R*)-Allyl substituted 2'-deoxyribosyl, 5'-stereorandom allyl substituted 2'-deoxyribosyl, unsubstituted β -L-2'-deoxyribosyl, unsubstituted β -D-2'-deoxyxylosyl, cEt, or morpholino sugar moiety.

100. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is at position 4 of the central region.

101. The oligomeric compound of embodiment 100, wherein the one modified sugar moiety of the central region is a 2'-F substituted ribosyl, 2'-MOE substituted ribosyl, 2'-O-Methyl substituted ribosyl, 4'-Methyl substituted 2'-deoxyribosyl, 5'-(*R*)-Methyl substituted 2'-deoxyribosyl, 5'-(*S*)-Methyl substituted 2'-deoxyribosyl, 5'-(*S*)-Ethyl substituted 2'-deoxyribosyl, 5'-(*R*)-Ethyl substituted 2'-deoxyribosyl, 5'-(*S*)-Allyl substituted 2'-deoxyribosyl, 5'-(*R*)-Allyl substituted 2'-deoxyribosyl, 5'-stereorandom allyl substituted 2'-deoxyribosyl, unsubstituted β -L-2'-deoxyribosyl, unsubstituted α -L-2'-deoxyribosyl, unsubstituted α -D-2'-deoxyribosyl, cEt, or morpholino sugar moiety.

102. The oligomeric compound of embodiment 100, wherein the one modified sugar moiety of the central region is a 2'-F substituted ribosyl, 2'-MOE substituted ribosyl, 2'-O-Methyl substituted ribosyl, 4'-Methyl substituted 2'-deoxyribosyl, 5'-(*R*)-Methyl substituted 2'-deoxyribosyl, 5'-(*S*)-Ethyl substituted 2'-deoxyribosyl, 5'-(*R*)-Ethyl substituted 2'-deoxyribosyl, 5'-(*S*)-Allyl substituted 2'-deoxyribosyl, 5'-(*R*)-Allyl substituted 2'-deoxyribosyl, 5'-stereorandom allyl substituted 2'-deoxyribosyl, unsubstituted β -L-2'-deoxyribosyl, unsubstituted α -L-2'-deoxyribosyl, unsubstituted α -D-2'-deoxyribosyl, cEt, or morpholino sugar moiety.

103. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is at position 5 of the central region.

104. The oligomeric compound of embodiment 103, wherein the one modified sugar moiety of the central region is a 2'-O-Methyl substituted ribosyl or unsubstituted β -L-2'-deoxyribosyl sugar moiety.

105. The oligomeric compound of embodiment 103, wherein the one modified sugar moiety of the central region is an unsubstituted β -L-2'-deoxyribosyl sugar moiety.

106. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is at position 6 of the central region.

107. The oligomeric compound of embodiment 106, wherein the one modified sugar moiety of the central region is a 2'-O-Methyl substituted ribosyl, unsubstituted β -L-2'-deoxyribosyl, unsubstituted α -D-2'-deoxyribosyl, or morpholino sugar moiety.
108. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is at position 7 of the central region.
109. The oligomeric compound of embodiment 108, wherein the one modified sugar moiety of the central region is a 2'-O-Methyl substituted ribosyl, unsubstituted β -L-2'-deoxyribosyl, or unsubstituted α -D-2'-deoxyribosyl sugar moiety.
110. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is at position 8 of the central region.
111. The oligomeric compound of embodiment 110, wherein the one modified sugar moiety of the central region is a 2'-O-Methyl substituted ribosyl, unsubstituted β -L-2'-deoxyribosyl, or unsubstituted α -D-2'-deoxyribosyl sugar moiety.
112. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is at position 9 of the central region.
113. The oligomeric compound of embodiment 112, wherein the one modified sugar moiety of the central region is a 2'-O-Methyl substituted ribosyl or unsubstituted β -L-2'-deoxyribosyl sugar moiety.
114. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is at position 10 of the central region.
115. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a morpholino modified sugar moiety at position 1 of the central region.
116. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 1 of the central region.
117. The oligomeric compound of embodiment 116, wherein the one modified sugar moiety of the central region is an unsubstituted β -L-2'-deoxyribosyl sugar moiety at position 1 of the central region.
118. The oligomeric compound of embodiment 116, wherein the one modified sugar moiety of the central region is an unsubstituted α -D-2'-deoxyribosyl sugar moiety
119. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 2'-substituted ribosyl sugar moiety at position 2 of the central region.
120. The oligomeric compound of embodiment 119, wherein the 2'-substituted ribosyl sugar moiety at position 2 of the central region is a 2'-F ribosyl sugar moiety.
121. The oligomeric compound of embodiment 119, wherein the 2'-substituted ribosyl sugar moiety at position 2 of the central region is a 2'-MOE ribosyl sugar moiety.

122. The oligomeric compound of embodiment 119, wherein the 2'-substituted ribosyl sugar moiety at position 2 of the central region is a 2'-O-methyl ribosyl sugar moiety.
123. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 2 of the central region.
124. The oligomeric compound of embodiment 123, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 2 of the central region is a 5'-(S)Me 2'-deoxyribosyl sugar moiety.
125. The oligomeric compound of embodiment 123, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 2 of the central region is a 5'-allyl 2'-deoxyribosyl sugar moiety.
126. The oligomeric compound of embodiment 125, wherein the 5'-allyl 2'-deoxyribosyl sugar moiety is stereorandom at the 5'-position of the 5'-allyl 2'-deoxyribosyl sugar moiety.
127. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 2 of the central region.
128. The oligomeric compound of embodiment 127, wherein the modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 2 of the central region is a α -D-2'-deoxyribosyl modified sugar moiety.
129. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a cEt or LNA sugar moiety at position 2 of the central region.
130. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 2'-substituted ribosyl sugar moiety at position 3 of the central region.
131. The oligomeric compound of embodiment 130, wherein the 2'-substituted ribosyl sugar moiety at position 3 of the central region is a 2'-F ribosyl sugar moiety.
132. The oligomeric compound of embodiment 130, wherein the 2'-substituted ribosyl sugar moiety at position 3 of the central region is a 2'-MOE ribosyl sugar moiety.
133. The oligomeric compound of embodiment 130, wherein the 2'-substituted ribosyl sugar moiety at position 3 of the central region is a 2'-O-methyl ribosyl sugar moiety.
134. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 4'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 3 of the central region.
135. The oligomeric compound of embodiment 134, wherein the 4'-substituted 2'-deoxyribosyl sugar moiety at position 3 of the central region is a 4'-methyl 2'-deoxyribosyl sugar moiety.
136. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 3 of the central region.

137. The oligomeric compound of embodiment 136, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 3 of the central region is a 5'-(*R*)-methyl 2'-deoxyribosyl sugar moiety.
138. The oligomeric compound of embodiment 136, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 3 of the central region is a 5'-(*S*)-methyl 2'-deoxyribosyl sugar moiety.
- 5 139. The oligomeric compound of embodiment 136, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 3 of the central region is a 5'-stereorandom methyl 2'-deoxyribosyl sugar moiety.
140. The oligomeric compound of embodiment 136, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 3 of the central region is a 5'-(*R*)-ethyl 2'-deoxyribosyl sugar moiety.
141. The oligomeric compound of embodiment 136, wherein the 5'-alkyl substituted 2'-deoxyribosyl
10 sugar moiety at position 3 of the central region is a 5'-(*S*)-ethyl 2'-deoxyribosyl sugar moiety.
142. The oligomeric compound of embodiment 136, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 3 of the central region is a 5'-stereorandom ethyl 2'-deoxyribosyl sugar moiety.
143. The oligomeric compound of embodiment 136, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 3 of the central region is a 5'-(*R*)-allyl 2'-deoxyribosyl sugar moiety.
- 15 144. The oligomeric compound of embodiment 136, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 3 of the central region is a 5'-(*S*)-allyl 2'-deoxyribosyl sugar moiety.
145. The oligomeric compound of embodiment 136, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 3 of the central region is a 5'-stereorandom allyl 2'-deoxyribosyl sugar moiety.
146. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar
20 moiety of the central region is a modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 3 of the central region.
147. The oligomeric compound of embodiment 146, wherein the modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 3 of the central region is an α -D-2'-deoxyribosyl modified sugar moiety.
- 25 148. The oligomeric compound of embodiment 146, wherein the modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 3 of the central region is an α -L-2'-deoxyribosyl modified sugar moiety.
149. The oligomeric compound of embodiment 146, wherein the modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 3 of the central region is an β -L-2'-deoxyribosyl modified sugar
30 moiety.
150. The oligomeric compound of embodiment 146, wherein the modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 3 of the central region is an β -D-2'-deoxyxylosyl modified sugar moiety.
151. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar
35 moiety of the central region is a bicyclic ribosyl sugar moiety at position 3 of the central region.

152. The oligomeric compound of embodiment 151, wherein the bicyclic ribosyl sugar moiety at position 3 of the central region is a cEt or LNA sugar moiety.
153. The oligomeric compound of embodiment 151, wherein the bicyclic ribosyl sugar moiety at position 3 of the central region is a cEt sugar moiety.
- 5 154. The oligomeric compound of embodiment 151, wherein the bicyclic ribosyl sugar moiety at position 3 of the central region is a LNA sugar moiety.
155. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a morpholino sugar moiety at position 3 of the central region.
156. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 2'-substituted ribosyl sugar moiety at position 4 of the central region.
- 10 157. The oligomeric compound of embodiment 156, wherein the 2'-substituted ribosyl sugar moiety at position 4 of the central region is a 2'-F ribosyl sugar moiety.
158. The oligomeric compound of embodiment 156, wherein the 2'-substituted ribosyl sugar moiety at position 4 of the central region is a 2'-MOE ribosyl sugar moiety.
- 15 159. The oligomeric compound of embodiment 156, wherein the 2'-substituted ribosyl sugar moiety at position 4 of the central region is a 2'-O-methyl ribosyl sugar moiety.
160. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 4'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 4 of the central region.
- 20 161. The oligomeric compound of embodiment 160, wherein the 4'-substituted 2'-deoxyribosyl sugar moiety at position 4 of the central region is a 4'-methyl 2'-deoxyribosyl sugar moiety.
162. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 4 of the central region.
- 25 163. The oligomeric compound of embodiment 162, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 4 of the central region is a 5'-(*R*)-methyl 2'-deoxyribosyl sugar moiety.
164. The oligomeric compound of embodiment 162, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 4 of the central region is a 5'-(*S*)-methyl 2'-deoxyribosyl sugar moiety.
165. The oligomeric compound of embodiment 162, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 4 of the central region is a 5'-stereorandom methyl 2'-deoxyribosyl sugar moiety.
- 30 166. The oligomeric compound of embodiment 162, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 4 of the central region is a 5'-(*R*)-ethyl 2'-deoxyribosyl sugar moiety.
167. The oligomeric compound of embodiment 162, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 4 of the central region is a 5'-(*S*)-ethyl 2'-deoxyribosyl sugar moiety.

168. The oligomeric compound of embodiment 162, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 4 of the central region is a 5'-stereorandom ethyl 2'-deoxyribosyl sugar moiety.
169. The oligomeric compound of embodiment 162, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 4 of the central region is a 5'-(*R*)-allyl 2'-deoxyribosyl sugar moiety.
- 5 170. The oligomeric compound of embodiment 162, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 4 of the central region is a 5'-(*S*)-allyl 2'-deoxyribosyl sugar moiety.
171. The oligomeric compound of embodiment 162, wherein the 5'-alkyl substituted 2'-deoxyribosyl sugar moiety at position 4 of the central region is a 5'-stereorandom allyl 2'-deoxyribosyl sugar moiety.
172. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 4 of the central region.
- 10 173. The oligomeric compound of embodiment 172, wherein the modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 4 of the central region is an α -D-2'-deoxyribosyl modified sugar moiety.
- 15 174. The oligomeric compound of embodiment 172, wherein the modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 4 of the central region is an α -L-2'-deoxyribosyl modified sugar moiety.
175. The oligomeric compound of embodiment 172, wherein the modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 4 of the central region is an β -L-2'-deoxyribosyl modified sugar moiety.
- 20 176. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a bicyclic ribosyl sugar moiety at position 4 of the central region.
177. The oligomeric compound of embodiment 176, wherein the bicyclic ribosyl sugar moiety at position 4 of the central region is a cEt or LNA sugar moiety.
- 25 178. The oligomeric compound of embodiment 176, wherein the bicyclic ribosyl sugar moiety at position 4 of the central region is a cEt sugar moiety.
179. The oligomeric compound of embodiment 176, wherein the bicyclic ribosyl sugar moiety at position 4 of the central region is a LNA sugar moiety.
180. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a morpholino sugar moiety at position 4 of the central region.
- 30 181. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 2'-O-methyl substituted ribosyl sugar moiety at position 5 of the central region.

182. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 5 of the central region.

183. The oligomeric compound of embodiment 182, wherein the modified, unsubstituted 2'-
5 deoxyfuranosyl sugar moiety at position 5 of the central region is a β -L-2'-deoxyribosyl sugar moiety.

184. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a morpholino sugar moiety at position 6 of the central region.

185. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 2'-O-methyl substituted ribosyl sugar moiety at position 6 of the central
10 region.

186. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 6 of the central region.

187. The oligomeric compound of embodiment 186, wherein the modified, unsubstituted 2'-
15 deoxyfuranosyl sugar moiety at position 6 of the central region is a β -L-2'-deoxyribosyl sugar moiety.

188. The oligomeric compound of embodiment 186, wherein the modified, unsubstituted 2'-
deoxyfuranosyl sugar moiety at position 6 of the central region is an α -D-2'-deoxyribosyl sugar moiety.

189. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 2'-O-methyl substituted ribosyl sugar moiety at position 7 of the central
20 region.

190. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 7 of the central region.

191. The oligomeric compound of embodiment 190, wherein the modified, unsubstituted 2'-
25 deoxyfuranosyl sugar moiety at position 7 of the central region is a β -L-2'-deoxyribosyl sugar moiety.

192. The oligomeric compound of embodiment 190, wherein the modified, unsubstituted 2'-
deoxyfuranosyl sugar moiety at position 7 of the central region is an α -D-2'-deoxyribosyl sugar moiety.

193. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 2'-O-methyl substituted ribosyl sugar moiety at position 8 of the central
30 region.

194. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 8 of the central region.

195. The oligomeric compound of embodiment 194, wherein the modified, unsubstituted 2'-
35 deoxyfuranosyl sugar moiety at position 8 of the central region is a β -L-2'-deoxyribosyl sugar moiety.

196. The oligomeric compound of embodiment 194, wherein the modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 8 of the central region is an α -D-2'-deoxyribosyl sugar moiety.
197. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 2'-O-methyl substituted ribosyl sugar moiety at position 9 of the central region.
198. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 9 of the central region.
199. The oligomeric compound of embodiment 198, wherein the modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 9 of the central region is a β -L-2'-deoxyribosyl sugar moiety.
200. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 2'-O-methyl substituted ribosyl sugar moiety at position 2, 3, 4, 5, 6, 7, 8, or 9 of the central region.
201. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 2'-O-methyl substituted ribosyl sugar moiety at position 2, 3, 4, 8, or 9 of the central region.
202. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 2'-F substituted ribosyl sugar moiety at position 2, 3, or 4 of the central region.
203. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 2'-F substituted ribosyl sugar moiety at position 3 or 4 of the central region.
204. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 2'-MOE substituted ribosyl sugar moiety at position 2, 3, or 4 of the central region.
205. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 4'-methyl substituted 2'-deoxyribosyl sugar moiety at position 3 or 4 of the central region.
206. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 5'-(*R*)-methyl substituted 2'-deoxyribosyl sugar moiety at position 3 or 4 of the central region.
207. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 5'-(*S*)-methyl substituted 2'-deoxyribosyl sugar moiety at position 2, 3, or 4 of the central region.

208. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 5'-(*R*)-ethyl substituted 2'-deoxyribosyl sugar moiety at position 3 or 4 of the central region.
209. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 5'-(*S*)-ethyl substituted 2'-deoxyribosyl sugar moiety at position 3 or 4 of the central region.
210. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 5'-(*R*)-allyl substituted 2'-deoxyribosyl sugar moiety at position 3 or 4 of the central region.
211. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 5'-(*S*)-allyl substituted 2'-deoxyribosyl sugar moiety at position 3 or 4 of the central region.
212. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a 5'-stereorandom allyl substituted 2'-deoxyribosyl sugar moiety at position 2, 3, or 4 of the central region.
213. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a cEt ribosyl sugar moiety at position 2, 3, or 4 of the central region.
214. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a cEt ribosyl sugar moiety at position 3 or 4 of the central region.
215. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a LNA ribosyl sugar moiety at position 2, 3, or 4 of the central region.
216. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a LNA ribosyl sugar moiety at position 3 or 4 of the central region.
217. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a morpholino sugar moiety at position 1, 3, 4, or 6 of the central region.
218. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a morpholino sugar moiety at position 1, 3, or 4 of the central region.
219. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a modified, unsubstituted 2'-deoxyfuranosyl sugar moiety.
220. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 1, 2, 3, 4, 5, 6, 7, 8, or 9 of the central region.
221. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is a modified, unsubstituted 2'-deoxyfuranosyl sugar moiety at position 1, 2, 3, 4, 5, or 9 of the central region.

222. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is an unsubstituted α -D-2'-deoxyribosyl sugar moiety.
223. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is an unsubstituted α -D-2'-deoxyribosyl sugar moiety at position 1, 2, 3, 4, 6, or 8 of the central region.
224. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is an unsubstituted α -D-2'-deoxyribosyl sugar moiety at position 1, 2, or 4 of the central region.
225. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is an unsubstituted α -L-2'-deoxyribosyl sugar moiety.
226. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is an unsubstituted α -L-2'-deoxyribosyl sugar moiety at position 3, 4, or 7 of the central region.
227. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is an unsubstituted β -L-2'-deoxyribosyl sugar moiety.
228. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is an unsubstituted β -L-2'-deoxyribosyl sugar moiety at position 1, 3, 4, 5, 6, 7, 8, or 9 of the central region.
229. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is an unsubstituted β -L-2'-deoxyribosyl sugar moiety at position 3, 4, 5, or 9 of the central region.
230. The oligomeric compound of any of embodiments 50-61 or 67-69, wherein the one modified sugar moiety of the central region is an unsubstituted β -D-2'-deoxyxylosyl sugar moiety.
231. The oligomeric compound of any of embodiments 53-55 or 60-230, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is a phosphonate or phosphotriester internucleoside linkage.
232. The oligomeric compound of embodiment 231, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is an alkyl phosphonate or alkoxy phosphonate internucleoside linkage.
233. The oligomeric compound of embodiment 232, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is a methoxypropyl internucleoside linkage.
234. The oligomeric compound of embodiment 232, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is a methyl phosphonate internucleoside linkage.
235. The oligomeric compound of embodiment 232, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is an isopropyl phosphonate internucleoside linkage.

236. The oligomeric compound of embodiment 232, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is an isobutyl phosphonate internucleoside linkage.
237. The oligomeric compound of embodiment 231, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is a phosphonoacetate internucleoside linkage.
- 5 238. The oligomeric compound of embodiment 231, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is an isopropyl phosphotriester internucleoside linkage.
239. The oligomeric compound of embodiment 231, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is a tetrahydropyran phosphotriester internucleoside linkage.
- 10 240. The oligomeric compound of any of embodiments 53, 55, or 60-230, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is a formacetal internucleoside linkage.
241. The oligomeric compound of any of embodiments 53, 55, or 60-230, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is an acetamide internucleoside linkage.
- 15 242. The oligomeric compound of any of embodiments 53, 55, or 60-230, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is a thioacetamide internucleoside linkage.
243. The oligomeric compound of any of embodiments 231-242, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is between the nucleosides at positions 1 and 2 of the central region.
- 20 244. The oligomeric compound of any of embodiments 231-242, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is between the nucleosides at positions 2 and 3 of the central region.
- 25 245. The oligomeric compound of any of embodiments 231-242, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is between the nucleosides at positions 3 and 4 of the central region.
246. The oligomeric compound of any of embodiments 231-242, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is between the nucleosides at positions 4 and 5 of the central region.
- 30 247. The oligomeric compound of any of embodiments 231-246, wherein the one modified internucleoside linkage of the central region other than phosphorothioate is directly linked to a nucleoside comprising a modified sugar moiety.
248. The oligomeric compound of any of embodiments 56-230, wherein the two neutral internucleoside linkages of the central region are independently selected from a phosphonate internucleoside linkage,
- 35

phosphotriester internucleoside linkage, and a neutral internucleoside linkage that does not contain phosphorus.

249. The oligomeric compound of embodiment 248, wherein at least one of the modified internucleoside linkages of the central region other than phosphorothioate is an alkyl phosphonate or alkoxy phosphonate internucleoside linkage.

250. The oligomeric compound of embodiment 248, wherein at least one of the modified internucleoside linkages of the central region other than phosphorothioate is a methoxypropyl internucleoside linkage.

251. The oligomeric compound of embodiment 248, wherein at least one of the modified internucleoside linkages of the central region other than phosphorothioate is a methyl phosphonate internucleoside linkage.

252. The oligomeric compound of embodiment 248, wherein at least one of the modified internucleoside linkages of the central region other than phosphorothioate is an isopropyl phosphonate internucleoside linkage.

253. The oligomeric compound of embodiment 248, wherein at least one of the modified internucleoside linkages of the central region other than phosphorothioate is an isobutyl phosphonate internucleoside linkage.

254. The oligomeric compound of embodiment 248, wherein at least one of the modified internucleoside linkages of the central region other than phosphorothioate is a phosphonoacetate internucleoside linkage.

255. The oligomeric compound of embodiment 248, wherein at least one of the modified internucleoside linkages of the central region other than phosphorothioate is an isopropyl phosphotriester internucleoside linkage.

256. The oligomeric compound of embodiment 248, wherein at least one of the modified internucleoside linkages of the central region other than phosphorothioate is a tetrahydropyran phosphotriester internucleoside linkage.

257. The oligomeric compound of embodiment 248, wherein at least one of the modified internucleoside linkages of the central region other than phosphorothioate is a formacetal internucleoside linkage.

258. The oligomeric compound of embodiment 248, wherein at least one of the modified internucleoside linkages of the central region other than phosphorothioate is an acetamide internucleoside linkage.

259. The oligomeric compound of embodiment 248, wherein at least one of the modified internucleoside linkages of the central region other than phosphorothioate is a thioacetamide internucleoside linkage.

260. The oligomeric compound of any of embodiments 248-259, wherein the two modified internucleoside linkages other than phosphorothioate of the central region are adjacent to each other.

261. The oligomeric compound of any of claims 248-260, wherein the two modified internucleoside linkages other than phosphorothioate of the central region are the same as one another.

262. The oligomeric compound of any of embodiments 248-261, wherein one of the modified internucleoside linkages of the central region other than phosphorothioate is between the nucleosides at positions 1 and 2 of the central region.
- 5 263. The oligomeric compound of any of embodiments 248-261, wherein one of the modified internucleoside linkages of the central region other than phosphorothioate is between the nucleosides at positions 2 and 3 of the central region.
264. The oligomeric compound of any of embodiments 248-261, wherein one of the modified internucleoside linkages of the central region other than phosphorothioate is between the nucleosides at positions 3 and 4 of the central region.
- 10 265. The oligomeric compound of any of embodiments 248-261, wherein one of the modified internucleoside linkages of the central region other than phosphorothioate is between the nucleosides at positions 4 and 5 of the central region.
266. The oligomeric compound of any of embodiments 248-261, wherein one of the modified internucleoside linkages of the central region other than phosphorothioate is directly linked to a nucleoside comprising a modified sugar moiety.
- 15 267. The oligomeric compound of any of embodiments 60-266, wherein the one modified nucleobase other than 5-methylcytosine of the central region is 2-thiothymine, 6-methyladenine, inosine, or pseudouracil.
268. The oligomeric compound of embodiment 267, wherein the one modified nucleobase other than 5-methylcytosine is at position 1, 2, 3, or 4 of the central region.
- 20 269. The oligomeric compound of embodiment 267, wherein the one modified nucleobase other than 5-methylcytosine is at position 2, 3, or 4 of the central region.
270. The oligomeric compound of embodiment 267, wherein the one modified nucleobase other than 5-methylcytosine is at position 1 of the central region.
- 25 271. The oligomeric compound of embodiment 267, wherein the one modified nucleobase other than 5-methylcytosine is at position 2 of the central region.
272. The oligomeric compound of embodiment 267, wherein the one modified nucleobase other than 5-methylcytosine is at position 3 of the central region.
273. The oligomeric compound of embodiment 267, wherein the one modified nucleobase other than 5-methylcytosine is at position 4 of the central region.
- 30 274. The oligomeric compound of any of embodiments 267 or 270, wherein the one modified nucleobase other than 5-methylcytosine is 2-thiothymine.
275. The oligomeric compound of any of embodiments 267 or 271, wherein the one modified nucleobase other than 5-methylcytosine is 6-methyladenine.

276. The oligomeric compound of any of embodiments 267 or 271, wherein the one modified nucleobase other than 5-methylcytosine is inosine.
277. The oligomeric compound of any of embodiments 267-273, wherein the one modified nucleobase other than 5-methylcytosine is pseudouracil.
- 5 278. The oligomeric compound of embodiment 277, wherein the nucleoside comprising the pseudouracil nucleobase comprises an unmodified ribosyl sugar moiety.
279. The oligomeric compound of any of embodiments 1-52, 60-230, or 267-278, wherein each internucleoside linkage of the central region is independently selected from among a phosphodiester or a phosphorothioate internucleoside linkage.
- 10 280. The oligomeric compound of embodiment 279, wherein each internucleoside of the central region is a phosphorothioate internucleoside linkage.
281. The oligomeric compound of any of embodiments 1-279, wherein the central region does not comprise any phosphodiester internucleoside linkages.
282. The oligomeric compound of any of embodiments 1-281, wherein each phosphorothioate
15 internucleoside linkage of the oligomeric compound is stereorandom.
283. The oligomeric compound of any of embodiments 1-281, wherein at least one phosphorothioate internucleoside linkage of the oligomeric compound is in the Rp configuration.
284. The oligomeric compound of any of embodiments 1-281, wherein at least one phosphorothioate internucleoside linkage of the oligomeric compound is in the Sp configuration.
- 20 285. The oligomeric compound of any of embodiments 1-284, wherein the nucleobase sequence of the modified oligonucleotide is complementary to a target RNA.
286. The oligomeric compound of embodiment 285, wherein the nucleobase sequence of the modified oligonucleotide is at least 75% complementary to the target RNA.
287. The oligomeric compound of embodiment 285, wherein the nucleobase sequence of the modified
25 oligonucleotide is at least 80% complementary to the target RNA.
288. The oligomeric compound of embodiment 285, wherein the nucleobase sequence of the modified oligonucleotide is at least 85% complementary to the target RNA.
289. The oligomeric compound of embodiment 285, wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to the target RNA.
- 30 290. The oligomeric compound of embodiment 285, wherein the nucleobase sequence of the modified oligonucleotide is at least 95% complementary to the target RNA.
291. The oligomeric compound of embodiment 285, wherein the nucleobase sequence of the modified oligonucleotide is 100% complementary to the target RNA.
292. The oligomeric compound of any of embodiments 285-291, wherein the target RNA is a target
35 mRNA or a target pre-mRNA.

293. The oligomeric compound of embodiment 292, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human PTEN RNA.
294. The oligomeric compound of embodiment 292 or 293, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human SRB-1 RNA.
- 5 295. The oligomeric compound of any of embodiments 292-294, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human MYD88 RNA.
296. The oligomeric compound of any of embodiments 292-295, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human HTT RNA, is not a mouse, rat, monkey, or human SOD1 RNA, and is not a mouse, rat, monkey, or human alpha-synuclein RNA.
- 10 297. The oligomeric compound of any of embodiments 285-296, wherein the target RNA is a human RNA.
298. The oligomeric compound of any of embodiments 285-297, wherein the target RNA is expressed in the liver.
299. The oligomeric compound of any of embodiments 285-298, wherein the target RNA is a liver target.
- 15 300. The oligomeric compound of any of embodiments 285-297, wherein the target RNA is not expressed in the liver.
301. The oligomeric compound of any of embodiments 285-298 or 300, wherein the target RNA is not a liver target.
302. The oligomeric compound of any of embodiments 285-299, wherein modulation of the expression of the target RNA in the liver is associated with treating a disorder or condition.
- 20 303. The oligomeric compound of embodiment 302, wherein the disorder or condition is a liver disorder or condition.
304. The oligomeric compound of any of embodiments 285-303, wherein the target RNA is expressed in the central nervous system.
- 25 305. The oligomeric compound of any of embodiments 285-303, wherein the target RNA is not expressed in the central nervous system.
306. The oligomeric compound of any of embodiments 285-298, 300, 301, or 304, wherein the target RNA is a central nervous system target.
307. The oligomeric compound of any of embodiments 285-305, wherein the target RNA is not a central nervous system target.
- 30 308. The oligomeric compound of any of embodiments 285-298, 300-301, 304, or 306, wherein the target RNA is a MeCP2, DUX4, HDAC2, APP, Ataxin 1, Ataxin 2, Ataxin 3, Ataxin 6, Ataxin 7, C9ORF72, UBE3A, Prion, PMP22, Tau, LRRK2, LINGO2, GYS1, KCNT1, IRF8, Progranulin, or GFAP RNA.

309. The oligomeric compound of any of embodiments 285-297, 300-301, 304, or 306, wherein the target RNA is a HTT RNA.
310. The oligomeric compound of embodiment 308, wherein the target RNA is a MeCP2 RNA.
311. The oligomeric compound of embodiment 308, wherein the target RNA is a DUX4 RNA.
- 5 312. The oligomeric compound of embodiment 308, wherein the target RNA is a HDAC2 RNA.
313. The oligomeric compound of embodiment 308, wherein the target RNA is a Ataxin 1 RNA.
314. The oligomeric compound of embodiment 308, wherein the target RNA is a Ataxin 2 RNA.
315. The oligomeric compound of embodiment 308, wherein the target RNA is a Ataxin 3 RNA.
316. The oligomeric compound of embodiment 308, wherein the target RNA is a Ataxin 6 RNA.
- 10 317. The oligomeric compound of embodiment 308, wherein the target RNA is a Ataxin 7 RNA.
318. The oligomeric compound of embodiment 308, wherein the target RNA is a C9ORF72 RNA.
319. The oligomeric compound of embodiment 285-297, 300-301, 304, or 306, wherein the target RNA is an alpha-synuclein RNA.
320. The oligomeric compound of embodiment 308, wherein the target RNA is an UBE3A RNA.
- 15 321. The oligomeric compound of embodiment 285-297, 300-301, 304, or 306, wherein the target RNA is a SOD1 RNA.
322. The oligomeric compound of embodiment 308, wherein the target RNA is a Prion RNA.
323. The oligomeric compound of embodiment 308, wherein the target RNA is a PMP22 RNA.
324. The oligomeric compound of embodiment 308, wherein the target RNA is a Tau RNA.
- 20 325. The oligomeric compound of embodiment 308, wherein the target RNA is a LRRK2 RNA.
326. The oligomeric compound of embodiment 308, wherein the target RNA is an APP RNA.
327. The oligomeric compound of embodiment 308, wherein the target RNA is a LINGO2 RNA.
328. The oligomeric compound of embodiment 308, wherein the target RNA is a GYS1 RNA.
329. The oligomeric compound of embodiment 308, wherein the target RNA is a KCNT1 RNA.
- 25 330. The oligomeric compound of embodiment 308, wherein the target RNA is a IRF8 RNA.
331. The oligomeric compound of embodiment 308, wherein the target RNA is a Progranulin RNA.
332. The oligomeric compound of embodiment 308, wherein the target RNA is a GFAP RNA.
333. The oligomeric compound of any of embodiments 304, 306, or 308-332, wherein modulation of the expression of the target RNA in the central nervous system is associated with treating a disorder or condition.
- 30 334. The oligomeric compound of embodiment 333, wherein the disorder or condition is a neurological disorder or condition.
335. The oligomeric compound of embodiment 333 or 334, wherein the disorder or condition alters the function of sensory or motor neurons.

336. The oligomeric compound of any of embodiments 333-335, wherein the disorder or condition alters the function of sensory neurons.
337. The oligomeric compound of any of embodiments 333-336, wherein the disorder or condition alters the function of motor neurons.
- 5 338. The oligomeric compound of any of embodiments 333-337, wherein the disorder or condition alters the function of glial cells.
339. The oligomeric compound of embodiment 338, wherein the disorder or condition alters the function of astrocytes.
340. The oligomeric compound of embodiment 338, wherein the disorder or condition alters the function of oligodendrocytes.
- 10 341. The oligomeric compound of embodiment 338, wherein the disorder or condition alters the function of microglia.
342. The oligomeric compound of embodiment 338, wherein the disorder or condition alters the function of ependymal cells.
- 15 343. The oligomeric compound of any of embodiments 333-342, wherein the disorder or condition is Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Parkinson's Disease, a Spinocerebellar ataxia, Angelman Syndrome, Alexander's Disease, Lafora Disease, Charcot-Marie Tooth Disease, Prion Disease, a dementia, neurodegeneration, McCP2 Duplication Syndrome, encephalopathy, neuroinflammation, or multiple sclerosis.
- 20 344. The oligomeric compound of embodiment 343, wherein the disorder or condition is Alzheimer's Disease.
345. The oligomeric compound of embodiment 343, wherein the disorder or condition is Amyotrophic Lateral Sclerosis.
346. The oligomeric compound of embodiment 343, wherein the disorder or condition is Parkinson's Disease.
- 25 347. The oligomeric compound of embodiment 343, wherein the disorder or condition is a Spinocerebellar ataxia.
348. The oligomeric compound of embodiment 343, wherein the disorder or condition is Angelman Syndrome.
- 30 349. The oligomeric compound of embodiment 343, wherein the disorder or condition is Alexander's Disease.
350. The oligomeric compound of embodiment 343, wherein the disorder or condition is Lafora Disease.
351. The oligomeric compound of embodiment 343, wherein the disorder or condition is Charcot-Marie Tooth Disease.
- 35 352. The oligomeric compound of embodiment 343, wherein the disorder or condition is Prion Disease.

353. The oligomeric compound of embodiment 343, wherein the disorder or condition is a dementia.
354. The oligomeric compound of embodiment 343, wherein the disorder or condition is neurodegeneration.
355. The oligomeric compound of embodiment 343, wherein the disorder or condition is MeCP2 Duplication Syndrome.
356. The oligomeric compound of embodiment 343, wherein the disorder or condition is encephalopathy.
357. The oligomeric compound of embodiment 343, wherein the disorder or condition is neuroinflammation.
358. The oligomeric compound of embodiment 343, wherein the disorder or condition is multiple sclerosis.
359. The oligomeric compound of any of embodiments 1-358, wherein the parent oligomeric compound of the oligomeric compound of any of embodiments 1-358 is cytotoxic in vitro.
360. The oligomeric compound of embodiment 359, wherein the parent oligomeric compound is cytotoxic in a standard in vitro cytotoxicity assay.
361. The oligomeric compound of any of embodiments 1-360, wherein administration to a mouse of the parent oligomeric compound of the oligomeric compound of any of embodiments 1-360 is hepatotoxic to the mouse.
362. The oligomeric compound of embodiment 361, wherein the administration of the parent oligomeric compound to the mouse is systemic administration.
363. The oligomeric compound of embodiment 362, wherein the systemic administration is subcutaneous administration.
364. The oligomeric compound of any of embodiments 361-363, wherein the mouse is a CD-1 mouse.
365. The oligomeric compound of any of embodiments 361-363, wherein the mouse is a C57BL/6 mouse.
366. The oligomeric compound of any of embodiments 361-363, wherein the mouse is a BALB/c mouse.
367. The oligomeric compound of any of embodiments 361-366, wherein the plasma ALT level in the mouse is higher than 500 units per liter following the administration of the parent oligomeric compound.
368. The oligomeric compound of any of embodiments 361-366, wherein the plasma AST level in the mouse is higher than 500 units per liter following the administration of the parent oligomeric compound.
369. The oligomeric compound of any of embodiments 361-366, wherein the plasma ALT level in the mouse is higher than 1000 units per liter following the administration of the parent oligomeric compound.
370. The oligomeric compound of any of embodiments 361-366, wherein the plasma AST level in the mouse is higher than 1000 units per liter following the administration of the parent oligomeric compound.

371. The oligomeric compound of any of embodiments 361-370, wherein the hepatotoxicity is measured 24-48 hours following the administration of the parent oligomeric compound.
372. The oligomeric compound of any of embodiments 361-370, wherein the hepatotoxicity is measured 72 hours following the administration of the parent oligomeric compound.
- 5 373. The oligomeric compound of any of embodiments 361-370, wherein the hepatotoxicity is measured 3 days following the administration of the parent oligomeric compound.
374. The oligomeric compound of any of embodiments 361-370, wherein the hepatotoxicity is measured 5 days following the administration of the parent oligomeric compound.
375. The oligomeric compound of any of embodiments 361-370, wherein the hepatotoxicity is measured 7
10 days following the administration of the parent oligomeric compound.
376. The oligomeric compound of any of embodiments 361-370, wherein the hepatotoxicity is measured 10 days following the administration of the parent oligomeric compound.
377. The oligomeric compound of any of embodiments 361-370, wherein the hepatotoxicity is measured 14 days following the administration of the parent oligomeric compound.
- 15 378. The oligomeric compound of any of embodiments 361-377, wherein 1-10 mg/kg of the parent oligomeric compound is administered to the mouse.
379. The oligomeric compound of any of embodiments 361-377, wherein 10-25 mg/kg of the parent oligomeric compound is administered to the mouse.
380. The oligomeric compound of any of embodiments 361-377, wherein 25-50 mg/kg of the parent
20 oligomeric compound is administered to the mouse.
381. The oligomeric compound of any of embodiments 361-377, wherein 50-100 mg/kg of the parent oligomeric compound is administered to the mouse.
382. The oligomeric compound of any of embodiments 361-377, wherein 100-150 mg/kg of the parent oligomeric compound is administered to the mouse.
- 25 383. The oligomeric compound of any of embodiments 361-363, 366-370, 372, or 382, wherein the mouse is a BALB/c mouse, wherein 150 mg/kg of the parent oligomeric compound is administered to the mouse, and wherein the plasma ALT level in the mouse is measured 72 hours following the administration of the parent oligomeric compound.
384. The oligomeric compound of any of embodiments 1-383, wherein administration of 50 mg/kg of the
30 oligomeric compound of any of embodiments 1-383 to a mouse is not hepatotoxic to the mouse.
385. The oligomeric compound of embodiment 384, wherein plasma ALT level in the mouse is lower than 100 units per liter following the administration of the oligomeric compound of embodiment 384.
386. The oligomeric compound of embodiment 384 or 385, wherein plasma ALT level in the mouse is at least 10-fold lower than plasma ALT level in a mouse administered the parent oligomeric compound
35 of the oligomeric compound of embodiment 384 or 385, wherein the administrations and plasma ALT

measurements of both the oligomeric compound of embodiment 384 or 385 and the parent oligomeric compound are completed in the same way.

387. The oligomeric compound of embodiment 386, wherein the plasma ALT level in the mouse is at least 100-fold lower than the plasma ALT level in the mouse administered the parent oligomeric compound.

5 388. The oligomeric compound of embodiment 386, wherein the plasma ALT level in the mouse is at least 500-fold lower than the plasma ALT level in the mouse administered the parent oligomeric compound.

389. The oligomeric compound of any of embodiments 359-388, wherein the therapeutic index in a mouse of the oligomeric compound of any of embodiments 359-388 is increased relative to the therapeutic index of the parent oligomeric compound.

10 390. The oligomeric compound of embodiment 389, wherein the therapeutic index in a mouse of the oligomeric compound of embodiment 365 is at least two-fold greater than the therapeutic index of the parent oligomeric compound.

391. The oligomeric compound of any of embodiments 1-390, wherein an otherwise identical oligomeric compound lacking the at least one modified internucleoside linkage other than phosphorothioate and/or at least one modified nucleoside comprising a modified nucleobase other than 5-methylcytosine and/or a modified sugar moiety in the central region is hepatotoxic following administration to a mouse; and wherein the otherwise identical oligomeric compound has a central region consisting of phosphorothioate internucleoside linkages, unmodified 2'- β -D-deoxyribose sugar moieties, and nucleobases selected from thymine, uracil, adenine, guanine, cytosine, and 5-methylcytosine.

20 392. The oligomeric compound of embodiment 391, wherein the at least one modified internucleoside linkage other than phosphorothioate and/or at least one modified nucleoside comprising a modified nucleobase other than 5-methylcytosine and/or a modified sugar moiety in the central region is a 2'-O-methyl modified sugar moiety.

393. The oligomeric compound of embodiment 392, wherein the 2'-O-methyl modified sugar moiety is at position 2 of the central region.

25 394. The oligomeric compound of embodiment 392 or 393, wherein the otherwise identical oligomeric compound lacks a 2'-O-methyl modified sugar moiety, and wherein the otherwise identical oligomeric compound comprises an unmodified 2'- β -D-deoxyribose sugar moiety in place of the 2'-O-methyl modified sugar moiety.

30 395. The oligomeric compound of any of embodiments 391-394, wherein the nucleobase sequence of the otherwise identical oligomeric compound is 100% complementary to the target RNA.

396. The oligomeric compound of any of embodiments 391-395, wherein the otherwise identical oligomeric compound is a parent oligomeric compound of the oligomeric compound of any of embodiments 391-395.

397. The oligomeric compound of any of embodiments 285-396, wherein the oligomeric compound inhibits the target RNA with an IC_{50} lower than 100 nM in a standard in vitro activity assay.
398. The oligomeric compound of any of embodiments 285-397, wherein the parent oligomeric compound of the oligomeric compound of any of embodiments 285-397 inhibits the target RNA with an IC_{50} lower than 100 nM in a standard in vitro activity assay.
399. The oligomeric compound of any of embodiments 285-398, wherein the difference between the IC_{50} of the parent oligomeric compound measured in a standard in vitro activity assay and the IC_{50} of the oligomeric compound of any of embodiments 285-398 measured in a standard in vitro activity assay is less than 4-fold.
400. The oligomeric compound of any of embodiments 285-398, wherein the difference between the IC_{50} of the parent oligomeric compound measured in a standard in vitro activity assay and the IC_{50} of the oligomeric compound of any of embodiments 285-398 measured in a standard in vitro activity assay is less than 3-fold.
401. The oligomeric compound of any of embodiments 285-398, wherein the difference between the IC_{50} of the parent oligomeric compound measured in a standard in vitro activity assay and the IC_{50} of the oligomeric compound of any of embodiments 285-398 measured in a standard in vitro activity assay is less than 2-fold.
402. The oligomeric compound of any of embodiments 359-390 or 396-401, wherein each sugar moiety of the central region of the parent oligomeric compound is an unmodified 2'- β -D-deoxyribosyl sugar moiety, and wherein each internucleoside linkage of the central region of the parent oligomeric compound is a phosphorothioate internucleoside linkage.
403. The oligomeric compound of any of embodiments 359-390 or 396-402, wherein the nucleobase sequence of the parent oligomeric compound is 100% complementary to the target RNA.
404. The oligomeric compound of any of embodiments 1-403, wherein administration of 10-50 mg of the oligomeric compound to a human is not hepatotoxic to the human.
405. The oligomeric compound of any of embodiments 1-403, wherein administration of 50-100 mg of the oligomeric compound to a human is not hepatotoxic to the human.
406. The oligomeric compound of any of embodiments 1-403, wherein administration of 100-300 mg of the oligomeric compound to a human is not hepatotoxic to the human.
407. The oligomeric compound of any of embodiments 404-406, wherein the administration is systemic administration.
408. A composition comprising the oligomeric compound of any of embodiments 1-407 and a second oligomeric compound, wherein the second oligomeric compound is complementary to the oligomeric compound of any of embodiments 1-407.

409. The composition of embodiment 408, wherein the second oligomeric compound comprises at least 14 contiguous linked nucleosides that are at least 90% complementary to the oligomeric compound of any of embodiments 1-407.
- 5 410. The composition of embodiment 408, wherein the second oligomeric compound comprises at least 14 contiguous linked nucleosides that are 100% complementary to the oligomeric compound of any of embodiments 1-407.
411. A pharmaceutical composition comprising the oligomeric compound of any of embodiments 1-407 or the composition of any of embodiments 408-410, comprising a pharmaceutically acceptable carrier or diluent.
- 10 412. A method comprising administering the oligomeric compound or composition of any of embodiments 1-411 to a human subject.
413. A method of treating a disease or disorder comprising administering the oligomeric compound or composition of any of embodiments 1-411 to a human subject.
- 15 414. A method of modulating the amount or activity of a target RNA in a human subject comprising administering the oligomeric compound or composition of any of embodiments 1-411 to the human subject; and thereby modulating the amount or activity of the target RNA in the human subject.
415. A method of treating a disease or disorder in a human subject comprising administering the oligomeric compound or composition of any of embodiments 1-411 to the human subject having the disease or disorder; and thereby treating the disease or disorder in the human subject.
- 20 416. The method of embodiment 413 or 415, wherein the disease or disorder is a liver disease, and wherein the oligomeric compound modulates the amount or activity of a liver target RNA.
417. The method of embodiment 413 or 415, wherein the disease or disorder is a central nervous system disease, and wherein the oligomeric compound modulates the amount or activity of a central nervous system target RNA.
- 25 418. The method of any of embodiments 413 or 415-417, wherein the disease or disorder is a cancer, a neurodegenerative disease, a cardiovascular disease, an immunological disease, a hereditary disease, a repeat expansion disease, a muscle-wasting disease, or a metabolic disease.
419. The method of any of embodiments 412-418, wherein the plasma ALT level of the human subject after the administration is not more than three times higher than it was prior to the administration.
- 30 420. The method of any of embodiments 412-418, wherein the plasma ALT level of the human subject after the administration is not more than 150 units per liter.
421. The method of any of embodiments 412-416 or 418-420, wherein the human subject is susceptible to liver damage.
- 35 422. The method of any of embodiments 412-416 or 418-420, wherein the human subject is susceptible to liver degeneration.

423. The method of any of embodiments 412-416 or 418-420, wherein the human subject is susceptible to elevated apoptosis in the liver.
424. The method of any of embodiments 412-416 or 418-423, wherein the human subject has a liver disease.
- 5 425. The method of any of embodiments 412-424, comprising administering the parent oligomeric compound of the oligomeric compound of any of embodiments 1-407 to a mouse.
426. The method of any of embodiments 412-424, comprising contacting a cell with the parent oligomeric compound of the oligomeric compound of any of embodiments 1-407.
- 10 427. The method of embodiment 425 or 426, wherein each sugar moiety of the central region of the parent oligomeric compound is an unmodified 2'-β-D-deoxyribosyl sugar moiety, and wherein each internucleoside linkage of the central region of the parent oligomeric compound is a phosphorothioate internucleoside linkage.
428. A method of designing an oligomeric compound comprising starting with a parent oligomeric compound and changing the design of that compound in order to arrive at an oligomeric compound of any one of embodiments 1 – 407.
- 15 429. A method of designing an oligomeric compound comprising identifying a parent oligomeric compound and changing the design of that parent oligomeric compound to arrive at a second oligomeric compound, wherein the second oligomeric compound is an oligomeric compound of any one of embodiments 1-407.
- 20 430. A method of improving hepatotoxicity of an oligomeric compound comprising the steps of (i) identifying a parent oligomeric compound that has plasma ALT levels above 300 units per liter in a mouse, and (ii) providing an oligomeric compound according to any one of embodiments 1-407.
431. The method of embodiment 428, wherein the method designs an oligomeric compound with improved therapeutic index relative to the parent oligomeric compound.
- 25 432. The method of embodiment 428 or 431, wherein the method designs an oligomeric compound with lower hepatotoxicity relative to the parent oligomeric compound.
433. The method of embodiment 429, wherein the second oligomeric compound has an improved therapeutic index relative to the parent oligomeric compound.
434. The method of embodiment 429 or 433, wherein the second oligomeric compound has reduced hepatotoxicity in a mouse relative to the parent oligomeric compound.
- 30 435. The method of embodiment 430, wherein the oligomeric compound according to any one of embodiments 1-407 has reduced hepatotoxicity relative to the parent oligomeric compound.
436. A method comprising administering an oligomeric compound of any of embodiments 1-407 to a mouse and separately administering the parent oligomeric compound of the oligomeric compound of any of embodiments 1-407 to a second mouse, wherein the therapeutic index of the oligomeric
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compound of any of embodiments 1-407 is improved relative to the therapeutic index of the parent oligomeric compound.

437. The method of any of embodiments 412-436, wherein the level of p21 RNA is measured in the mouse, the cell, and/or the human subject.

5 438. A method comprising administering an oligomeric compound to a subject and measuring the level of p21 RNA in the subject.

439. A method comprising administering an oligomeric compound of any of embodiments 1-407 to a subject and measuring the level of p21 RNA in the subject.

440. The method of embodiment 438 or 439, wherein the subject is a mouse.

10 441. The method of embodiment 438 or 439, wherein the subject is a human.

442. The method of any of embodiments 437-441, wherein the p21 RNA level is measured within 24 hours of the administration.

443. The method of any of embodiments 437-441, wherein the p21 RNA level is measured 24-48 hours following the administration.

15 444. An oligomeric compound or composition of any one of embodiments 1-411, for use in medical therapy.

445. A method comprising contacting a cell with an oligomeric compound and detecting the cellular localization of p54nrb protein in the cell.

20 446. The method of embodiment 445, comprising determining the relative amount of p54nrb protein in the nucleolus relative to other cells contacted with different oligomeric compounds.

447. The method of embodiment 445 or 446, comprising determining the relative amount of p54nrb in the nucleolus relative to the amount of p54nrb in the rest of the cell.

448. The method of any of embodiments 445-447, wherein the cell is in a plate containing at least 96 wells.

25 449. The method of any of embodiments 445-448, wherein the detection of the cellular localization of p54nrb comprises contacting the cell with a p54nrb antibody.

450. A method of screening for a tolerable oligomeric compound comprising any of the methods of embodiments 445-449.

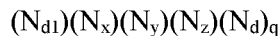
30 451. The method of any of embodiments 445-450, wherein the oligomeric compound is the oligomeric compound of any of embodiments 1-407.

452. An oligomeric compound comprising a modified oligonucleotide consisting of 12-23 linked nucleosides, wherein the modified oligonucleotide comprises a 5'-region, a central region, and a 3'-region wherein:

the 5'-region consists of 1-5 linked modified nucleosides;

35 the 3'-region consists of 1-5 linked modified nucleosides; and

the central region consists of 7-11 linked nucleosides and has the formula:



wherein one of N_x , N_y , and N_z is a safety enhancing nucleoside;

the other two of N_x , N_y , and N_z are independently selected from an unmodified 2'- β -D-deoxyribosyl, a DNA isomer, and a DNA mimic;

N_{d1} and each N_d is independently selected from an unmodified 2'- β -D-deoxyribosyl, a DNA isomer, and a DNA mimic; and wherein

q is 2-7.

453. The oligomeric compound of embodiment 1, wherein the safety enhancing nucleoside is N_x or N_y .

454. The oligomeric compound of embodiment 1, wherein the safety enhancing nucleoside is N_x .

455. The oligomeric compound of embodiment 1, wherein the safety enhancing nucleoside is N_y .

456. The oligomeric compound of embodiment 1, wherein the safety enhancing nucleoside is N_z .

457. The oligomeric compound of any of embodiments 452-456, wherein the safety enhancing nucleoside has a sugar moiety selected from among a sugar surrogate, a bicyclic furanosyl sugar moiety, a non-bicyclic 2'-modified furanosyl sugar moiety, a non-bicyclic 4'-modified furanosyl sugar moiety, or a non-bicyclic 5'-modified furanosyl sugar moiety.

458. The oligomeric compound of any of embodiments 452-457, wherein the safety-enhancing nucleoside has a sugar moiety selected from among a morpholino, a 2'-O-methyl-2'- β -D-deoxyribose sugar moiety, a cEt bicyclic sugar moiety, a LNA sugar moiety, an ENA sugar moiety, a 5'-methyl substituted 2'-deoxyribosyl sugar moiety, 5'-ethyl substituted 2'-deoxyribosyl sugar moiety, a 5'-allyl substituted 2'-deoxyribosyl sugar moiety and a 2'- β -L-deoxyxylosyl sugar moiety.

459. The oligomeric compound of any of embodiments 452-458, wherein the safety-enhancing nucleoside has a sugar moiety selected from among a 2'-O-methyl-modified sugar moiety and a 5'-modified sugar moiety.

460. The oligomeric compound of embodiment 459, wherein the safety-enhancing nucleoside has a 2'-O-methyl substituted ribosyl sugar moiety.

461. The oligomeric compound of any of embodiments 452-457, wherein the safety-enhancing nucleoside is a sugar surrogate.

462. The oligomeric compound of embodiment 461, wherein the sugar surrogate is selected from among a morpholino, a modified morpholino, and F-HNA.

463. The oligomeric compound of any of embodiments 452-462, wherein N_{d1} is an unmodified 2'- β -D-deoxyribosyl sugar moiety.

464. The oligomeric compound of any of embodiments 452-462, wherein N_{d1} is a DNA isomer.

465. The oligomeric compound of any of embodiments 452-462, wherein N_{d1} is a DNA mimic.

466. The oligomeric compound of any of embodiments 452-465, wherein no more than 3 of the central region nucleosides comprise a sugar moiety other than 2'-β-D-deoxyribosyl.
467. The oligomeric compound of any of embodiments 452-466, wherein each DNA isomer has a sugar moiety independently selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl.
468. The oligomeric compound of any of embodiments 452-467, wherein each DNA mimic has a sugar moiety is independently selected from among 5'-methyl-2'-β-D-deoxyribosyl and 5'-ethyl-2'-β-D-deoxyribosyl.
469. The oligomeric compound of any of embodiments 452-463, wherein each nucleoside of the central region other than the safety-enhancing nucleoside has a 2'-β-D-deoxyribosyl sugar moiety.
470. The oligomeric compound of any of 452-469, wherein at least one internucleoside linkage is a phosphorothioate linkage.
471. The oligomeric compound of any of embodiments 452-470, wherein at least 4 internucleoside linkages are phosphorothioate linkages.
472. The oligomeric compound of any of embodiments 452-471, wherein at least one internucleoside linkage is a neutral internucleoside linkage.
473. The oligomeric compound of any of embodiments 452-472, wherein at least one neutral internucleoside linkage is a phosphonate internucleoside linkage.
474. The oligomeric compound of any of embodiments 452-474, wherein at least one neutral internucleoside linkage is a methoxypropyl internucleoside linkage.
475. The oligomeric compound of any of embodiments 452-475, wherein at least one internucleoside linkage of the central region selected from among: the internucleoside Nd1 to Nx, Nx to Ny, Ny to Nz, or Nz to the adjacent Nd is a neutral internucleoside linkage.
476. The oligomeric compound of embodiment 475, wherein the modified oligonucleotide comprises one neutral linkage and the other internucleoside linkages are each independently selected from phosphodiester and phosphorothioate.
477. The oligomeric compound of any of embodiments 542-454 or embodiments 457-476, wherein the safety enhancing nucleoside is N_x and is a 2'-O-methyl-substituted nucleoside.
478. The oligomeric compound of any of embodiments 2-453, 455, or embodiments 457-476, wherein the safety enhancing nucleoside is N_y and is a 2'-O-methyl-substituted nucleoside.
479. The oligomeric compound of any of embodiments 452-453, 455, or embodiments 457-476, wherein the safety enhancing nucleoside is N_y and has a 5'-substituted 2'-deoxyribosyl sugar moiety.
480. The oligomeric compound of any of embodiments 452 or embodiments 457-476, wherein the safety enhancing nucleoside is N_z and has a 5'-substituted 2'-deoxyribosyl sugar moiety.

481. The oligomeric compound of embodiments 479 or 480, wherein the 5'-substituted ribosyl sugar moiety is a 5'-methyl, 5'-ethyl, or 5'-allyl substituted 2'-deoxyribosyl sugar moiety.
482. The oligomeric compound of embodiments 477 – 481, wherein at least one nucleoside of the 5'-region comprises a bicyclic furanosyl sugar moiety.
- 5 483. The oligomeric compound of any of embodiments 477 – 482, wherein each nucleoside of the 5'-region comprises a bicyclic furanosyl sugar moiety.
484. The oligomeric compound of any of embodiments 482 or 483, wherein each bicyclic sugar moiety of the 5'-region is selected from among cEt, LNA, and ENA.
485. The oligomeric compound of any of embodiments 452-482 or 484, wherein at least one nucleoside of the 5'-region comprises a non-bicyclic sugar moiety.
- 10 486. The oligomeric compound of embodiment 485, wherein the non-bicyclic sugar moiety of the at least one nucleoside of the 5'-region is a 2'-substituted ribosyl sugar moiety.
487. The oligomeric compound of any of embodiments 485-487, wherein each non-bicyclic sugar moiety of the 5'-region has a 2'-substituent selected from among 2'-MOE, 2'-OMe, and 2'-NMA.
- 15 488. The oligomeric compound of any of embodiments 477-480, wherein the 5'-region comprises a 2'-MOE modified nucleoside and an LNA modified nucleoside.
489. The oligomeric compound of any of embodiments 477-480, wherein the 5'-region comprises a 2'-MOE modified nucleoside and a cEt modified nucleoside.
490. The oligomeric compound of embodiments 477 – 489, wherein at least one nucleoside of the 3'-region comprises a bicyclic furanosyl sugar moiety.
- 20 491. The oligomeric compound of any of embodiments 477-490, wherein each nucleoside of the 3'-region comprises a bicyclic furanosyl sugar moiety.
492. The oligomeric compound of any of embodiments 490 or 491, wherein each bicyclic sugar moiety of the 3'-region is selected from among cEt, LNA, and ENA.
- 25 493. The oligomeric compound of any of embodiments 490 or 492, wherein at least one nucleoside of the 3'-region comprises a non-bicyclic sugar moiety.
494. The oligomeric compound of embodiment 493, wherein the non-bicyclic sugar moiety of the at least one nucleoside of the 3'-region is a 2'-substituted ribosyl sugar moiety.
495. The oligomeric compound of any of embodiments 490 or 492-494, wherein each non-bicyclic sugar moiety of the 3'-region has a 2'-substituent selected from among 2'-MOE, 2'-OMe, and 2'-NMA.
- 30 496. The oligomeric compound of any of embodiments 477-490 or 492-495, wherein the 3'-region comprises a 2'-MOE modified nucleoside and an LNA modified nucleoside.
497. The oligomeric compound of any of embodiments 477-490 or 492-495, wherein the 3'-region comprises a 2'-MOE modified nucleoside and a cEt modified nucleoside.

498. The oligomeric compound of any of embodiments 477-480, wherein each nucleoside of the 5'-region comprises a bicyclic furanosyl sugar moiety and each nucleoside of the 3'-region comprises a non-bicyclic sugar moiety.
499. The oligomeric compound of any of embodiments 477-480, wherein each nucleoside of the 5'-region comprises an LNA sugar moiety and each nucleoside of the 3'-region comprises a 2'MOE sugar moiety.
500. The oligomeric compound of any of embodiments 477-480, wherein each nucleoside of the 5'-region comprises cEt sugar moiety and each nucleoside of the 3'-region comprises a 2'MOE sugar moiety.
501. The oligomeric compound of any of embodiments 452-500, wherein the modified oligonucleotide has a nucleobase sequence complementary to a target RNA; wherein the target RNA is a mRNA or pre-mRNA.
502. The oligomeric compound of embodiment 501, wherein the target RNA encodes a protein that is expressed in the liver.
503. The oligomeric compound of embodiment 502, wherein the target RNA encodes a protein that is expressed in the CNS.
504. The oligomeric compound of any of embodiments 452-503, wherein the oligomeric compound is not toxic.
505. The oligomeric compound of any of embodiment 452-504, wherein a comparator compound is toxic; wherein the comparator compound is identical to the oligomeric compound except that each nucleoside of the central region of the comparator compound is a nucleoside comprising 2'-β-D-deoxyribosyl sugar moiety.
506. The oligomeric compound of embodiment 505, wherein administering a dose of the oligomeric compound to an animal results in a circulating ALT level that is at least 3-fold lower than the ALT level that results from administering the same dose of the comparator compound to an animal for at least one matched dose.
507. The oligomeric compound of embodiment 505 or 506, wherein the lowest dose of the oligomeric compound that raises circulating ALT to over 300 units per liter is at least three-fold higher than the lowest dose of the comparator compound that raises circulating ALT to over 300 units per liter.
508. The oligomeric compound of any of embodiments 502-507, wherein the oligomeric compound is capable of reducing the target RNA in a cell.
509. The oligomeric compound of embodiment 508, wherein the oligomeric compound has RNA-reducing activity comparable to a comparator compound, wherein the comparator compound is identical to the oligomeric compound except that each nucleoside of the central region of the comparator compound is a nucleoside comprising 2'-β-D-deoxyribosyl sugar moiety.

510. The oligomeric compound of embodiment 509 having RNA-reducing activity that is no more than 2-fold worse than the RNA-reducing activity of the comparator compound.
511. An oligomeric compound comprising a modified oligonucleotide consisting of 12-23 linked nucleosides, wherein the modified oligonucleotide comprises a 5'-region, a central region, and a 3'-region wherein:
- 5 the 5'-region consists of 1-5 linked nucleosides; wherein at least one 5'-region nucleoside is modified;
- the 3'-region consists of 1-5 linked nucleosides; wherein at least one 3'-region nucleoside is modified; and
- 10 the central region consists of 7-11 linked nucleosides, and has the formula:
 $(N_{d1})_{L1}(N_{d2})_{L2}(N_{d3})_{L3}(N_{d4})_{L4}(N_d)_q$;
 wherein N_{d1} , N_{d2} , N_{d3} , N_{d4} , and each N_d are independently selected from among
 a nucleoside comprising an unmodified 2'-β-D-deoxyribose sugar moiety, a DNA isomer sugar moiety, or a DNA mimic sugar moiety;
- 15 wherein each $L1$, $L2$, $L3$, and $L4$ is an internucleoside linkage; and wherein
 at least one of $L1$, $L2$, $L3$, and $L4$ is a neutral internucleoside linkage.
512. The oligomeric compound of embodiment 511, wherein $L1$ is a neutral internucleoside linkage.
513. The oligomeric compound of embodiment 511, wherein $L2$ is a neutral internucleoside linkage.
514. The oligomeric compound of embodiment 511, wherein $L3$ is a neutral internucleoside linkage.
- 20 515. The oligomeric compound of any of embodiments 511-514, wherein the neutral linkage is a phosphonate internucleoside linkage.
516. The oligomeric compound of any of embodiments 511-515, wherein the neutral linkage is a methoxypropyl internucleoside linkage.
- 25 517. The oligomeric compound of any of embodiments 511-516, wherein each remaining internucleoside linkage is a phosphodiester or phosphorothioate internucleoside linkage.
518. A method comprising administering the oligomeric compound or composition of any of embodiments 452-517 to a human subject.
519. A method of treating a disease or disorder comprising administering the oligomeric compound or
 30 composition of any of embodiments 452-517 to a human subject.
520. A method of modulating the amount or activity of a target RNA in a human subject comprising administering the oligomeric compound or composition of any of embodiments 452-517 to the human subject; and thereby modulating the amount or activity of the target RNA in the human subject.

521. A method of treating a disease or disorder in a human subject comprising administering the oligomeric compound or composition of any of embodiments 452-517 to the human subject having the disease or disorder; and thereby treating the disease or disorder in the human subject.
522. The method of embodiment 520 or 521, wherein the disease or disorder is a liver disease, and
5 wherein the oligomeric compound modulates the amount or activity of a liver target RNA.
523. The method of embodiment 520 or 521, wherein the disease or disorder is a central nervous system disease, and wherein the oligomeric compound modulates the amount or activity of a central nervous system target RNA.
524. The method of any of embodiments 519-523, wherein the disease or disorder is a cancer, a
10 neurodegenerative disease, a cardiovascular disease, an immunological disease, a hereditary disease, a repeat expansion disease, a muscle-wasting disease, or a metabolic disease.
525. The method of any of embodiments 518-524, wherein the plasma ALT level of the human subject after the administration is not more than three times higher than it was prior to the administration.
526. The method of any of embodiments 518-525, wherein the plasma ALT level of the human subject
15 after the administration is not more than 150 units per liter.
527. The method of any of embodiments 518-526, wherein the human subject is susceptible to liver damage.
528. The method of any of embodiments 518-527, wherein the human subject is susceptible to liver degeneration.
- 20 529. The method of any of embodiments 518-528, wherein the human subject is susceptible to elevated apoptosis in the liver.
530. The method of any of embodiments 518-529, wherein the human subject has a liver disease.
531. The method of any of embodiments 518-530, comprising administering the parent oligomeric compound of the oligomeric compound of any of embodiments 452-517 to a mouse.
- 25 532. The method of any of embodiments 518-531, comprising contacting a cell with the parent oligomeric compound of the oligomeric compound of any of embodiments 452-517.
533. The method of embodiment 518-532, wherein each sugar moiety of the central region of the parent oligomeric compound is an unmodified 2'-β-D-deoxyribosyl sugar moiety, and wherein each
internucleoside linkage of the central region of the parent oligomeric compound is a
30 phosphorothioate internucleoside linkage.
534. A method of designing an oligomeric compound comprising starting with a parent oligomeric compound and changing the design of that compound in order to arrive at an oligomeric compound of any one of embodiments 452-517.
535. A method of designing an oligomeric compound comprising identifying a parent oligomeric
35 compound and changing the design of that parent oligomeric compound to arrive at a second

oligomeric compound, wherein the second oligomeric compound is an oligomeric compound of any one of embodiments 452-517.

536. A method of improving hepatotoxicity of an oligomeric compound comprising the steps of (i) identifying a parent oligomeric compound that has plasma ALT levels above 300 units per liter in a mouse, and (ii) providing an oligomeric compound according to any one of embodiments 452-517.
537. The method of embodiment 536, wherein the method designs an oligomeric compound with improved therapeutic index relative to the parent oligomeric compound.
538. The method of embodiment 534-537, wherein the method designs an oligomeric compound with lower hepatotoxicity relative to the parent oligomeric compound.
539. The method of embodiment 535-538, wherein the second oligomeric compound has an improved therapeutic index relative to the parent oligomeric compound.
540. The method of embodiment 535-539, wherein the second oligomeric compound has reduced hepatotoxicity in a mouse relative to the parent oligomeric compound.
541. The method of embodiment 540, wherein the oligomeric compound according to any one of embodiments 452-517 has reduced hepatotoxicity relative to the parent oligomeric compound.
542. A method comprising administering an oligomeric compound of any of embodiments 452-517 to a mouse and separately administering the parent oligomeric compound of the oligomeric compound of any of embodiments 452-517 to a second mouse, wherein the therapeutic index of the oligomeric compound of any of embodiments 452-517 is improved relative to the therapeutic index of the parent oligomeric compound.
543. The method of any of embodiments 518-542, wherein the level of p21 RNA is measured in the mouse, the cell, and/or the human subject.
544. A method comprising administering an oligomeric compound of any of embodiments 452-517 to a subject and measuring the level of p21 RNA in the subject.
545. The method of embodiment 543 or 544, wherein the subject is a mouse.
546. The method of embodiment 543 or 544, wherein the subject is a human.
547. The method of any of embodiments 543-546, wherein the p21 RNA level is measured within 24 hours of the administration.
548. The method of any of embodiments 437-441, wherein the p21 RNA level is measured 24-48 hours following the administration.
549. An oligomeric compound or composition of any one of embodiments 452-517, for use in medical therapy.
550. The method of any of embodiments 445-449, wherein the oligomeric compound is the oligomeric compound of any of embodiments 452-517.

551. An oligomeric compound comprising a modified oligonucleotide consisting of 12-21 linked nucleosides, wherein the modified oligonucleotide has the formula A-B-C, wherein A is a 5'-region, B is a central region, and C is a 3'-region; wherein:
 the 5'-region consists of 1-5 linked nucleosides, wherein at least one nucleoside of the 5'-region is a modified nucleoside comprising a modified sugar;
 the 3'-region consists of 1-5 linked nucleosides wherein at least one nucleoside of the 3'-region is a modified nucleoside comprising a modified sugar; and
 the central region consists of 7-11 linked nucleosides, wherein
 the 5'-most portion of the central region has the following formula:
 $(N_{da})(N_x)(N_y)(N_z)(N_{db})$
 wherein one of N_x , N_y , and N_z is a safety-enhancing nucleoside;
 the other two of N_x , N_y , and N_z are independently selected from a DNA nucleoside, a DNA isomer, a modified DNA isomer, and a DNA mimic; and
 N_{da} and N_{db} are each independently selected from a DNA nucleoside, a DNA isomer, a modified DNA isomer, and a DNA mimic.
552. The oligomeric compound of embodiment 551, wherein the 5'-region consists of one nucleoside.
553. The oligomeric compound of embodiment 551, wherein the 5'-region consists of 2-5 linked nucleosides.
554. The oligomeric compound of embodiment 551, wherein the 5'-region consists of 2-4 linked nucleosides.
555. The oligomeric compound of embodiment 551, wherein the 5'-region consists of 2 linked nucleosides.
556. The oligomeric compound of embodiment 551, wherein the 5'-region consists of 3 linked nucleosides.
557. The oligomeric compound of embodiment 551, wherein the 5'-region consists of 4 linked nucleosides.
558. The oligomeric compound of embodiment 551, wherein the 5'-region consists of 5 linked nucleosides.
559. The oligomeric compound of any of embodiments 551-558, wherein each nucleoside of the 5'-region is a modified nucleoside.
560. The oligomeric compound of any of embodiments 551-559, wherein each nucleoside of the 5'-region is a modified nucleoside comprising a modified sugar.
561. The oligomeric compound of any of embodiments 551-560, wherein each modified nucleoside of the 5'-region has the same modification.

562. The oligomeric compound of and of embodiments 551-560, wherein at least two nucleosides of the 5'-region are modified nucleosides having different modifications.
563. The oligomeric compound of any of embodiments 551-562, wherein each nucleoside of the 5'-region comprises a 2'-modified ribosyl sugar moiety.
- 5 564. The oligomeric compound of any of embodiments 551-563, wherein at least one nucleoside of the 5'-region comprises a bicyclic furanosyl sugar moiety.
565. The oligomeric compound of any of embodiments 551-564, wherein each nucleoside of the 5'-region comprises a bicyclic furanosyl sugar moiety.
566. The oligomeric compound of any of embodiments 551-565, wherein at least one nucleoside of the 5'-
10 region comprises a non-bicyclic sugar moiety.
567. The oligomeric compound of embodiment 566, wherein the non-bicyclic sugar moiety of the at least one nucleoside of the 5'-region is a 2'-substituted ribosyl sugar moiety.
568. The oligomeric compound of any of embodiments 551-567, wherein each nucleoside of the 5'-region comprises a non-bicyclic sugar moiety.
- 15 569. The oligomeric compound of embodiment 568, wherein each nucleoside of the 5'-region comprises a 2'-substituted furanosyl sugar moiety.
570. The oligomeric compound of any of embodiments 551-569, wherein each nucleoside of the 5'-region comprises a 2'-modified furanosyl sugar moiety independently selected from a bicyclic sugar moiety and a non-bicyclic 2'-substituted ribosyl sugar moiety.
- 20 571. The oligomeric compound of any of embodiments 551-570, wherein each nucleoside of the 5'-region comprises a bicyclic sugar moiety.
572. The oligomeric compound of any of embodiments 551-571, wherein each nucleoside of the 5'-region comprises a non-bicyclic 2'-substituted ribosyl sugar moiety.
573. The oligomeric compound of any of embodiments 551-572, wherein each bicyclic sugar moiety of
25 the 5'-region is selected from among cEt, LNA, and ENA.
574. The oligomeric compound of any of embodiments 551-573, wherein each bicyclic sugar moiety of the 5'-region is a cEt sugar moiety.
575. The oligomeric compound of any of embodiments 551-574, wherein each bicyclic sugar moiety of the 5'-region is an LNA sugar moiety.
- 30 576. The oligomeric compound of any of embodiments 551-575, wherein each non-bicyclic sugar moiety of the 5'-region has a 2'-substituent selected from among 2'-MOE, 2'-OMe, and 2'-NMA.
577. The oligomeric compound of any of embodiments 551-576, wherein none of the nucleosides of the 5'-region comprise a sugar moiety having a 2'-F substituent.
578. The oligomeric compound of any of embodiments 551-577, wherein none of the nucleosides of the
35 5'-region comprise a sugar moiety having a 2'-MOE substituent.

579. The oligomeric compound of any of embodiments 551-578, wherein none of the nucleosides of the 5'-region comprise a sugar moiety having a 2'-OMe substituent.
580. The oligomeric compound of any of embodiments 551-579, wherein none of the nucleosides of the 5'-region comprise a cEt sugar moiety.
- 5 581. The oligomeric compound of any of embodiments 551-580, wherein none of the nucleosides of the 5'-region comprise a LNA sugar moiety.
582. The oligomeric compound of any of embodiments 551-581, wherein each nucleobase of the 5'-region is independently selected from among thymine, uracil, guanine, cytosine, 5-methylcytosine, and adenine.
- 10 583. The oligomeric compound of any of embodiments 551-582, wherein each internucleoside linkage of the 5'-region is selected from among phosphodiester and phosphorothioate internucleoside linkages.
584. The oligomeric compound of any of embodiments 551-583, wherein the 3'-region consists of one nucleoside.
585. The oligomeric compound of any of embodiments 551-583, wherein the 3'-region consists of 2-5
15 linked nucleosides.
586. The oligomeric compound of any of embodiments 551-583, wherein the 3'-region consists of 2-4 linked nucleosides.
587. The oligomeric compound of any of embodiments 551-583, wherein the 3'-region consists of 2 linked nucleosides.
- 20 588. The oligomeric compound of any of embodiments 551-583, wherein the 3'-region consists of 3 linked nucleosides.
589. The oligomeric compound of any of embodiments 551-583, wherein the 3'-region consists of 4 linked nucleosides.
590. The oligomeric compound of any of embodiments 551-583, wherein the 3'-region consists of 5
25 linked nucleosides.
591. The oligomeric compound of any of embodiments 551-590, wherein each nucleoside of the 3'-region is a modified nucleoside.
592. The oligomeric compound of any of embodiments 551-591, wherein each nucleoside of the 3'-region is a modified nucleoside comprising a modified sugar moiety.
- 30 593. The oligomeric compound of any of embodiments 551-592, wherein each modified nucleoside of the 3'-region has the same modification.
594. The oligomeric compound of and of embodiments 551-592, wherein at least two nucleosides of the 3'-region are modified nucleosides having different modifications.
595. The oligomeric compound of any of embodiments 551-594, wherein each nucleoside of the 3'-region
35 comprises a 2'-modified ribosyl sugar moiety.

596. The oligomeric compound of any of embodiments 551-595, wherein at least one nucleoside of the 3'-region comprises a bicyclic furanosyl sugar moiety.
597. The oligomeric compound of any of embodiments 551-596, wherein each nucleoside of the 3'-region comprises a bicyclic furanosyl sugar moiety.
- 5 598. The oligomeric compound of any of embodiments 551-597, wherein at least one nucleoside of the 3'-region comprises a non-bicyclic sugar moiety.
599. The oligomeric compound of embodiment 598, wherein the non-bicyclic sugar moiety of the at least one nucleoside of the 3'-region is a 2'-substituted ribosyl sugar moiety.
- 10 600. The oligomeric compound of any of embodiments 551-599, wherein each nucleoside of the 3'-region comprises a non-bicyclic sugar moiety.
601. The oligomeric compound of embodiment 600, wherein each nucleoside of the 3'-region comprises a 2'-substituted furanosyl sugar moiety.
602. The oligomeric compound of any of embodiments 551-601, wherein each nucleoside of the 3'-region comprises a 2'-modified furanosyl sugar moiety independently selected from a bicyclic sugar moiety and a non-bicyclic 2'-substituted ribosyl sugar moiety.
- 15 603. The oligomeric compound of any of embodiments 551-602, wherein each nucleoside of the 3'-region comprises a bicyclic sugar moiety.
604. The oligomeric compound of any of embodiments 551-602, wherein each nucleoside of the 3'-region comprises a non-bicyclic 2'-substituted ribosyl sugar moiety.
- 20 605. The oligomeric compound of any of embodiments 551-603, wherein each bicyclic sugar moiety of the 3'-region is selected from among cEt, LNA, and ENA.
606. The oligomeric compound of any of embodiments 551-605, wherein each bicyclic sugar moiety of the 3'-region is a cEt sugar moiety.
607. The oligomeric compound of any of embodiments 551-606, wherein each bicyclic sugar moiety of the 3'-region is an LNA sugar moiety.
- 25 608. The oligomeric compound of any of embodiments 551-607, wherein each non-bicyclic sugar moiety of the 3'-region has a 2'-substituent selected from among 2'-MOE, 2'-OMe, and 2'-NMA.
609. The oligomeric compound of any of embodiments 551-608, wherein none of the nucleosides of the 3'-region comprise a sugar moiety having a 2'-F substituent.
- 30 610. The oligomeric compound of any of embodiments 551-609, wherein none of the nucleosides of the 3'-region comprise a sugar moiety having a 2'-MOE substituent.
611. The oligomeric compound of any of embodiments 551-610, wherein none of the nucleosides of the 3'-region comprise a sugar moiety having a 2'-OMe substituent.
612. The oligomeric compound of any of embodiments 551-611, wherein none of the nucleosides of the 35 3'-region comprise a cEt sugar moiety.

613. The oligomeric compound of any of embodiments 551-612, wherein none of the nucleosides of the 3'-region comprise a LNA sugar moiety.
614. The oligomeric compound of any of embodiments 551-613, wherein each nucleobase of the 3'-region is independently selected from among thymine, uracil, guanine, cytosine, 5-methylcytosine, and adenine.
615. The oligomeric compound of any of embodiments 551-614, wherein each internucleoside linkage of the 3'-region is selected from among phosphodiester and phosphorothioate internucleoside linkages.
616. The oligomeric compound of any of embodiments 551-615, wherein the modified nucleosides of the 5'-region have the same modifications as the modifications of the modified nucleosides of the 3'-region.
617. The oligomeric compound of any of embodiments 551-615, wherein at least one modified nucleoside of the 5'-region and one modified nucleoside of the 3'-region comprise modifications that differ from one another.
618. The oligomeric compound of any of embodiments 551-617, wherein the 5'-region and the 3'-region together include at least one non-bicyclic 2'-substituted modified nucleoside and at least one bicyclic nucleoside.
619. The oligomeric compound of any of embodiment 618, where the bicyclic nucleoside is a cEt nucleoside.
620. The oligomeric compound of embodiment 618, where the bicyclic nucleoside is an LNA nucleoside.
621. The oligomeric compound of any of embodiments 618-620, wherein the non-bicyclic 2'-modified nucleoside is a 2'-MOE nucleoside.
622. The oligomeric compound of any of embodiments 618-620, wherein the non-bicyclic 2'-modified nucleoside is a 2'-OMe nucleoside.
623. The oligomeric compound of any of embodiments 618-622, wherein at least one nucleoside of the 5'-region or the 3'-region is an unmodified DNA nucleoside.
624. The oligomeric compound of any of embodiments 551-623, wherein the central region has the formula:

$$(N_{da})(N_x)(N_y)(N_z)(N_{db})(N_{dc})_q$$
 wherein each N_{dc} is independently selected from an unmodified DNA nucleoside, a DNA isomer, a 2'-modified DNA isomer, and a DNA mimic; and q is 2-6.
625. The oligomeric compound of any of embodiments 551-624, wherein the central region consists of 7 linked nucleosides.
626. The oligomeric compound of any of embodiments 551-624, wherein the central region consists of 8 linked nucleosides.

627. The oligomeric compound of any of embodiments 551-624, wherein the central region consists of 9 linked nucleosides.
628. The oligomeric compound of any of embodiments 551-624, wherein the central region consists of 10 linked nucleosides.
- 5 629. The oligomeric compound of any of embodiments 551-624, wherein the central region consists of 11 linked nucleosides.
630. The oligomeric compound of any of embodiments 551-629, wherein Nx is the safety-enhancing nucleoside.
631. The oligomeric compound of any of embodiments 551-629, wherein Ny is the safety-enhancing
10 nucleoside.
632. The oligomeric compound of any of embodiments 551-629, wherein Nz is the safety-enhancing nucleoside.
633. The oligomeric compound of any of embodiments 551-632, wherein the safety enhancing nucleoside is a DNA isomer or a modified DNA isomer, or a modified nucleoside comprising either a sugar
15 surrogate, a bicyclic furanosyl sugar moiety, or a non-bicyclic modified furanosyl sugar moiety.
634. The oligomeric compound of any of embodiments 551-33, wherein the safety enhancing nucleoside is a DNA isomer or a modified DNA isomer, or comprises either a sugar surrogate, a bicyclic furanosyl sugar moiety, a non -bicyclic, 2'-modified furanosyl sugar moiety, a non-bicyclic 3'-modified furanosyl sugar moiety, a non-bicyclic, 4'-modified furanosyl sugar moiety, or a non-
20 bicyclic 5'-modified furanosyl sugar moiety.
635. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing nucleoside comprises a sugar surrogate selected from a morpholino, a modified morpholino, a modified cyclohexenyl, or a modified tetrahydropyran.
636. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing nucleoside
25 comprises a sugar surrogate selected from a morpholino, a modified morpholino, CeNA, F-CeNA, HNA, OMe-HNA or F-HNA.
637. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing nucleoside is a DNA isomer comprising a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 2'-α-D-deoxyribosyl, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl.
30
638. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing nucleoside is a DNA isomer comprising a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, and 2'-β-L-deoxyribosyl.
639. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing nucleoside
35 is a modified DNA isomer comprising a 2'-modified sugar moiety, wherein the sugar moiety has the

conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a hydroxyl, a fluoro, or O-C₁-C₁₀ alkoxy substituent.

640. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing nucleoside is a modified DNA isomer comprising a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a hydroxyl, a fluoro, or OMe substituent.

641. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing nucleoside is a modified DNA isomer comprising a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a fluoro or OMe substituent.

642. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing nucleoside is a modified DNA isomer comprising a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, and 2'-β-L-deoxyribosyl and the 2' position is further substituted with a hydroxyl, fluoro, or OMe substituent.

643. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing nucleoside is a modified nucleoside comprising a bicyclic furanosyl sugar moiety

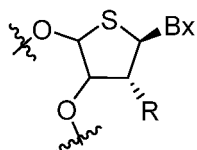
644. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing nucleoside is selected from among cEt, LNA, α-L-LNA, and ENA.

645. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing nucleoside comprises a 2'-substituted furanosyl sugar moiety.

646. The oligomeric compound of embodiment 645, wherein the 2'-substituted furanosyl sugar moiety of the safety enhancing nucleoside has a 2' substituent selected from: halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, 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-alkylenyl-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.

647. The oligomeric compound of embodiment 645, wherein the 2'-substituted furanosyl sugar moiety of the safety enhancing nucleoside has a 2' substituent selected from: halo, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, S-alkyl, N(R_m)-alkyl, 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.

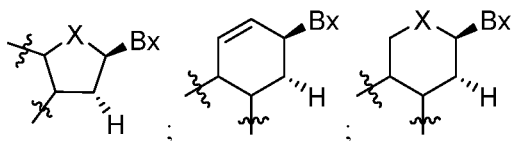
648. The oligomeric compound of embodiment 645, wherein the 2'-substituted furanosyl sugar moiety of the safety enhancing nucleoside has a 2' substituent selected from: fluoro, OMe, MOE, NMA.
649. The oligomeric compound of any of embodiments 551-648, wherein the safety enhancing nucleoside comprises a 2'-substituted furanosyl sugar moiety comprising a 2'-OMe or 2'-MOE.
- 5 650. The oligomeric compound of any of embodiments 551-649, wherein the safety enhancing nucleoside comprises a 2'-substituted furanosyl sugar moiety comprising a 2'-OMe.
651. The oligomeric compound of any of embodiments 551-650, wherein the safety enhancing nucleoside comprises a 2'-OMe modified 2'-β-D-deoxyribose sugar moiety.
652. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing
10 nucleoside comprises a 3'-modified furanosyl sugar moiety having a 3' substituent selected from: halo, allyl, amino, azido, SH, CN, CF₃, OCF₃, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, S-alkyl, N(R_m)-alkyl, N(R_m)-alkenyl, N(R_m)-alkynyl, O-alkylenyl-O-alkyl, alkynyl, alkaryl, or aralkyl.
653. The oligomeric compound of any of embodiments 551-634 or embodiment 652, wherein the safety
15 enhancing nucleoside comprises a 3'-modified furanosyl sugar moiety having a 3' substituent selected from: C₁-C₁₀ alkyl, or C₁-C₁₀ substituted alkyl.
654. The oligomeric compound of any of embodiments 551-634 or 652-653, wherein the safety enhancing nucleoside comprises a 3'-methyl furanosyl sugar moiety.
655. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing nucleoside
20 comprises a 4'-modified furanosyl sugar moiety having a 4' substituent selected from: halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, 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-alkylenyl-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,
25 independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ alkyl.
656. The oligomeric compound of any of embodiments 551-634 or 655, wherein the safety enhancing nucleoside comprises a 4'-modified furanosyl sugar moiety having a 4'-methyl.
657. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing nucleoside has the structure shown below, wherein R represents an optional 2' substituent group and Bx is a
30 heterocyclic base moiety:



658. The oligomeric compound of embodiment 657, wherein in R is selected from among H, OH, OMe, F, or MOE.

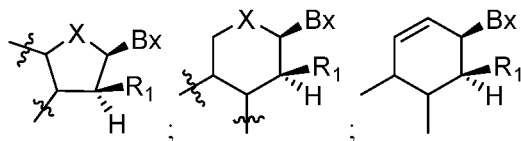
659. The oligomeric compound of any of embodiments 551-634, wherein the safety enhancing nucleoside comprises a 5'-modified furanosyl sugar moiety having a 5' substituent selected from: halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, C₁-C₁₀ 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-alkylenyl-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.
660. The oligomeric compound of any of embodiments 551-634 or 659, wherein the safety enhancing nucleoside comprises a 5'-modified furanosyl sugar moiety with a 5' substituent selected from: 5'-methyl, 5'-ethyl or a 5'-allyl.
661. The oligomeric compound of any of embodiments 551-634 or 659-660, wherein the safety enhancing nucleoside comprises a 5'-modified furanosyl sugar moiety with a 5' substituent selected from: 5'-(*R*)-methyl- or 5'-(*R*)-ethyl.
662. The oligomeric compound of any of embodiments 551-634 or 659-661, wherein the safety enhancing nucleoside comprises a 5'-(*R*)-methyl-2'-β-D-deoxyribosyl sugar moiety.
663. The oligomeric compound of any of embodiments 551-634 or 659-662, wherein the safety enhancing nucleoside comprises a 5'-(*R*)-ethyl-2'-β-D-deoxyribosyl sugar moiety.
664. The oligomeric compound of any of embodiments 551-663, wherein the safety enhancing nucleoside does not comprise a 2'-F modified sugar moiety.
665. The oligomeric compound of any of embodiments 551-664, wherein the safety enhancing nucleoside does not comprise a cEt modified sugar moiety.
666. The oligomeric compound of any of embodiments 551-665, wherein the safety enhancing nucleoside does not comprise a 2'-MOE modified sugar moiety.
667. The oligomeric compound of any of embodiments 551-666, wherein the safety enhancing nucleoside comprises a hypoxanthine nucleobase.
668. The oligomeric compound of any of embodiments 551-667, wherein the safety enhancing nucleoside comprises a nucleobase selected from among A, T, G, C, ¹³C, and U.
669. The oligomeric compound of any of embodiments 551-668, wherein the safety enhancing nucleoside is a modified nucleoside other than cEt, MOE, LNA, or FANA.
670. The oligomeric compound of any of embodiments 551-669, wherein each Nd is independently selected from among a DNA nucleoside, a DNA isomer, a modified DNA isomer, and a DNA mimic.
671. The oligomeric compound of embodiment 670, wherein each DNA isomer comprises a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 2'-α-D-deoxyribosyl, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl.

672. The oligomeric compound of embodiment 671, wherein each DNA isomer comprises a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, and 2'-β-L-deoxyribosyl.
673. The oligomeric compound of embodiment 670, wherein each modified DNA isomer comprises a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a hydroxyl, a fluoro, or O-C1-C10 alkoxy substituent.
674. The oligomeric compound of embodiment 673, wherein each modified DNA isomer comprises a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a hydroxyl, a fluoro, or OMe substituent.
675. The oligomeric compound of embodiment 674, wherein each modified DNA isomer comprises a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a fluoro or OMe substituent.
676. The oligomeric compound of embodiment 675, wherein each modified DNA isomer comprises a 2'-modified sugar moiety, wherein the sugar moiety is selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, and 2'-β-L-deoxyribosyl and the 2' position is further substituted with a hydroxyl, fluoro, or OMe substituent.
677. The oligomeric compound of embodiment 670, wherein each DNA mimic comprises a structure represented by one of the formulas below:



wherein X is O or S and Bx represents a heterocyclic base moiety.

678. The oligomeric compound of embodiment 670, wherein each DNA mimic comprises a structure represented by one of the formulas below:



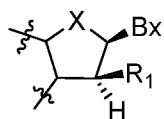
wherein X is O or S, Bx represents a heterocyclic base moiety, and R1 is selected from among H, OH, halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, S-alkyl, N(R_m)-alkyl, O-alkenyl, S-alkenyl, N(R_m)-alkenyl, O-alkynyl, S-alkynyl, N(R_m)-alkynyl, O-alkylenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-

alkaryl, O-aralkyl, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(R_m)(R_n)$ or $OCH_2C(=O)-N(R_m)(R_n)$, where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C_1 - C_{10} alkyl.

679. The oligomeric compound of embodiment 678, wherein R_1 is H, OH, OMe, or F.

680. The oligomeric compound of embodiment 678, wherein R_1 is not F.

5 681. The oligomeric compound of embodiment 670, wherein each DNA mimic comprises a structure represented by the formula below:



; wherein X is O, Bx represents a heterocyclic base moiety, and R_1 is H.

682. The oligomeric compound of embodiment 670, wherein DNA mimic has a sugar moiety selected from among: 5'-methyl-2'-β-D-deoxyribosyl, 5'-ethyl-2'-β-D-deoxyribosyl, and 5'-allyl-2'-β-D-deoxyribosyl.

683. The oligomeric compound of embodiment 670, wherein DNA mimic comprises a 2'-fluoro-β-D-arabinofuranosyl sugar moiety

684. The oligomeric compound of embodiment 670, wherein the DNA mimic does not comprise a 2'-fluoro-β-D-arabinofuranosyl sugar moiety.

685. The oligomeric compound of any of embodiments 551-684, wherein each Nd is a DNA nucleoside.

686. The oligomeric compound of any of embodiments 551-685, wherein the central region comprises no more than four nucleosides selected from among DNA isomers, modified DNA isomers, and DNA mimics.

687. The oligomeric compound of any of embodiments 551-685, wherein the central region comprises no more than three nucleosides selected from among DNA isomers, modified DNA isomers, and DNA mimics.

688. The oligomeric compound of any of embodiments 551-685, wherein the central region comprises no more than two nucleosides selected from among DNA isomers, modified DNA isomers, and DNA mimics.

689. The oligomeric compound of any of embodiments 551-685, wherein the central region comprises no more than one nucleoside selected from among DNA isomers, modified DNA isomers, and DNA mimics.

690. The oligomeric compound of any of embodiments 551-689, wherein the central region contains exactly one safety enhancing nucleoside and the remainder of nucleosides in the central region are DNA nucleosides.

691. The oligomeric compound of any of embodiments 551-690, wherein at least one internucleoside linkage of the central region selected from among: the internucleoside N_d to N_x , N_x to N_y , N_y to N_z , or N_z to the adjacent N_{db} is a neutral internucleoside linkage.

692. The oligomeric compound of embodiments 691, wherein the neutral linkage is a phosphonate internucleoside linkage.
693. The oligomeric compound of embodiments 691, wherein the neutral linkage is a methoxypropyl internucleoside linkage.
- 5 694. The oligomeric compound of embodiments 691, wherein each remaining internucleoside linkage is a phosphodiester or phosphorothioate internucleoside linkage.
695. A chirally enriched population of modified oligonucleotides of any of embodiments 551-690, wherein the central region has at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.
- 10 696. The chirally enriched population of embodiment 695, wherein the central region has at least one phosphorothioate internucleoside linkage having the (*Sp*) configuration.
697. The chirally enriched population of embodiment 695, wherein central region has at least one phosphorothioate internucleoside linkage having the (*Rp*) configuration.
698. The chirally enriched population of embodiment 695, wherein the central region has a particular,
15 independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.
699. The chirally enriched population of embodiment 698, wherein the each phosphorothioate internucleoside linkage of the central region has the (*Sp*) configuration.
700. The chirally enriched population of embodiment 698, wherein the central region has one
20 phosphorothioate internucleoside linkage having the (*Rp*) configuration and wherein each remaining central region phosphorothioate internucleoside linkage has the (*Sp*) configuration.
701. The chirally enriched population of embodiment 695, wherein the central region has an (*Rp*) phosphorothioate internucleoside linkage adjacent to an (*Sp*) phosphorothioate internucleoside linkage.
- 25 702. The chirally enriched population of embodiment 695, wherein the central region has an (*Rp*) phosphorothioate internucleoside linkage adjacent to a second (*Rp*) phosphorothioate internucleoside linkage.
703. The chirally enriched population of embodiment 695, wherein the central region has an (*Rp*) phosphorothioate internucleoside linkage adjacent to a second (*Rp*) phosphorothioate internucleoside
30 linkage, and wherein each remaining central region phosphorothioate internucleoside linkage has the (*Sp*) configuration.
704. The chirally enriched population of any of embodiments 696, 697, 701, or 702 wherein each phosphorothioate internucleoside linkage that does not have the (*Rp*) or (*Sp*) configuration is stereorandom.
- 35 705. The oligomeric compound of any of embodiments 551-704 comprising a conjugate group.

706. The oligomeric compound of embodiment 705, wherein the conjugate group comprises a linking group attaching the remainder of the conjugate group to the modified oligonucleotide, wherein the linking group comprises 1-5 nucleosides.
707. The oligomeric compound of any of embodiments 1-705, wherein the oligomeric compound does not
5 comprise additional nucleosides beyond those of the modified oligonucleotide.
708. The oligomeric compound of any of embodiments 551-707, wherein the nucleobase sequence of the modified oligonucleotide is complementary to a target RNA.
709. The oligomeric compound of embodiment 708, wherein the nucleobase sequence of the modified oligonucleotide is at least 85% complementary to the target RNA.
- 10 710. The oligomeric compound of embodiment 708, wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to the target RNA.
711. The oligomeric compound of embodiment 708, wherein the nucleobase sequence of the modified oligonucleotide is at least 95% complementary to the target RNA.
712. The oligomeric compound of embodiment 711, wherein the nucleobase sequence of the modified
15 oligonucleotide is 100% complementary to the target RNA.
713. The oligomeric compound of any of embodiments 708-712, wherein the target RNA is a target mRNA or a target pre-mRNA.
714. The oligomeric compound of embodiment 713, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human PTEN RNA.
- 20 715. The oligomeric compound of embodiment 713 or 714, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human SRB-1 RNA.
716. The oligomeric compound of any of embodiments 713-715, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human MYD88 RNA.
717. The oligomeric compound of any of embodiments 713-716, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human HTT RNA, is not a mouse, rat, monkey, or human
25 SOD1 RNA, and is not a mouse, rat, monkey, or human alpha-synuclein RNA.
718. The oligomeric compound of any of embodiments 708-717, wherein the target RNA is a human RNA.
719. The oligomeric compound of any of embodiments 708-718, wherein the target RNA is expressed in
30 the liver.
720. The oligomeric compound of any of embodiments 708-719, wherein the target RNA is a liver target.
721. The oligomeric compound of any of embodiments 708-718, wherein the target RNA is not expressed in the liver.
722. The oligomeric compound of any of embodiments 708-718 or 721, wherein the target RNA is not a
35 liver target.

723. The oligomeric compound of any of embodiments 708-722, wherein modulation of the expression of the target RNA in the liver is associated with treating a disorder or condition.
724. The oligomeric compound of embodiment 723, wherein the disorder or condition is a liver disorder or condition.
- 5 725. The oligomeric compound of any of embodiments 708-724, wherein the target RNA is expressed in the central nervous system.
726. The oligomeric compound of any of embodiments 708-724, wherein the target RNA is not expressed in the central nervous system.
- 10 727. The oligomeric compound of any of embodiments 708-725, wherein the target RNA is a central nervous system target.
728. The oligomeric compound of any of embodiments 708-726, wherein the target RNA is not a central nervous system target.
- 15 729. The oligomeric compound of any of embodiments 708-727, wherein the target RNA is a MeCP2, DUX4, HDAC2, APP, Ataxin 1, Ataxin 2, Ataxin 3, Ataxin 6, Ataxin 7, C9ORF72, UBE3A, Prion, PMP22, Tau, LRRK2, LINGO2, GYS1, KCNT1, IRF8, Progranulin, or GFAP RNA.
730. The oligomeric compound of any of embodiments 708-729, wherein the target RNA is a HTT RNA.
731. The oligomeric compound of embodiment 729, wherein the target RNA is a MeCP2 RNA.
732. The oligomeric compound of embodiment 729, wherein the target RNA is a DUX4 RNA.
733. The oligomeric compound of embodiment 729, wherein the target RNA is a HDAC2 RNA.
- 20 734. The oligomeric compound of embodiment 729, wherein the target RNA is a Ataxin 1 RNA.
735. The oligomeric compound of embodiment 729, wherein the target RNA is a Ataxin 2 RNA.
736. The oligomeric compound of embodiment 729, wherein the target RNA is a Ataxin 3 RNA.
737. The oligomeric compound of embodiment 729, wherein the target RNA is a Ataxin 6 RNA.
738. The oligomeric compound of embodiment 729, wherein the target RNA is a Ataxin 7 RNA.
- 25 739. The oligomeric compound of embodiment 729, wherein the target RNA is a C9ORF72 RNA.
740. The oligomeric compound of embodiment 708-727, wherein the target RNA is an alpha-synuclein RNA.
741. The oligomeric compound of embodiment 729, wherein the target RNA is an UBE3A RNA.
742. The oligomeric compound of any of embodiments 708-727, wherein the target RNA is a SOD1 RNA.
- 30 743. The oligomeric compound of any of embodiments 708-727, wherein the target RNA is a Prion RNA.
744. The oligomeric compound of any of embodiments 708-727, wherein the target RNA is a PMP22 RNA.
745. The oligomeric compound of any of embodiments 708-727, wherein the target RNA is a Tau RNA.
746. The oligomeric compound of any of embodiments 708-727, wherein the target RNA is a LRRK2 RNA.
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747. The oligomeric compound of any of embodiments 708-727, wherein the target RNA is an APP RNA.
748. The oligomeric compound of any of embodiments 708-727, wherein the target RNA is a LINGO2 RNA.
749. The oligomeric compound of any of embodiments 708-727, wherein the target RNA is a GYS1 RNA.
- 5 750. The oligomeric compound of any of embodiments 708-727, wherein the target RNA is a KCNT1 RNA.
751. The oligomeric compound of any of embodiments 708-727, wherein the target RNA is a IRF8 RNA.
752. The oligomeric compound of any of embodiments 708-727, wherein the target RNA is a Progranulin RNA.
- 10 753. The oligomeric compound of any of embodiments 708-727, wherein the target RNA is a GFAP RNA.
754. The oligomeric compound of any of embodiments 725-753, wherein modulation of the expression of the target RNA in the central nervous system is associated with treating a disorder or condition.
755. The oligomeric compound of embodiment 754, wherein the disorder or condition is a neurological disorder or condition.
- 15 756. The oligomeric compound of embodiment 754-755, wherein the disorder or condition alters the function of sensory or motor neurons.
757. The oligomeric compound of any of embodiments 754-756, wherein the disorder or condition alters the function of sensory neurons.
- 20 758. The oligomeric compound of any of embodiments 754-757, wherein the disorder or condition alters the function of motor neurons.
759. The oligomeric compound of any of embodiments 754-758, wherein the disorder or condition alters the function of glial cells.
760. The oligomeric compound of any of embodiments 754-759, wherein the disorder or condition alters the function of astrocytes.
- 25 761. The oligomeric compound of any of embodiments 754-760, wherein the disorder or condition alters the function of oligodendrocytes.
762. The oligomeric compound of any of embodiments 754-761, wherein the disorder or condition alters the function of microglia.
- 30 763. The oligomeric compound of any of embodiments 754-762, wherein the disorder or condition alters the function of ependymal cells.
764. The oligomeric compound of any of embodiments 754-763, wherein the disorder or condition is Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Parkinson's Disease, a Spinocerebellar ataxia, Angelman Syndrome, Alexander's Disease, Lafora Disease, Charcot-Marie Tooth Disease, Prion

Disease, a dementia, neurodegeneration, McCP2 Duplication Syndrome, encephalopathy, neuroinflammation, or multiple sclerosis.

765. The oligomeric compound of embodiment 764, wherein the disorder or condition is Alzheimer's Disease.

5 766. The oligomeric compound of embodiment 764, wherein the disorder or condition is Amyotrophic Lateral Sclerosis.

767. The oligomeric compound of embodiment 764, wherein the disorder or condition is Parkinson's Disease.

10 768. The oligomeric compound of embodiment 764, wherein the disorder or condition is a Spinocerebellar ataxia.

769. The oligomeric compound of embodiment 764, wherein the disorder or condition is Angelman Syndrome.

770. The oligomeric compound of embodiment 764, wherein the disorder or condition is Alexander's Disease.

15 771. The oligomeric compound of embodiment 764, wherein the disorder or condition is Lafora Disease.

772. The oligomeric compound of embodiment 764, wherein the disorder or condition is Charcot-Marie Tooth Disease.

773. The oligomeric compound of embodiment 764, wherein the disorder or condition is Prion Disease.

774. The oligomeric compound of embodiment 764, wherein the disorder or condition is a dementia.

20 775. The oligomeric compound of embodiment 764, wherein the disorder or condition is neurodegeneration.

776. The oligomeric compound of embodiment 764, wherein the disorder or condition is McCP2 Duplication Syndrome.

777. The oligomeric compound of embodiment 764, wherein the disorder or condition is encephalopathy.

25 778. The oligomeric compound of embodiment 764, wherein the disorder or condition is neuroinflammation.

779. The oligomeric compound of embodiment 764, wherein the disorder or condition is multiple sclerosis.

30 780. The oligomeric compound of any of embodiments 551-779, wherein the parent oligomeric compound of the oligomeric compound of any of embodiments 551-779 is cytotoxic in vitro.

781. The oligomeric compound of embodiment 780, wherein the parent oligomeric compound is cytotoxic in a standard in vitro cytotoxicity assay.

35 782. The oligomeric compound of any of embodiments 551-781 wherein administration to a mouse of the parent oligomeric compound of the oligomeric compound of any of embodiments 551-781 is hepatotoxic to the mouse.

783. The oligomeric compound of embodiment 782, wherein the administration of the parent oligomeric compound to the mouse is systemic administration.
784. The oligomeric compound of embodiment 783, wherein the systemic administration is subcutaneous administration.
- 5 785. The oligomeric compound of any of embodiments 782-784, wherein the mouse is a CD-1 mouse.
786. The oligomeric compound of any of embodiments 782-784, wherein the mouse is a C57BL/6 mouse.
787. The oligomeric compound of any of embodiments 782-784, wherein the mouse is a BALB/c mouse.
788. The oligomeric compound of any of embodiments 782-784, wherein the plasma ALT level in the mouse is higher than 500 units per liter following the administration of the parent oligomeric compound.
- 10
789. The oligomeric compound of any of embodiments 782-788, wherein the plasma AST level in the mouse is higher than 500 units per liter following the administration of the parent oligomeric compound.
790. The oligomeric compound of any of embodiments 782-789, wherein the plasma ALT level in the mouse is higher than 1000 units per liter following the administration of the parent oligomeric compound.
- 15
791. The oligomeric compound of any of embodiments 782-790, wherein the plasma AST level in the mouse is higher than 1000 units per liter following the administration of the parent oligomeric compound.
792. The oligomeric compound of any of embodiments 782-791, wherein the hepatotoxicity is measured 24-48 hours following the administration of the parent oligomeric compound.
- 20 793. The oligomeric compound of any of embodiments 782-791, wherein the hepatotoxicity is measured 72 hours following the administration of the parent oligomeric compound.
794. The oligomeric compound of any of embodiments 782-791, wherein the hepatotoxicity is measured 3 days following the administration of the parent oligomeric compound.
795. The oligomeric compound of any of embodiments 782-791, wherein the hepatotoxicity is measured 5 days following the administration of the parent oligomeric compound.
- 25
796. The oligomeric compound of any of embodiments 782-791, wherein the hepatotoxicity is measured 7 days following the administration of the parent oligomeric compound.
797. The oligomeric compound of any of embodiments 782-791, wherein the hepatotoxicity is measured 10 days following the administration of the parent oligomeric compound.
- 30 798. The oligomeric compound of any of embodiments 782-791, wherein the hepatotoxicity is measured 14 days following the administration of the parent oligomeric compound.
799. The oligomeric compound of any of embodiments 782-791, wherein 1-10 mg/kg of the parent oligomeric compound is administered to the mouse.
800. The oligomeric compound of any of embodiments 782-791, wherein 10-25 mg/kg of the parent oligomeric compound is administered to the mouse.
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801. The oligomeric compound of any of embodiments 782-791, wherein 25-50 mg/kg of the parent oligomeric compound is administered to the mouse.
802. The oligomeric compound of any of embodiments 782-791, wherein 50-100 mg/kg of the parent oligomeric compound is administered to the mouse.
- 5 803. The oligomeric compound of any of embodiments 782-791, wherein 100-150 mg/kg of the parent oligomeric compound is administered to the mouse.
804. The oligomeric compound of any of embodiments 782-791, wherein the mouse is a BALB/c mouse, wherein 150 mg/kg of the parent oligomeric compound is administered to the mouse, and wherein the plasma ALT level in the mouse is measured 72 hours following the administration of the parent
10 oligomeric compound.
805. The oligomeric compound of any of embodiments 551-804, wherein administration of 50 mg/kg of the oligomeric compound of any of embodiments 551-804 to a mouse is not hepatotoxic to the mouse.
806. The oligomeric compound of embodiment 805, wherein plasma ALT level in the mouse is lower than 100 units per liter following the administration of the oligomeric compound of embodiment 805.
- 15 807. The oligomeric compound of embodiment 805 or 806, wherein plasma ALT level in the mouse is at least 10-fold lower than plasma ALT level in a mouse administered the parent oligomeric compound of the oligomeric compound of embodiment 384 or 385, wherein the administrations and plasma ALT measurements of both the oligomeric compound of embodiment 384 or 385 and the parent oligomeric compound are completed in the same way.
- 20 808. The oligomeric compound of embodiment 807, wherein the plasma ALT level in the mouse is at least 100-fold lower than the plasma ALT level in the mouse administered the parent oligomeric compound.
809. The oligomeric compound of embodiment 807, wherein the plasma ALT level in the mouse is at least 500-fold lower than the plasma ALT level in the mouse administered the parent oligomeric compound.
810. The oligomeric compound of any of embodiments 782-809, wherein the therapeutic index in a mouse
25 of the oligomeric compound of any of embodiments 782-809 is increased relative to the therapeutic index of the parent oligomeric compound.
811. The oligomeric compound of embodiment 810, wherein the therapeutic index in a mouse of the oligomeric compound of embodiment 365 is at least two-fold greater than the therapeutic index of the parent oligomeric compound.
- 30 812. The oligomeric compound of any of embodiments 551-811, wherein an otherwise identical oligomeric compound lacking the at least one modified internucleoside linkage other than phosphorothioate and/or at least one modified nucleoside comprising a modified nucleobase other than 5-methylcytosine and/or a modified sugar moiety in the central region is hepatotoxic following administration to a mouse;

and wherein the otherwise identical oligomeric compound has a central region consisting of phosphorothioate internucleoside linkages, unmodified 2'- β -D-deoxyribosyl sugar moieties, and nucleobases selected from thymine, uracil, adenine, guanine, cytosine, and 5-methylcytosine.

813. The oligomeric compound of embodiment 812, wherein the at least one modified internucleoside linkage other than phosphorothioate and/or at least one modified nucleoside comprising a modified nucleobase other than 5-methylcytosine and/or a modified sugar moiety in the central region is a 2'-O-methyl modified sugar moiety.

814. The oligomeric compound of embodiment 813, wherein the 2'-O-methyl modified sugar moiety is at position 2 of the central region.

815. The oligomeric compound of embodiment 812-814, wherein the otherwise identical oligomeric compound lacks a 2'-O-methyl modified sugar moiety, and wherein the otherwise identical oligomeric compound comprises an unmodified 2'- β -D-deoxyribosyl sugar moiety in place of the 2'-O-methyl modified sugar moiety.

816. The oligomeric compound of any of embodiments 812-815, wherein the nucleobase sequence of the otherwise identical oligomeric compound is 100% complementary to the target RNA.

817. The oligomeric compound of any of embodiments 812-816, wherein the otherwise identical oligomeric compound is a parent oligomeric compound of the oligomeric compound of any of embodiments 812-816.

818. The oligomeric compound of any of embodiments 708-817, wherein the oligomeric compound inhibits the target RNA with an IC_{50} lower than 100 nM in a standard in vitro activity assay.

819. The oligomeric compound of any of embodiments 708-818, wherein the parent oligomeric compound of the oligomeric compound of any of embodiments 708-818 inhibits the target RNA with an IC_{50} lower than 100 nM in a standard in vitro activity assay.

820. The oligomeric compound of any of embodiments 708-819, wherein the difference between the IC_{50} of the parent oligomeric compound measured in a standard in vitro activity assay and the IC_{50} of the oligomeric compound of any of embodiments 708-819 measured in a standard in vitro activity assay is less than 4-fold.

821. The oligomeric compound of any of embodiments 708-820, wherein the difference between the IC_{50} of the parent oligomeric compound measured in a standard in vitro activity assay and the IC_{50} of the oligomeric compound of any of embodiments 708-820 measured in a standard in vitro activity assay is less than 3-fold.

822. The oligomeric compound of any of embodiments 708-821, wherein the difference between the IC_{50} of the parent oligomeric compound measured in a standard in vitro activity assay and the IC_{50} of the oligomeric compound of any of embodiments 708-821 measured in a standard in vitro activity assay is less than 2-fold.

823. The oligomeric compound of any of embodiments 708-822, wherein each sugar moiety of the central region of the parent oligomeric compound is an unmodified 2'- β -D-deoxyribosyl sugar moiety, and wherein each internucleoside linkage of the central region of the parent oligomeric compound is a phosphorothioate internucleoside linkage.
- 5 824. The oligomeric compound of any of embodiments 708-823, wherein the nucleobase sequence of the parent oligomeric compound is 100% complementary to the target RNA.
825. The oligomeric compound of any of embodiments 551-824, wherein administration of 10-50 mg of the oligomeric compound to a human is not hepatotoxic to the human.
826. The oligomeric compound of any of embodiments 551-824, wherein administration of 50-100 mg of
10 the oligomeric compound to a human is not hepatotoxic to the human.
827. The oligomeric compound of any of embodiments 551-824, wherein administration of 100-300 mg of the oligomeric compound to a human is not hepatotoxic to the human.
828. The oligomeric compound of any of embodiments 825-827, wherein the administration is systemic administration.
- 15 829. A composition comprising the oligomeric compound of any of embodiments 551-828 and a second oligomeric compound, wherein the second oligomeric compound is complementary to the oligomeric compound of any of embodiments 551-828.
830. The composition of embodiment 829, wherein the second oligomeric compound comprises at least 14 contiguous linked nucleosides that are at least 90% complementary to the oligomeric compound of
20 any of embodiments 551-828.
831. The composition of embodiment 830, wherein the second oligomeric compound comprises at least 14 contiguous linked nucleosides that are 100% complementary to the oligomeric compound of any of embodiments 551-828.
832. A pharmaceutical composition comprising the oligomeric compound of any of embodiments 551-828
25 or the composition of any of embodiments 829-831, comprising a pharmaceutically acceptable carrier or diluent.
833. A method comprising administering the oligomeric compound or composition of any of embodiments 551-832 to a human subject.
834. A method of treating a disease or disorder comprising administering the oligomeric compound or
30 composition of any of embodiments 551-832 to a human subject.
835. A method of modulating the amount or activity of a target RNA in a human subject comprising administering the oligomeric compound or composition of any of embodiments 551-832 to the human subject; and thereby modulating the amount or activity of the target RNA in the human subject.

836. A method of treating a disease or disorder in a human subject comprising administering the oligomeric compound or composition of any of embodiments 551-832 to the human subject having the disease or disorder; and thereby treating the disease or disorder in the human subject.
837. The method of embodiment 835-836, wherein the disease or disorder is a liver disease, and wherein the oligomeric compound modulates the amount or activity of a liver target RNA.
838. The method of embodiment 835-837, wherein the disease or disorder is a central nervous system disease, and wherein the oligomeric compound modulates the amount or activity of a central nervous system target RNA.
839. The method of any of embodiments 834-838, wherein the disease or disorder is a cancer, a neurodegenerative disease, a cardiovascular disease, an immunological disease, a hereditary disease, a repeat expansion disease, a muscle-wasting disease, or a metabolic disease.
840. The method of any of embodiments 834-839, wherein the plasma ALT level of the human subject after the administration is not more than three times higher than it was prior to the administration.
841. The method of any of embodiments 834-840, wherein the plasma ALT level of the human subject after the administration is not more than 150 units per liter.
842. The method of any of embodiments 834-841, wherein the human subject is susceptible to liver damage.
843. The method of any of embodiments 834-842, wherein the human subject is susceptible to liver degeneration.
844. The method of any of embodiments 834-843, wherein the human subject is susceptible to elevated apoptosis in the liver.
845. The method of any of embodiments 834-844, wherein the human subject has a liver disease.
846. The method of any of embodiments 834-841, comprising administering the parent oligomeric compound of the oligomeric compound of any of embodiments 551-832 to a mouse.
847. The method of any of embodiments 833-846, comprising contacting a cell with the parent oligomeric compound of the oligomeric compound of any of embodiments 551-832.
848. The method of embodiment 846-847, wherein each sugar moiety of the central region of the parent oligomeric compound is an unmodified 2'-β-D-deoxyribosyl sugar moiety, and wherein each internucleoside linkage of the central region of the parent oligomeric compound is a phosphorothioate internucleoside linkage.
849. A method of designing an oligomeric compound comprising starting with a parent oligomeric compound and changing the design of that compound in order to arrive at an oligomeric compound of any one of embodiments 551-833.
850. A method of designing an oligomeric compound comprising identifying a parent oligomeric compound and changing the design of that parent oligomeric compound to arrive at a second

oligomeric compound, wherein the second oligomeric compound is an oligomeric compound of any one of embodiments 551-833.

851. A method of improving hepatotoxicity of an oligomeric compound comprising the steps of (i) identifying a parent oligomeric compound that has plasma ALT levels above 300 units per liter in a mouse, and (ii) providing an oligomeric compound according to any one of embodiments 551-833.
852. The method of embodiment 851, wherein the method designs an oligomeric compound with improved therapeutic index relative to the parent oligomeric compound.
853. The method of embodiment 851-852, wherein the method designs an oligomeric compound with lower hepatotoxicity relative to the parent oligomeric compound.
854. The method of embodiment 853, wherein the second oligomeric compound has an improved therapeutic index relative to the parent oligomeric compound.
855. The method of embodiment 851-852, wherein the second oligomeric compound has reduced hepatotoxicity in a mouse relative to the parent oligomeric compound.
856. The method of embodiment 855, wherein the oligomeric compound according to any one of embodiments 551-833 has reduced hepatotoxicity relative to the parent oligomeric compound.
857. A method comprising administering an oligomeric compound of any of embodiments 551-833 to a mouse and separately administering the parent oligomeric compound of the oligomeric compound of any of embodiments 551-833 to a second mouse, wherein the therapeutic index of the oligomeric compound of any of embodiments 551-833 is improved relative to the therapeutic index of the parent oligomeric compound.
858. The method of any of embodiments 833-857, wherein the level of p21 RNA is measured in the mouse, the cell, and/or the human subject.
859. A method comprising administering an oligomeric compound of any of embodiments 551-833 to a subject and measuring the level of p21 RNA in the subject.
860. The method of embodiment 858 or 859, wherein the subject is a mouse.
861. The method of embodiment 858 or 859, wherein the subject is a human.
862. The method of any of embodiments 858-861, wherein the p21 RNA level is measured within 24 hours of the administration.
863. The method of any of embodiments 858-862, wherein the p21 RNA level is measured 24-48 hours following the administration.
864. An oligomeric compound or composition of any one of embodiments 551-832, for use in medical therapy.
865. The oligomeric compound of any of embodiments 551-832, wherein the oligomeric compound is not toxic.

866. The oligomeric compound of any of embodiment 551-832, wherein a comparator compound is toxic; wherein the comparator compound is identical to the oligomeric compound except that each nucleoside of the central region of the comparator compound is a nucleoside comprising 2'-β-D-deoxyribyl sugar moiety.
- 5 867. The oligomeric compound of embodiment 866, wherein administering a dose of the oligomeric compound to an animal results in a circulating ALT level that is at least 3-fold lower than the ALT level that results from administering the same dose of the comparator compound to an animal for at least one matched dose.
- 10 868. The oligomeric compound of embodiment 866 or 867, wherein the lowest dose of the oligomeric compound that raises circulating ALT to over 300 units per liter is at least three-fold higher than the lowest dose of the comparator compound that raises circulating ALT to over 300 units per liter.
869. The oligomeric compound of any of embodiments 865-868, wherein the oligomeric compound is capable of reducing the target RNA in a cell.
- 15 870. The oligomeric compound of embodiment 869, wherein the oligomeric compound has RNA-reducing activity comparable to a comparator compound, wherein the comparator compound is identical to the oligomeric compound except that each nucleoside of the central region of the comparator compound is a nucleoside comprising 2'-β-D-deoxyribosyl sugar moiety.
871. The oligomeric compound of embodiment 870 having RNA-reducing activity that is no more than 2-fold worse than the RNA-reducing activity of the comparator compound.
- 20 872. A method of modulating the amount or activity of a target RNA in a human subject comprising administering the oligomeric compound or composition of any of embodiments 551-832 to the human subject; and thereby modulating the amount or activity of the target RNA in the human subject.
- 25 873. A method of treating a disease or disorder in a human subject comprising administering the oligomeric compound or composition of any of embodiments 551-832 to the human subject having the disease or disorder; and thereby treating the disease or disorder in the human subject.
874. The method of embodiment 872-873, wherein the disease or disorder is a liver disease, and wherein the oligomeric compound modulates the amount or activity of a liver target RNA.
875. The method of embodiment 872-873, wherein the disease or disorder is a central nervous system disease, and wherein the oligomeric compound modulates the amount or activity of a central nervous system target RNA.
- 30 876. The method of any of embodiments 872-874, wherein the disease or disorder is a cancer, a neurodegenerative disease, a cardiovascular disease, an immunological disease, a hereditary disease, a repeat expansion disease, a muscle-wasting disease, or a metabolic disease.

877. The method of any of embodiments 872-876, wherein the plasma ALT level of the human subject after the administration is not more than three times higher than it was prior to the administration.
878. The method of any of embodiments 872-877, wherein the plasma ALT level of the human subject after the administration is not more than 150 units per liter.
- 5 879. A method of treating a disease or disorder in a human subject comprising administering the oligomeric compound or composition of any of embodiments 1-410, 452-518, 551-828, or 864-871 to the human subject having the disease or disorder; and thereby treating the disease or disorder in the human subject.
880. The method of embodiment 879, wherein the disease or disorder is not a CNS disease or disorder.
- 10 881. The method of embodiment 879, wherein the disease or disorder is a disease or disorder of the muscle.
882. The method of embodiment 879, wherein the disease or disorder is a disease or disorder of the lung.
883. The method of embodiment 879, wherein the disease or disorder is a disease or disorder of the kidney.
- 15 884. The method of embodiment 879, wherein the disease or disorder is a disease or disorder of the eye.
885. The method of embodiment 879, wherein the disease or disorder is a disease or disorder of the pancreas.
886. A method of screening a library of oligomeric compounds for activity against a target RNA, wherein the library of oligomeric compounds comprises a plurality of oligomeric compounds of any of
- 20 embodiments 1-410, 452-218, 551-831, or 864-871.
887. An oligomeric compound comprising a modified oligonucleotide consisting of 12-21 linked nucleosides, wherein the modified oligonucleotide has the formula A-B-C, wherein A is a 5'-region, B is a central region, and C is a 3'-region; wherein:
- the 5'-region consists of 1-5 linked nucleosides, wherein at least one nucleoside of the 5'-region is a
- 25 modified nucleoside comprising a modified sugar;
- the 3'-region consists of 1-5 linked nucleosides wherein at least one nucleoside of the 3'-region is a modified nucleoside comprising a modified sugar; and
- the central region consists of 7-11 linked nucleosides, wherein
- the 5'-most portion of the central region has the following formula:
- 30
$$(N_{da})(N_x)(N_y)(N_z)(N_{db})$$
- wherein one of N_x , N_y , and N_z is a safety-enhancing nucleoside;
- the other two of N_x , N_y , and N_z are independently selected from a DNA nucleoside, a DNA isomer, a modified DNA isomer, and a DNA mimic; and
- N_{da} and N_{db} are each independently selected from a DNA nucleoside, a DNA isomer, a
- 35 modified DNA isomer, and a DNA mimic.

888. The oligomeric compound of embodiment 887, wherein the 5'-region consists of one nucleoside.
889. The oligomeric compound of embodiment 887, wherein the 5'-region consists of 2-5 linked nucleosides.
- 5 890. The oligomeric compound of embodiment 887, wherein the 5'-region consists of 2-4 linked nucleosides.
891. The oligomeric compound of embodiment 887, wherein the 5'-region consists of 2 linked nucleosides.
892. The oligomeric compound of embodiment 887, wherein the 5'-region consists of 3 linked
10 nucleosides.
893. The oligomeric compound of embodiment 887, wherein the 5'-region consists of 4 linked nucleosides.
894. The oligomeric compound of embodiment 887, wherein the 5'-region consists of 5 linked nucleosides.
- 15 895. The oligomeric compound of any of embodiments 887-894, wherein each nucleoside of the 5'-region is a modified nucleoside.
896. The oligomeric compound of any of embodiments 887-895, wherein each nucleoside of the 5'-region is a modified nucleoside comprising a modified sugar.
897. The oligomeric compound of any of embodiments 887-896, wherein each modified nucleoside of the
20 5'-region has the same modification.
898. The oligomeric compound of any of embodiments 887-896, wherein at least two nucleosides of the 5'-region are modified nucleosides having different modifications.
899. The oligomeric compound of any of embodiments 887-898, wherein each nucleoside of the 5'-region comprises a 2'-modified ribosyl sugar moiety.
- 25 900. The oligomeric compound of any of embodiments 887-899, wherein at least one nucleoside of the 5'-region comprises a bicyclic furanosyl sugar moiety.
901. The oligomeric compound of any of embodiments 887-900, wherein each nucleoside of the 5'-region comprises a bicyclic furanosyl sugar moiety.
902. The oligomeric compound of any of embodiments 887-900, wherein at least one nucleoside of the 5'-
30 region comprises a non-bicyclic sugar moiety.
903. The oligomeric compound of embodiment 902, wherein the non-bicyclic sugar moiety of the at least one nucleoside of the 5'-region is a 2'-substituted ribosyl sugar moiety.
904. The oligomeric compound of any of embodiments 887-889 or 902-903, wherein each nucleoside of the 5'-region comprises a non-bicyclic sugar moiety.

905. The oligomeric compound of embodiment 904, wherein each nucleoside of the 5'-region comprises a 2'-substituted furanosyl sugar moiety.

906. The oligomeric compound of any of embodiments 887-905, wherein each nucleoside of the 5'-region comprises a 2'-modified furanosyl sugar moiety independently selected from a bicyclic sugar moiety and a non-bicyclic 2'-substituted ribosyl sugar moiety.

907. The oligomeric compound of any of embodiments 887-901 or 906, wherein each nucleoside of the 5'-region comprises a bicyclic sugar moiety.

908. The oligomeric compound of any of embodiments 887-889 or 902-906, wherein each nucleoside of the 5'-region comprises a non-bicyclic 2'-substituted ribosyl sugar moiety.

909. The oligomeric compound of any of embodiments 887-903 or 906-907, wherein each bicyclic sugar moiety of the 5'-region is selected from among cEt, LNA, and ENA.

910. The oligomeric compound of any of embodiments 887-903 or 906-909, wherein each bicyclic sugar moiety of the 5'-region is a cEt sugar moiety.

911. The oligomeric compound of any of embodiments 887-903, or 906-907 or 909 wherein each bicyclic sugar moiety of the 5'-region is an LNA sugar moiety.

912. The oligomeric compound of any of embodiments 887-900, 902-906, or 908-911, wherein each non-bicyclic sugar moiety of the 5'-region has a 2'-substituent selected from among 2'-MOE, 2'-OMe, and 2'-NMA.

913. The oligomeric compound of any of embodiments 887-912, wherein none of the nucleosides of the 5'-region comprise a sugar moiety having a 2'-F substituent.

914. The oligomeric compound of any of embodiments 887-913, wherein none of the nucleosides of the 5'-region comprise a sugar moiety having a 2'-MOE substituent.

915. The oligomeric compound of any of embodiments 887-914, wherein none of the nucleosides of the 5'-region comprise a sugar moiety having a 2'-OMe substituent.

916. The oligomeric compound of any of embodiments 887-915, wherein none of the nucleosides of the 5'-region comprise a cEt sugar moiety.

917. The oligomeric compound of any of embodiments 887-916, wherein none of the nucleosides of the 5'-region comprise a LNA sugar moiety.

918. The oligomeric compound of any of embodiments 887-917, wherein each nucleobase of the 5'-region is independently selected from among thymine, uracil, guanine, cytosine, 5-methylcytosine, and adenine.

919. The oligomeric compound of any of embodiments 887-918, wherein each internucleoside linkage of the 5'-region is independently selected from among phosphodiester and phosphorothioate internucleoside linkages.

920. The oligomeric compound of any of embodiments 887-919, wherein the 3'-region consists of one nucleoside.

921. The oligomeric compound of any of embodiments 887-919, wherein the 3'-region consists of 2-5 linked nucleosides.

922. The oligomeric compound of any of embodiments 887-919, wherein the 3'-region consists of 2-4 linked nucleosides.

923. The oligomeric compound of any of embodiments 887-919, wherein the 3'-region consists of 2 linked nucleosides.

924. The oligomeric compound of any of embodiments 887-919, wherein the 3'-region consists of 3 linked nucleosides.

925. The oligomeric compound of any of embodiments 887-919, wherein the 3'-region consists of 4 linked nucleosides.

926. The oligomeric compound of any of embodiments 887-919, wherein the 3'-region consists of 5 linked nucleosides.

927. The oligomeric compound of any of embodiments 887-926, wherein each nucleoside of the 3'-region is a modified nucleoside.

928. The oligomeric compound of any of embodiments 887-927, wherein each nucleoside of the 3'-region is a modified nucleoside comprising a modified sugar moiety.

929. The oligomeric compound of any of embodiments 887-928, wherein each modified nucleoside of the 3'-region has the same modification.
- 5 930. The oligomeric compound of and of embodiments 887-928, wherein at least two nucleosides of the 3'-region are modified nucleosides having different modifications.
931. The oligomeric compound of any of embodiments 887-930, wherein each nucleoside of the 3'-region comprises a 2'-modified ribosyl sugar moiety.
- 10 932. The oligomeric compound of any of embodiments 887-931, wherein at least one nucleoside of the 3'-region comprises a bicyclic furanosyl sugar moiety.
933. The oligomeric compound of any of embodiments 887-932, wherein each nucleoside of the 3'-region comprises a bicyclic furanosyl sugar moiety.
- 15 934. The oligomeric compound of any of embodiments 887-933, wherein at least one nucleoside of the 3'-region comprises a non-bicyclic sugar moiety.
935. The oligomeric compound of embodiment 934, wherein the non-bicyclic sugar moiety of the at least one nucleoside of the 3'-region is a 2'-substituted ribosyl sugar moiety.
- 20 936. The oligomeric compound of any of embodiments 887-935, wherein each nucleoside of the 3'-region comprises a non-bicyclic sugar moiety.
- 25 937. The oligomeric compound of embodiment 936, wherein each nucleoside of the 3'-region comprises a 2'-substituted furanosyl sugar moiety.
938. The oligomeric compound of any of embodiments 887-937, wherein each nucleoside of the 3'-region comprises a 2'-modified furanosyl sugar moiety independently selected from a bicyclic sugar moiety and a non-bicyclic 2'-substituted ribosyl sugar moiety.
- 30 939. The oligomeric compound of any of embodiments 887-935, or 938 wherein each nucleoside of the 3'-region comprises a bicyclic sugar moiety.

940. The oligomeric compound of any of embodiments 887-932 or 934-938, wherein each nucleoside of the 3'-region comprises a non-bicyclic 2'-substituted ribosyl sugar moiety.
941. The oligomeric compound of any of embodiments 887-935 or 938-939, wherein each bicyclic sugar moiety of the 3'-region is selected from among cEt, LNA, and ENA.
942. The oligomeric compound of any of embodiments 887-935, 938-939, or 941, wherein each bicyclic sugar moiety of the 3'-region is a cEt sugar moiety.
943. The oligomeric compound of any of embodiments 887-935, 938-939, or 941, wherein each bicyclic sugar moiety of the 3'-region is an LNA sugar moiety.
944. The oligomeric compound of any of embodiments 887-932, 934-938 or 940, wherein each non-bicyclic sugar moiety of the 3'-region has a 2'-substituent selected from among 2'-MOE, 2'-OMe, and 2'-NMA.
945. The oligomeric compound of any of embodiments 887-944, wherein none of the nucleosides of the 3'-region comprise a sugar moiety having a 2'-F substituent.
946. The oligomeric compound of any of embodiments 887-945, wherein none of the nucleosides of the 3'-region comprise a sugar moiety having a 2'-MOE substituent.
947. The oligomeric compound of any of embodiments 887-946, wherein none of the nucleosides of the 3'-region comprise a sugar moiety having a 2'-OMe substituent.
948. The oligomeric compound of any of embodiments 887-947, wherein none of the nucleosides of the 3'-region comprise a cEt sugar moiety.
949. The oligomeric compound of any of embodiments 887-948, wherein none of the nucleosides of the 3'-region comprise a LNA sugar moiety.
950. The oligomeric compound of any of embodiments 887-949, wherein each nucleobase of the 3'-region is independently selected from among thymine, uracil, guanine, cytosine, 5-methylcytosine, and adenine.

951. The oligomeric compound of any of embodiments 887-950, wherein each internucleoside linkage of the 3'-region is independently selected from among phosphodiester and phosphorothioate internucleoside linkages.

952. The oligomeric compound of any of embodiments 887-951, wherein the modified nucleosides of the 5'-region have the same modifications as the modifications of the modified nucleosides of the 3'-region.

953. The oligomeric compound of any of embodiments 887-951, wherein at least one modified nucleoside of the 5'-region and one modified nucleoside of the 3'-region comprise modifications that differ from one another.

954. The oligomeric compound of any of embodiments 887-898, 900, 902-903, 906, 909-932, 934-935, 938, 941-953, wherein the 5'-region and the 3'-region together include at least one non-bicyclic 2'-substituted modified nucleoside and at least one bicyclic nucleoside.

955. The oligomeric compound of embodiment 954, where the bicyclic nucleoside is a cEt nucleoside.

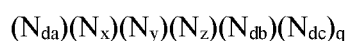
956. The oligomeric compound of embodiment 954, where the bicyclic nucleoside is an LNA nucleoside.

957. The oligomeric compound of any of embodiments 954-956, wherein the non-bicyclic 2'-modified nucleoside is a 2'-MOE nucleoside.

958. The oligomeric compound of any of embodiments 954-956, wherein the non-bicyclic 2'-modified nucleoside is a 2'-OMe nucleoside.

959. The oligomeric compound of any of embodiments 954-958, wherein at least one nucleoside of the 5'-region or the 3'-region is an unmodified DNA nucleoside.

960. The oligomeric compound of any of embodiments 887-959, wherein the central region has the formula:



wherein each N_{dc} is independently selected from an unmodified DNA nucleoside, a DNA isomer, a modified DNA isomer, and a DNA mimic; and q is 2-6.

961. The oligomeric compound of any of embodiments 887-960, wherein the central region consists of 7 linked nucleosides.

962. The oligomeric compound of any of embodiments 887-960, wherein the central region consists of 8 linked nucleosides.

963. The oligomeric compound of any of embodiments 887-960, wherein the central region consists of 9 linked nucleosides.

964. The oligomeric compound of any of embodiments 887-960, wherein the central region consists of 10 linked nucleosides.

965. The oligomeric compound of any of embodiments 887-960, wherein the central region consists of 11 linked nucleosides.

966. The oligomeric compound of any of embodiments 887-965, wherein Nx is the safety-enhancing nucleoside.

967. The oligomeric compound of any of embodiments 887-965, wherein Ny is the safety-enhancing nucleoside.

968. The oligomeric compound of any of embodiments 887-965, wherein Nz is the safety-enhancing nucleoside.

969. The oligomeric compound of any of embodiments 887-968, wherein the safety enhancing nucleoside is a DNA isomer or a modified DNA isomer, or a modified nucleoside comprising either a sugar surrogate, a bicyclic furanosyl sugar moiety, or a non-bicyclic modified furanosyl sugar moiety.

970. The oligomeric compound of any of embodiments 887-969, wherein the safety enhancing nucleoside is a DNA isomer or a modified DNA isomer, or comprises either a sugar surrogate, a bicyclic furanosyl sugar moiety, a non-bicyclic, 2'-modified furanosyl sugar moiety, a non-bicyclic 3'-modified furanosyl sugar moiety, a non-bicyclic, 4'-modified furanosyl sugar moiety, or a non-bicyclic 5'-modified furanosyl sugar moiety.

971. The oligomeric compound of any of embodiments 887-970, wherein the safety enhancing nucleoside comprises a sugar surrogate selected from a morpholino, a modified morpholino, a modified cyclohexenyl, or a modified tetrahydropyran.

972. The oligomeric compound of any of embodiments 887-970, wherein the safety enhancing nucleoside comprises a sugar surrogate selected from a morpholino, a modified morpholino, CeNA, F-CeNA, HNA, OMe-HNA or F-HNA.

973. The oligomeric compound of any of embodiments 887-970, wherein the safety enhancing nucleoside is a DNA isomer comprising a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 2'-α-D-deoxyribosyl, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl.

974. The oligomeric compound of any of embodiments 887-970 or 973, wherein the safety enhancing nucleoside is a DNA isomer comprising a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, and 2'-β-L-deoxyribosyl.

975. The oligomeric compound of any of embodiments 887-970, wherein the safety enhancing nucleoside is a modified DNA isomer comprising a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a hydroxyl, a fluoro, or O-C₁-C₁₀ alkoxy substituent.

976. The oligomeric compound of any of embodiments 887-970 or 975, wherein the safety enhancing nucleoside is a modified DNA isomer comprising a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a hydroxyl, a fluoro, or OMe substituent.

977. The oligomeric compound of any of embodiments 887-970 or 975-976, wherein the safety enhancing nucleoside is a modified DNA isomer comprising a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a fluoro or OMe substituent.

978. The oligomeric compound of any of embodiments 887-970 or 975-977, wherein the safety enhancing nucleoside is a modified DNA isomer comprising a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, and 2'-β-L-deoxyribosyl and the 2' position is further substituted with a hydroxyl, fluoro, or OMe substituent.

979. The oligomeric compound of any of embodiments 887-970, wherein the safety enhancing nucleoside is a modified nucleoside comprising a bicyclic furanosyl sugar moiety.

980. The oligomeric compound of any of embodiments 887-970, wherein the safety enhancing nucleoside is selected from among cEt, LNA, α -L-LNA, and ENA.

981. The oligomeric compound of any of embodiments 887-970, wherein the safety enhancing nucleoside comprises a 2'-substituted furanosyl sugar moiety.

982. The oligomeric compound of embodiment 981, wherein the 2'-substituted furanosyl sugar moiety of the safety enhancing nucleoside has a 2' substituent selected from: halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, 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-alkylenyl-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.

983. The oligomeric compound of embodiment 981, wherein the 2'-substituted furanosyl sugar moiety of the safety enhancing nucleoside has a 2' substituent selected from: halo, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, S-alkyl, N(R_m)-alkyl, 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.

984. The oligomeric compound of embodiment 981, wherein the 2'-substituted furanosyl sugar moiety of the safety enhancing nucleoside has a 2' substituent selected from: fluoro, OMe, MOE, NMA.

985. The oligomeric compound of any of embodiments 887-978 or 981-984, wherein the safety enhancing nucleoside comprises a 2'-substituted furanosyl sugar moiety comprising a 2'-OMe or 2'-MOE.

986. The oligomeric compound of any of embodiments 887-978 or 981-986, wherein the safety enhancing nucleoside comprises a 2'-substituted furanosyl sugar moiety comprising a 2'-OMe.

987. The oligomeric compound of any of embodiments 887-978 or 981-986, wherein the safety enhancing nucleoside comprises a 2'-OMe modified 2'- β -D-deoxyribosyl sugar moiety.

988. The oligomeric compound of any of embodiments 887-970, wherein the safety enhancing nucleoside comprises a 3'-modified furanosyl sugar moiety having a 3' substituent selected from: halo, allyl, amino, azido, SH, CN, CF₃, OCF₃, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, S-alkyl, N(R_m)-alkyl, N(R_m)-alkenyl, N(R_m)-alkynyl, O-alkylenyl-O-alkyl, alkynyl, alkaryl, or aralkyl.

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989. The oligomeric compound of any of embodiments 887-970 or embodiment 988, wherein the safety enhancing nucleoside comprises a 3'-modified furanosyl sugar moiety having a 3' substituent selected from: C₁-C₁₀ alkyl, or C₁-C₁₀ substituted alkyl.

10 990. The oligomeric compound of any of embodiments 887-970 or 988-989, wherein the safety enhancing nucleoside comprises a 3'-methyl furanosyl sugar moiety.

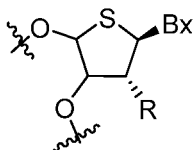
991. The oligomeric compound of any of embodiments 887-970, wherein the safety enhancing nucleoside comprises a 4'-modified furanosyl sugar moiety having a 4' substituent selected from: halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, C₁-C₁₀ 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-alkylenyl-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.

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992. The oligomeric compound of any of embodiments 887-970 or 991, wherein the safety enhancing nucleoside comprises a 4'-modified furanosyl sugar moiety having a 4'-methyl.

993. The oligomeric compound of any of embodiments 887-970, wherein the safety enhancing nucleoside has the structure shown below, wherein R represents an optional 2' substituent group and Bx is a heterocyclic base moiety:

25



994. The oligomeric compound of embodiment 993, wherein in R is selected from among H, OH, OMe, F, or MOE.

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995. The oligomeric compound of any of embodiments 887-970, wherein the safety enhancing nucleoside comprises a 5'-modified furanosyl sugar moiety having a 5' substituent selected from: halo, allyl, amino,

azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, 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-alkylenyl-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.

996. The oligomeric compound of any of embodiments 887-970 or 995, wherein the safety enhancing nucleoside comprises a 5'-modified furanosyl sugar moiety with a 5' substituent selected from: 5'-methyl, 5'-ethyl or a 5'-allyl.

997. The oligomeric compound of any of embodiments 887-970 or 995-996, wherein the safety enhancing nucleoside comprises a 5'-modified furanosyl sugar moiety with a 5' substituent selected from: 5'-(*R*)-methyl- or 5'-(*R*)-ethyl.

998. The oligomeric compound of any of embodiments 887-970 or 995-997, wherein the safety enhancing nucleoside comprises a 5'-(*R*)-methyl-2'-β-D-deoxyribosyl sugar moiety.

999. The oligomeric compound of any of embodiments 887-970 or 995-998, wherein the safety enhancing nucleoside comprises a 5'-(*R*)-ethyl-2'-β-D-deoxyribosyl sugar moiety.

1000. The oligomeric compound of any of embodiments 887-999, wherein the safety enhancing nucleoside does not comprise a 2'-F modified sugar moiety.

1001. The oligomeric compound of any of embodiments 887-1000, wherein the safety enhancing nucleoside does not comprise a cEt modified sugar moiety.

1002. The oligomeric compound of any of embodiments 887-1001, wherein the safety enhancing nucleoside does not comprise a 2'-MOE modified sugar moiety.

1003. The oligomeric compound of any of embodiments 887-1002, wherein the safety enhancing nucleoside comprises a hypoxanthine nucleobase.

1004. The oligomeric compound of any of embodiments 887-1003, wherein the safety enhancing nucleoside comprises a nucleobase selected from among thymine, uracil, guanine, cytosine, 5-methylcytosine, and adenine.

1005. The oligomeric compound of any of embodiments 887-1004, wherein the safety enhancing nucleoside is a modified nucleoside other than cEt, MOE, LNA, or FANA.

1006. The oligomeric compound of any of embodiments 887-1005, wherein each Nd is independently selected from among a DNA nucleoside, a DNA isomer, a 2'-modified DNA isomer, and a DNA mimic.

1007. The oligomeric compound of embodiment 1006, wherein each DNA isomer comprises a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 2'-α-D-deoxyribosyl, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl.

1008. The oligomeric compound of embodiment 1007, wherein each DNA isomer comprises a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, and 2'-β-L-deoxyribosyl.

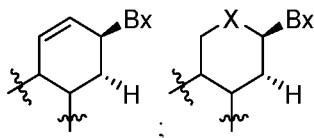
1009. The oligomeric compound of embodiment 1006, wherein each modified DNA isomer comprises a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a hydroxyl, a fluoro, or O-C₁-C₁₀ alkoxy substituent.

1010. The oligomeric compound of embodiment 1009, wherein each modified DNA isomer comprises a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a hydroxyl, a fluoro, or OMe substituent.

1011. The oligomeric compound of embodiment 1010, wherein each modified DNA isomer comprises a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a fluoro or OMe substituent.

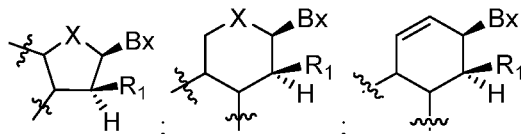
1012. The oligomeric compound of embodiment 1011, wherein each modified DNA isomer comprises a 2'-modified sugar moiety, wherein the sugar moiety is selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, and 2'-β-L-deoxyribosyl and the 2' position is further substituted with a hydroxyl, fluoro, or OMe substituent.

1013. The oligomeric compound of embodiment 1006, wherein each DNA mimic comprises a structure represented by one of the formulas below:



wherein X is O or S and Bx represents a heterocyclic base moiety.

- 5 1014. The oligomeric compound of embodiment 1006, wherein each DNA mimic comprises a structure represented by one of the formulas below:

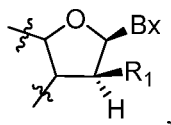


wherein X is O or S;

Bx represents a heterocyclic base moiety; and

- 10 R₁ is selected from among H, OH, halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, 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-alkylenyl-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
15 unsubstituted C₁-C₁₀ alkyl;

wherein if the DNA mimic comprises the structure:

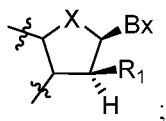


R₁ is other than H.

- 20 1015. The oligomeric compound of embodiment 1014, wherein R₁ is H, OH, OMe, or F.

1016. The oligomeric compound of embodiment 1014, wherein R₁ is not F.

- 25 1017. The oligomeric compound of embodiment 1006, wherein each DNA mimic comprises a structure represented by the formula below:



wherein X is S, Bx represents a heterocyclic base moiety, and R₁ is H.

1018. The oligomeric compound of embodiment 1006, wherein the DNA mimic has a sugar moiety selected from among: 5'-methyl-2'- β -D-deoxyribosyl, 5'-ethyl-2'- β -D-deoxyribosyl, and 5'-allyl-2'- β -D-deoxyribosyl.

1019. The oligomeric compound of embodiment 1006, wherein the DNA mimic comprises a 2'-fluoro- β -D-arabinofuranosyl sugar moiety.

1020. The oligomeric compound of embodiment 1006, wherein the DNA mimic does not comprise a 2'-fluoro- β -D-arabinofuranosyl sugar moiety.

1021. The oligomeric compound of any of embodiments 887-1020, wherein each N_d is a DNA nucleoside.

1022. The oligomeric compound of any of embodiments 887-1021, wherein the central region comprises no more than four nucleosides selected from among DNA isomers, modified DNA isomers, and DNA mimics.

1023. The oligomeric compound of any of embodiments 887-1021, wherein the central region comprises no more than three nucleosides selected from among DNA isomers, modified DNA isomers, and DNA mimics.

1024. The oligomeric compound of any of embodiments 887-1021, wherein the central region comprises no more than two nucleosides selected from among DNA isomers, modified DNA isomers, and DNA mimics.

1025. The oligomeric compound of any of embodiments 887-1021, wherein the central region comprises no more than one nucleoside selected from among DNA isomers, modified DNA isomers, and DNA mimics.

1026. The oligomeric compound of any of embodiments 887-1025, wherein the central region contains exactly one safety enhancing nucleoside and the remainder of nucleosides in the central region are DNA nucleosides.

1027. The oligomeric compound of any of embodiments 887-1026, wherein at least one internucleoside linkage of the central region selected from among: the internucleoside N_d to N_x , N_x to N_y , N_y to N_z , or N_z to the adjacent N_{db} is a neutral internucleoside linkage.

1028. The oligomeric compound of embodiments 1027, wherein the neutral linkage is a phosphonate internucleoside linkage.

1029. The oligomeric compound of embodiments 1027, wherein the neutral linkage is a methoxypropyl internucleoside linkage.

1030. The oligomeric compound of embodiments 1027, wherein each remaining internucleoside linkage is a phosphodiester or phosphorothioate internucleoside linkage.

1031. A chirally enriched population of modified oligonucleotides of any of embodiments 887-1026, wherein the central region has at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

1032. The chirally enriched population of embodiment 1031, wherein the central region has at least one phosphorothioate internucleoside linkage having the (*Sp*) configuration.

1033. The chirally enriched population of embodiment 1031, wherein central region has at least one phosphorothioate internucleoside linkage having the (*Rp*) configuration.

1034. The chirally enriched population of embodiment 1031, wherein the central region has a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

1035. The chirally enriched population of embodiment 1034, wherein the each phosphorothioate internucleoside linkage of the central region has the (*Sp*) configuration.

1036. The chirally enriched population of embodiment 1034, wherein the central region has one phosphorothioate internucleoside linkage having the (*Rp*) configuration and wherein each remaining central region phosphorothioate internucleoside linkage has the (*Sp*) configuration.

1037. The chirally enriched population of embodiment 1031, wherein the central region has an (*Rp*) phosphorothioate internucleoside linkage adjacent to an (*Sp*) phosphorothioate internucleoside linkage.

1038. The chirally enriched population of embodiment 1031, wherein the central region has an (*Rp*) phosphorothioate internucleoside linkage adjacent to a second (*Rp*) phosphorothioate internucleoside linkage.

1039. The chirally enriched population of embodiment 1031, wherein the central region has an (*Rp*) phosphorothioate internucleoside linkage adjacent to a second (*Rp*) phosphorothioate internucleoside

linkage, and wherein each remaining central region phosphorothioate internucleoside linkage has the (*Sp*) configuration.

1040. The chirally enriched population of any of embodiments 1032, 1033, 1037, or 1038 wherein each phosphorothioate internucleoside linkage that does not have the (*Rp*) or (*Sp*) configuration is stereorandom.

1041. The oligomeric compound of any of embodiments 887-1040 comprising a conjugate group.

1042. The oligomeric compound of embodiment 1041, wherein the conjugate group comprises a linking group attaching the remainder of the conjugate group to the modified oligonucleotide, wherein the linking group comprises 1-5 nucleosides.

1043. The oligomeric compound of any of embodiments 887-1041, wherein the oligomeric compound does not comprise additional nucleosides beyond those of the modified oligonucleotide.

1044. The oligomeric compound of any of embodiments 887-1043, wherein the nucleobase sequence of the modified oligonucleotide is complementary to a target RNA.

1045. The oligomeric compound of embodiment 1044, wherein the nucleobase sequence of the modified oligonucleotide is at least 85% complementary to the target RNA.

1046. The oligomeric compound of embodiment 1044, wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to the target RNA.

1047. The oligomeric compound of embodiment 1044, wherein the nucleobase sequence of the modified oligonucleotide is at least 95% complementary to the target RNA.

1048. The oligomeric compound of embodiment 1047, wherein the nucleobase sequence of the modified oligonucleotide is 100% complementary to the target RNA.

1049. The oligomeric compound of any of embodiments 1044-1048, wherein the target RNA is a target mRNA or a target pre-mRNA.

1050. The oligomeric compound of embodiment 1049, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human PTEN RNA.

1051. The oligomeric compound of embodiment 1049 or 1050, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human SRB-1 RNA.

1052. The oligomeric compound of any of embodiments 1049-1051, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human MYD88 RNA.

1053. The oligomeric compound of any of embodiments 1049-1052, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human HTT RNA, is not a mouse, rat, monkey, or human SOD1 RNA, and is not a mouse, rat, monkey, or human alpha-synuclein RNA.

1054. The oligomeric compound of any of embodiments 1044-1053, wherein the target RNA is a human RNA.

1055. The oligomeric compound of any of embodiments 1044-1054, wherein the target RNA is expressed in the liver.

1056. The oligomeric compound of any of embodiments 1044-1055, wherein the target RNA is a liver target.

1057. The oligomeric compound of any of embodiments 1044-1054, wherein the target RNA is not expressed in the liver.

1058. The oligomeric compound of any of embodiments 1044-1054 or 1057, wherein the target RNA is not a liver target.

1059. The oligomeric compound of any of embodiments 1044-1056, wherein modulation of the expression of the target RNA in the liver is associated with treating a disorder or condition.

1060. The oligomeric compound of embodiment 1059, wherein the disorder or condition is a liver disorder or condition.

1061. The oligomeric compound of any of embodiments 1044-1060, wherein the target RNA is expressed in the central nervous system.

1062. The oligomeric compound of any of embodiments 1044-1060, wherein the target RNA is not expressed in the central nervous system.

1063. The oligomeric compound of any of embodiments 1044-1061, wherein the target RNA is a central nervous system target.

5 1064. The oligomeric compound of any of embodiments 1044-1062, wherein the target RNA is not a central nervous system target.

1065. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in white fat cells.

10 1066. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in brown fat cells.

1067. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in adipocytes.

1068. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in macrophages.

20 1069. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in cancer cells.

1070. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in tumor cells.

25 1071. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in smooth muscle cells.

1072. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in lymphocytes.

1073. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in pulmonary cells.

35 1074. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in heart muscle cells.

1075. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in cardiomyocytes.

1076. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in endothelial cells.

5 1077. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in fibroblasts.

1078. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in glial cells.

10 1079. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in Schwann cells.

1080. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in pancreatic cells.

1081. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in kidney cells.

20 1082. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in beta cells.

1083. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in non-parenchymal cells.

25 1084. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in hepatocytes.

1085. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in oligodendrocytes.

1086. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in astrocytes.

35 1087. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in microglia.

1088. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in ependymal cells.

1089. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in sensory neurons.

1090. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in motor neurons.

1091. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in skeletal muscle.

1092. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in cardiac muscle.

1093. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in smooth muscle.

1094. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in adipose tissue.

1095. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in white adipose tissue.

1096. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the spleen.

1097. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the bone.

1098. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the bone marrow.

1099. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the intestine.

1100. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the adrenal glands.

1101. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the testes.

1102. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed
5 in the ovaries.

1103. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the pancreas.

10 1104. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the pituitary gland.

1105. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the prostate gland.

15 1106. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the skin.

1107. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed
20 in the epidermis.

1108. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the uterus.

25 1109. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the bladder.

1110. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the brain.

30 1111. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the glomerulus.

1112. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed
35 in the distal tubular epithelium.

1113. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in breast tissue.

1114. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the lung.

1115. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the heart.

1116. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the kidney.

1117. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the ganglion.

1118. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the frontal cortex.

1119. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the spinal cord.

1120. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the trigeminal ganglion.

1121. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the sciatic nerve.

1122. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the dorsal root ganglion.

1123. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the epidymal fat.

1124. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the diaphragm.

1125. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is expressed in the colon.

1126. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a white fat cell target.

1127. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a brown fat cell target.

1128. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is an adipocyte target.

1129. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a macrophage target.

1130. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a cancer cell target.

1131. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a tumor cell target.

1132. The oligomeric compound of any of embodiments 158-178, wherein the target RNA is a smooth muscle cell target.

1133. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a lymphocyte target.

1134. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a pulmonary cell target.

1135. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a heart muscle cell target.

1136. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a cardiomyocyte target.

1137. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a endothelial cell target.

1138. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a fibroblast target.

1139. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a glial cell target.

1140. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a Schwann cell target.
1141. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a pancreatic cell target.
1142. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a kidney cell target.
1143. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a beta cell target.
1144. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a non-parenchymal cell target.
1145. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a hepatocyte target.
1146. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is an oligodendrocyte target.
1147. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is an astrocyte target.
1148. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a microglia target.
1149. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is an ependymal cell target.
1150. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a sensory neuron target.
1151. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a motor neuron target.
1152. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a skeletal muscle target.

1153. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a cardiac muscle target.

1154. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a smooth muscle target.

1155. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a adipose tissue target.

1156. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a white adipose tissue target.

1157. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a spleen target.

1158. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a bone target.

1159. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a bone marrow target.

1160. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is an intestinal target.

1161. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is an adrenal gland target.

1162. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a testicular target.

1163. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is an ovarian target.

1164. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a pancreatic target.

1165. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a pituitary gland target.

1166. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a prostate gland target.

1167. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a skin target.

1168. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is an epidermal target.

1169. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a uterine target.

1170. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a bladder target.

1171. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a brain target.

1172. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a glomerulus target.

1173. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a distal tubular epithelium target.

1174. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a breast tissue target.

1175. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a lung target.

1176. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a heart target.

1177. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a kidney target.

1178. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a ganglion target.

1179. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a frontal cortex target.

1180. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a spinal cord target.

1181. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a trigeminal ganglion target.

1182. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a sciatic nerve target.

1183. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a dorsal root ganglion target.

1184. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is an epidural fat target.

1185. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a diaphragm target.

1186. The oligomeric compound of any of embodiments 1044-1064, wherein the target RNA is a colon target.

1187. The oligomeric compound of any of embodiments 1044-1186, wherein the target RNA is a MeCP2, DUX4, HDAC2, APP, Ataxin 1, Ataxin 2, Ataxin 3, Ataxin 6, Ataxin 7, C9ORF72, UBE3A, Prion, PMP22, Tau, LRRK2, LINGO2, GYS1, KCNT1, IRF8, Progranulin, or GFAP RNA.

1188. The oligomeric compound of any of embodiments 1044-1186, wherein the target RNA is a HTT RNA.

1189. The oligomeric compound of embodiment 1187, wherein the target RNA is a MeCP2 RNA.

1190. The oligomeric compound of embodiment 1187, wherein the target RNA is a DUX4 RNA.

1191. The oligomeric compound of embodiment 1187, wherein the target RNA is a HDAC2 RNA.
1192. The oligomeric compound of embodiment 1187, wherein the target RNA is a Ataxin 1 RNA.
- 5 1193. The oligomeric compound of embodiment 1187, wherein the target RNA is a Ataxin 2 RNA.
1194. The oligomeric compound of embodiment 1187, wherein the target RNA is a Ataxin 3 RNA.
1195. The oligomeric compound of embodiment 1187, wherein the target RNA is a Ataxin 6 RNA.
- 10 1196. The oligomeric compound of embodiment 1187, wherein the target RNA is a Ataxin 7 RNA.
1197. The oligomeric compound of embodiment 1187, wherein the target RNA is a C9ORF72 RNA.
- 15 1198. The oligomeric compound of embodiment 1044-1186, wherein the target RNA is an alpha-synuclein RNA.
1199. The oligomeric compound of embodiment 1187, wherein the target RNA is an UBE3A RNA.
- 20 1200. The oligomeric compound of any of embodiments 1044-1186, wherein the target RNA is a SOD1 RNA.
1201. The oligomeric compound of embodiment 1187, wherein the target RNA is a Prion RNA.
- 25 1202. The oligomeric compound of embodiment 1187, wherein the target RNA is a PMP22 RNA.
1203. The oligomeric compound of any of embodiments 1044-1187, wherein the target RNA is a Tau RNA.
- 30 1204. The oligomeric compound of embodiment 1187, wherein the target RNA is a LRRK2 RNA.
1205. The oligomeric compound of embodiment 1187, wherein the target RNA is an APP RNA.
1206. The oligomeric compound of 1187, wherein the target RNA is a LINGO2 RNA.

1207. The oligomeric compound of any of embodiments 1187, wherein the target RNA is a GYS1 RNA.
1208. The oligomeric compound of any of embodiments 1187, wherein the target RNA is a KCNT1 RNA.
- 5 1209. The oligomeric compound of any of embodiments 1187, wherein the target RNA is a IRF8 RNA.
1210. The oligomeric compound of any of embodiments 1187, wherein the target RNA is a Progranulin RNA.
- 10 1211. The oligomeric compound of any of embodiments 1187, wherein the target RNA is a GFAP RNA.
1212. The oligomeric compound of any of embodiments 1044-1211, wherein modulation of the expression of the target RNA is associated with treating a disorder or condition.
- 15 1213. The oligomeric compound of any of embodiments 1212, wherein the disorder or condition is Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Parkinson's Disease, a Spinocerebellar ataxia, Angelman Syndrome, Alexander's Disease, Lafora Disease, Charcot-Marie Tooth Disease, Prion Disease, a dementia, neurodegeneration, McCP2 Duplication Syndrome, encephalopathy, neuroinflammation, or multiple sclerosis.
- 20 1214. The oligomeric compound of embodiment 1212, wherein the disorder or condition is Alzheimer's Disease.
1215. The oligomeric compound of embodiment 1212, wherein the disorder or condition is Amyotrophic Lateral Sclerosis.
- 25 1216. The oligomeric compound of embodiment 1212, wherein the disorder or condition is Parkinson's Disease.
- 30 1217. The oligomeric compound of embodiment 1212, wherein the disorder or condition is a Spinocerebellar ataxia.
1218. The oligomeric compound of embodiment 1212, wherein the disorder or condition is Angelman Syndrome.
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1219. The oligomeric compound of embodiment 1212, wherein the disorder or condition is Alexander's Disease.

1220. The oligomeric compound of embodiment 1212, wherein the disorder or condition is Lafora Disease.

1221. The oligomeric compound of embodiment 1212, wherein the disorder or condition is Charcot-Marie Tooth Disease.

1222. The oligomeric compound of embodiment 1212, wherein the disorder or condition is Prion Disease.

1223. The oligomeric compound of embodiment 1212, wherein the disorder or condition is a dementia.

1224. The oligomeric compound of embodiment 1212, wherein the disorder or condition is neurodegeneration.

1225. The oligomeric compound of embodiment 1212, wherein the disorder or condition is McCP2 Duplication Syndrome.

1226. The oligomeric compound of embodiment 1212, wherein the disorder or condition is encephalopathy.

1227. The oligomeric compound of embodiment 1212, wherein the disorder or condition is neuroinflammation.

1228. The oligomeric compound of embodiment 1212, wherein the disorder or condition is multiple sclerosis.

1229. The oligomeric compound of any of embodiments 887-1228, wherein the parent oligomeric compound of the oligomeric compound of any of embodiments 887-1228 is cytotoxic in vitro.

1230. The oligomeric compound of embodiment 1228, wherein the parent oligomeric compound is cytotoxic in a standard in vitro cytotoxicity assay.

1231. The oligomeric compound of any of embodiments 887-1229 wherein administration to a mouse of the parent oligomeric compound of the oligomeric compound of any of embodiments 887-1229 is hepatotoxic to the mouse.

1232. The oligomeric compound of embodiment 1230, wherein the administration of the parent oligomeric compound to the mouse is systemic administration.
- 5 1233. The oligomeric compound of embodiment 1230, wherein the systemic administration is subcutaneous administration.
1234. The oligomeric compound of any of embodiments 1230-1232, wherein the mouse is a CD-1 mouse.
- 10 1235. The oligomeric compound of any of embodiments 1230-1232, wherein the mouse is a C57BL/6 mouse.
1236. The oligomeric compound of any of embodiments 1230-1232, wherein the mouse is a BALB/c mouse.
1237. The oligomeric compound of any of embodiments 1230-1236, wherein the plasma ALT level in the
15 mouse is higher than 500 units per liter following the administration of the parent oligomeric compound.
1238. The oligomeric compound of any of embodiments 1230-1237, wherein the plasma AST level in the mouse is higher than 500 units per liter following the administration of the parent oligomeric compound.
- 20 1239. The oligomeric compound of any of embodiments 1230-1238, wherein the plasma ALT level in the mouse is higher than 1000 units per liter following the administration of the parent oligomeric compound.
1240. The oligomeric compound of any of embodiments 1230-1239, wherein the plasma AST level in the mouse is higher than 1000 units per liter following the administration of the parent oligomeric compound.
- 25 1241. The oligomeric compound of any of embodiments 1230-1240, wherein the hepatotoxicity is measured 24-48 hours following the administration of the parent oligomeric compound.
1242. The oligomeric compound of any of embodiments 1230-1241, wherein the hepatotoxicity is measured
30 72 hours following the administration of the parent oligomeric compound.
1243. The oligomeric compound of any of embodiments 1230-1241, wherein the hepatotoxicity is measured 3 days following the administration of the parent oligomeric compound.

1244. The oligomeric compound of any of embodiments 1230-1241, wherein the hepatotoxicity is measured 5 days following the administration of the parent oligomeric compound.

1245. The oligomeric compound of any of embodiments 1230-1241, wherein the hepatotoxicity is measured 7 days following the administration of the parent oligomeric compound.

1246. The oligomeric compound of any of embodiments 1230-1241, wherein the hepatotoxicity is measured 10 days following the administration of the parent oligomeric compound.

1247. The oligomeric compound of any of embodiments 1230-1241, wherein the hepatotoxicity is measured 14 days following the administration of the parent oligomeric compound.

1248. The oligomeric compound of any of embodiments 1230-1241, wherein 1-10 mg/kg of the parent oligomeric compound is administered to the mouse.

1249. The oligomeric compound of any of embodiments 1230-1241, wherein 10-25 mg/kg of the parent oligomeric compound is administered to the mouse.

1250. The oligomeric compound of any of embodiments 1230-1241, wherein 25-50 mg/kg of the parent oligomeric compound is administered to the mouse.

1251. The oligomeric compound of any of embodiments 1230-1241, wherein 50-100 mg/kg of the parent oligomeric compound is administered to the mouse.

1252. The oligomeric compound of any of embodiments 1230-1241, wherein 100-150 mg/kg of the parent oligomeric compound is administered to the mouse.

1253. The oligomeric compound of any of embodiments 1230-1241, wherein the mouse is a BALB/c mouse, wherein 150 mg/kg of the parent oligomeric compound is administered to the mouse, and wherein the plasma ALT level in the mouse is measured 72 hours following the administration of the parent oligomeric compound.

1254. The oligomeric compound of any of embodiments 887-1253, wherein administration of 50 mg/kg of the oligomeric compound of any of embodiments 887-1253 to a mouse is not hepatotoxic to the mouse.

1255. The oligomeric compound of embodiment 1254, wherein plasma ALT level in the mouse is lower than 100 units per liter following the administration of the oligomeric compound of embodiment 1254.

1256. The oligomeric compound of embodiment 1254 or 1255, wherein plasma ALT level in the mouse is at least 10-fold lower than plasma ALT level in a mouse administered the parent oligomeric compound of the oligomeric compound of embodiment 1254 or 1255, wherein the administrations and plasma ALT measurements of both the oligomeric compound of embodiment 1254 or 1255 and the parent oligomeric compound are completed in the same way.

1257. The oligomeric compound of embodiment 1256, wherein the plasma ALT level in the mouse is at least 100-fold lower than the plasma ALT level in the mouse administered the parent oligomeric compound.

1258. The oligomeric compound of embodiment 1256, wherein the plasma ALT level in the mouse is at least 500-fold lower than the plasma ALT level in the mouse administered the parent oligomeric compound.

1259. The oligomeric compound of any of embodiments 1230-1258, wherein the therapeutic index in a mouse of the oligomeric compound of any of embodiments 1230-1258 is increased relative to the therapeutic index of the parent oligomeric compound.

1260. The oligomeric compound of embodiment 1259, wherein the therapeutic index in a mouse of the oligomeric compound of embodiment 1259 is at least two-fold greater than the therapeutic index of the parent oligomeric compound.

1261. The oligomeric compound of any of embodiments 887-1229, wherein an otherwise identical oligomeric compound lacking the at least one modified internucleoside linkage other than phosphorothioate and/or at least one modified nucleoside comprising a modified nucleobase other than 5-methylcytosine and/or a modified sugar moiety in the central region is hepatotoxic following administration to a mouse; and wherein the otherwise identical oligomeric compound has a central region consisting of phosphorothioate internucleoside linkages, unmodified 2'- β -D-deoxyribose sugar moieties, and nucleobases selected from thymine, uracil, adenine, guanine, cytosine, and 5-methylcytosine.

1262. The oligomeric compound of embodiment 1261, wherein the at least one modified internucleoside linkage other than phosphorothioate and/or at least one modified nucleoside comprising a modified nucleobase other than 5-methylcytosine and/or a modified sugar moiety in the central region is a 2'-O-methyl modified sugar moiety.

1263. The oligomeric compound of embodiment 1262, wherein the 2'-O-methyl modified sugar moiety is at position 2 of the central region.

1264. The oligomeric compound of embodiment 1261-1263, wherein the otherwise identical oligomeric compound lacks a 2'-O-methyl modified sugar moiety, and wherein the otherwise identical oligomeric compound comprises an unmodified 2'-β-D-deoxyribosyl sugar moiety in place of the 2'-O-methyl modified sugar moiety.

1265. The oligomeric compound of any of embodiments 1261-1264, wherein the nucleobase sequence of the otherwise identical oligomeric compound is 100% complementary to the target RNA.

1266. The oligomeric compound of any of embodiments 1261-1265, wherein the otherwise identical oligomeric compound is a parent oligomeric compound of the oligomeric compound of any of embodiments 1202-1206.

1267. The oligomeric compound of any of embodiments 1044-1266, wherein the oligomeric compound inhibits the target RNA with an IC₅₀ lower than 100 nM in a standard in vitro activity assay.

1268. The oligomeric compound of any of embodiments 1044-1266, wherein the parent oligomeric compound of the oligomeric compound of any of embodiments 1044-1266 inhibits the target RNA with an IC₅₀ lower than 100 nM in a standard in vitro activity assay.

1269. The oligomeric compound of any of embodiments 1044-1268, wherein the difference between the IC₅₀ of the parent oligomeric compound measured in a standard in vitro activity assay and the IC₅₀ of the oligomeric compound of any of embodiments 1044-1268 measured in a standard in vitro activity assay is less than 4-fold.

1270. The oligomeric compound of any of embodiments 1044-1268, wherein the difference between the IC₅₀ of the parent oligomeric compound measured in a standard in vitro activity assay and the IC₅₀ of the oligomeric compound of any of embodiments 1044-1268 measured in a standard in vitro activity assay is less than 3-fold.

1271. The oligomeric compound of any of embodiments 1044-1268, wherein the difference between the IC₅₀ of the parent oligomeric compound measured in a standard in vitro activity assay and the IC₅₀ of the

oligomeric compound of any of embodiments 1044-1268 measured in a standard in vitro activity assay is less than 2-fold.

1272. The oligomeric compound of any of embodiments 1044-1271, wherein each sugar moiety of the central region of the parent oligomeric compound is an unmodified 2'- β -D-deoxyribosyl sugar moiety, and wherein each internucleoside linkage of the central region of the parent oligomeric compound is a phosphorothioate internucleoside linkage.

1273. The oligomeric compound of any of embodiments 1044-1272, wherein the nucleobase sequence of the parent oligomeric compound is 100% complementary to the target RNA.

1274. The oligomeric compound of any of embodiments 887-1273, wherein administration of 10-50 mg of the oligomeric compound to a human is not hepatotoxic to the human.

1275. The oligomeric compound of any of embodiments 887-1273, wherein administration of 50-100 mg of the oligomeric compound to a human is not hepatotoxic to the human.

1276. The oligomeric compound of any of embodiments 887-1273, wherein administration of 100-300 mg of the oligomeric compound to a human is not hepatotoxic to the human.

1277. The oligomeric compound of any of embodiments 1274-1276, wherein the administration is systemic administration.

1278. A composition comprising the oligomeric compound of any of embodiments 887-1277, and a second oligomeric compound, wherein the second oligomeric compound is complementary to the oligomeric compound of any of embodiments 887-1277.

1279. The composition of embodiment 1278, wherein the second oligomeric compound comprises at least 14 contiguous linked nucleosides that are at least 90% complementary to the oligomeric compound of any of embodiments 887-1277.

1280. The composition of embodiment 1278, wherein the second oligomeric compound comprises at least 14 contiguous linked nucleosides that are 100% complementary to the oligomeric compound of any of embodiments 887-1277.

1281. A pharmaceutical composition comprising the oligomeric compound of any of embodiments 887-1277 or the composition of any of embodiments 1278-1280, comprising a pharmaceutically acceptable carrier or diluent.

5 1282. A method comprising administering the oligomeric compound or composition of any of embodiments 887-1281 to a human subject.

1283. A method of treating a disease or disorder comprising administering the oligomeric compound or composition of any of embodiments 887-1281 to a human subject.

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1284. A method of modulating the amount or activity of a target RNA in a human subject comprising administering the oligomeric compound or composition of any of embodiments 887-1281 to the human subject; and thereby modulating the amount or activity of the target RNA in the human subject.

15 1285. A method of treating a disease or disorder in a human subject comprising administering the oligomeric compound or composition of any of embodiments 887-1281 to the human subject having the disease or disorder; and thereby treating the disease or disorder in the human subject.

20 1286. The method of embodiment 1284 or 1285, wherein the disease or disorder is a liver disease, and wherein the oligomeric compound modulates the amount or activity of a liver target RNA.

1287. The method of embodiment 1284 or 1285, wherein the disease or disorder is a central nervous system disease, and wherein the oligomeric compound modulates the amount or activity of a central nervous system target RNA.

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1288. The method of any of embodiments 1284-1287, wherein the disease or disorder is a cancer, a neurodegenerative disease, a cardiovascular disease, an immunological disease, a hereditary disease, a repeat expansion disease, a muscle-wasting disease, or a metabolic disease.

30 1289. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a white fat cell target.

1290. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a brown fat cell target.

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1291. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of an adipocyte target.

1292. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a macrophage target.

1293. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a cancer cell target.

1294. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a tumor cell target.

1295. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a smooth muscle cell target.

1296. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a lymphocyte target.

1297. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a pulmonary cell target.

1298. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a heart muscle cell target.

1299. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a cardiomyocyte target.

1300. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of an endothelial cell target.

1301. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a fibroblast target.

1302. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a glial cell target.

1303. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a Schwann cell target.

1304. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a pancreatic cell target.

1305. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a kidney cell target.

1306. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a beta cell target.

1307. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a non-parenchymal cell target.

1308. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a hepatocyte target.

1309. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of an oligodendrocyte target.

1310. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of an astrocyte target.

1311. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a microglia target.

1312. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of an ependymal cell target.

1313. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a sensory neuron target.

1314. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a motor neuron target.

1315. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a skeletal muscle target.

1316. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a cardiac muscle target.

1317. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a smooth muscle target.

1318. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a adipose tissue target.

1319. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a white adipose tissue target.

1320. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a spleen target.

1321. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a bone target.

1322. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a bone marrow target.

1323. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of an intestinal target.

1324. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of an adrenal gland target.

1325. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a testicular target.

1326. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of an ovarian target.

1327. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a pancreatic target.

1328. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a pituitary gland target.

1329. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a prostate gland target.

1330. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a skin target.

1331. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of an epidermal target.

1332. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a uterine target.

1333. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a bladder target.

1334. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a brain target.

1335. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a glomerulus target.

1336. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a distal tubular epithelium target.

1337. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a breast tissue target.

1338. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a lung target.

1339. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a heart target.

1340. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a kidney target.

1341. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a ganglion target.

1342. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a frontal cortex target.

1343. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a spinal cord target.

1344. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a trigeminal ganglion target.

1345. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a sciatic nerve target.

1346. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a dorsal root ganglion target.

1347. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of an epididymal fat target.

1348. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a diaphragm target.

1349. The method of embodiment 1284 or 1285, wherein the oligomeric compound modulates the amount or activity of a colon target.

1350. The method of any of embodiments 1282-1349, wherein the plasma ALT level of the human subject after the administration is not more than three times higher than it was prior to the administration.

1351. The method of any of embodiments 1282-1350, wherein the plasma ALT level of the human subject after the administration is not more than 150 units per liter.

1352. The method of any of embodiments 1282-1351, wherein the human subject is susceptible to liver damage.

1353. The method of any of embodiments 1282-1352, wherein the human subject is susceptible to liver degeneration.

1354. The method of any of embodiments 1282-1353, wherein the human subject is susceptible to elevated apoptosis in the liver.

1355. The method of any of embodiments 1282-1354, wherein the human subject has a liver disease.

1356. The method of any of embodiments 1282-1355, wherein the human subject has kidney disease.

1357. The method of any of embodiments 1282-1356, wherein the human subject is susceptible to kidney damage.

1358. The method of any of embodiments 1282-1357, wherein the human subject has heart disease.

1359. The method of any of embodiments 1282-1358, wherein the human subject is susceptible to heart damage.

1360. The method of any of embodiments 1282-1359, wherein the human subject has pancreatitis.

1361. The method of any of embodiments 1282-1360, wherein the human subject is susceptible to pancreatic damage.

1362. The method of any of embodiments 1282-1361, wherein the human subject has a neurological disease.

1363. The method of any of embodiments 1282-1362, wherein the human subject is susceptible to neurological damage.

1364. The method of any of embodiments 1282-1363, comprising administering the parent oligomeric compound of the oligomeric compound of any of embodiments 887-1281 to a mouse.

1365. The method of any of embodiments 1282-1363, comprising contacting a cell with the parent oligomeric compound of the oligomeric compound of any of embodiments 887-1281.

1366. The method of embodiment 1364 or 1365, wherein each sugar moiety of the central region of the parent oligomeric compound is an unmodified 2'-β-D-deoxyribosyl sugar moiety, and wherein each internucleoside linkage of the central region of the parent oligomeric compound is a phosphorothioate internucleoside linkage.

1367. A method of designing an oligomeric compound comprising starting with a parent oligomeric compound and changing the design of that compound in order to arrive at an oligomeric compound of any one of embodiments 887-1281.

1368. A method of designing an oligomeric compound comprising identifying a parent oligomeric compound and changing the design of that parent oligomeric compound to arrive at a second oligomeric compound, wherein the second oligomeric compound is an oligomeric compound of any one of
5 embodiments 887-1281.

1369. A method of improving hepatotoxicity of an oligomeric compound comprising the steps of (i) identifying a parent oligomeric compound that has plasma ALT levels above 300 units per liter in a mouse, and (ii) providing an oligomeric compound according to any one of embodiments 887-1281.
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1370. The method of embodiment 1368 or 1369, wherein the method designs an oligomeric compound with improved therapeutic index relative to the parent oligomeric compound.

1371. The method of embodiment 1368 or 1369, wherein the method designs an oligomeric compound with
15 lower hepatotoxicity relative to the parent oligomeric compound.

1372. The method of embodiment 1368, wherein the second oligomeric compound has an improved therapeutic index relative to the parent oligomeric compound.

20 1373. The method of embodiment 1368 or 1369, wherein the second oligomeric compound has reduced hepatotoxicity in a mouse relative to the parent oligomeric compound.

1374. The method of embodiment 1368, wherein the oligomeric compound according to any one of
25 embodiments 887-1281 has reduced hepatotoxicity relative to the parent oligomeric compound.

1375. A method comprising administering an oligomeric compound of any of embodiments 887-1281 to a mouse and separately administering the parent oligomeric compound of the oligomeric compound of any of embodiments 887-1281 to a second mouse, wherein the therapeutic index of the oligomeric compound of any of embodiments 887-1281 is improved relative to the therapeutic index of the parent oligomeric
30 compound.

1376. The method of any of embodiments 1282-1375, wherein the level of p21 RNA is measured in the mouse, the cell, and/or the human subject.

35 1377. A method comprising administering an oligomeric compound of any of embodiments 887-1281 to a subject and measuring the level of p21 RNA in the subject.

1378. The method of embodiment 1377, wherein the subject is a mouse.

1379. The method of embodiment 1377, wherein the subject is a human.

1380. The method of any of embodiments 1377-1379, wherein the p21 RNA level is measured within 24 hours of the administration.

1381. The method of any of embodiments 1377-1380, wherein the p21 RNA level is measured 24-48 hours following the administration.

1382. An oligomeric compound or composition of any one of embodiments 887-1281, for use in medical therapy.

1383. The oligomeric compound of any of embodiments 887-1281, wherein the oligomeric compound is not toxic.

1384. The oligomeric compound of any of embodiment 887-1281, wherein a comparator compound is toxic; wherein the comparator compound is identical to the oligomeric compound except that each nucleoside of the central region of the comparator compound is a nucleoside comprising 2'- β -D-deoxyribosyl sugar moiety.

1385. The oligomeric compound of embodiment 1384, wherein administering a dose of the oligomeric compound to an animal results in a circulating ALT level that is at least 3-fold lower than the ALT level that results from administering the same dose of the comparator compound to an animal for at least one matched dose.

1386. The oligomeric compound of embodiment 1384 or 1385, wherein the lowest dose of the oligomeric compound that raises circulating ALT to over 300 units per liter is at least three-fold higher than the lowest dose of the comparator compound that raises circulating ALT to over 300 units per liter.

1387. The oligomeric compound of any of embodiments 1384-1386, wherein the oligomeric compound is capable of reducing the target RNA in a cell.

1388. The oligomeric compound of embodiment 1387, wherein the oligomeric compound has RNA-reducing activity comparable to a comparator compound, wherein the comparator compound is identical

to the oligomeric compound except that each nucleoside of the central region of the comparator compound is a nucleoside comprising 2'- β -D-deoxyribosyl sugar moiety.

1389. The oligomeric compound of embodiment 1388 having RNA-reducing activity that is no more than 2-fold worse than the RNA-reducing activity of the comparator compound.

1390. A method of modulating the amount or activity of a target RNA in a human subject comprising administering the oligomeric compound or composition of any of embodiments 887-1281 to the human subject; and thereby modulating the amount or activity of the target RNA in the human subject.

1391. A method of treating a disease or disorder in a human subject comprising administering the oligomeric compound or composition of any of embodiments 887-1281 to the human subject having the disease or disorder; and thereby treating the disease or disorder in the human subject.

1392. The method of embodiment 1390 or 1391, wherein the disease or disorder is a liver disease, and wherein the oligomeric compound modulates the amount or activity of a liver target RNA.

1393. The method of embodiment 1390 or 1391, wherein the disease or disorder is a central nervous system disease, and wherein the oligomeric compound modulates the amount or activity of a central nervous system target RNA.

1394. The method of any of embodiments 1390-1393, wherein the disease or disorder is a cancer, a neurodegenerative disease, a cardiovascular disease, an immunological disease, a hereditary disease, a repeat expansion disease, a muscle-wasting disease, or a metabolic disease.

1395. The method of any of embodiments 1390-1394, wherein the plasma ALT level of the human subject after the administration is not more than three times higher than it was prior to the administration.

1396. The method of any of embodiments 1390-1395, wherein the plasma ALT level of the human subject after the administration is not more than 150 units per liter.

1397. A method of treating a disease or disorder in a human subject comprising administering the oligomeric compound or composition of any of embodiments 887-1281 to the human subject having the disease or disorder; and thereby treating the disease or disorder in the human subject.

1398. The method of embodiment 1397, wherein the disease or disorder is not a CNS disease or disorder.

1399. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the white fat cells.

1400. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the brown fat cells.

1401. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the adipocytes.

1402. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the macrophages.

1403. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the cancer cells.

1404. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the tumor cells.

1405. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the smooth muscle cells.

1406. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the lymphocytes.

1407. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the pulmonary cells.

1408. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the heart muscle cells.

1409. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the cardiomyocytes.

1410. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the endothelial cells.

1411. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the fibroblasts.

1412. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the glial cells.

1413. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the Schwann cells.

1414. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the pancreatic cells.

1415. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the kidney cells.

1416. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the beta cells.

1417. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the non-parenchymal cells.

1418. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the hepatocytes.

1419. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the oligodendrocytes.

1420. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the astrocytes.

1421. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the microglia.

1422. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the ependymal cells.

1423. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the sensory neurons.

1424. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the motor neurons.

1425. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the skeletal muscle.

1426. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the cardiac muscle.

1427. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the smooth muscle.

1428. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the adipose tissue.

1429. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the white adipose tissue.

1430. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the spleen.

1431. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the bone.

1432. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the bone marrow.

1433. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the intestine.

1434. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the adrenal glands.

1435. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the testes.

1436. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the ovaries.

1437. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the pancreas.

1438. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the pituitary gland.

1439. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the prostate gland.

1440. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the skin.

1441. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the epidermis.

1442. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the uterus.

1443. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the bladder.

1444. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the brain.

1445. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the glomerulus.

1446. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the distal tubular epithelium.

1447. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the breast tissue.

1448. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the lung.

1449. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the heart.

1450. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the kidney.

1451. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the ganglion.

1452. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the frontal cortex.

1453. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the spinal cord.

1454. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the trigeminal ganglion.

1455. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the sciatic nerve.

1456. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the dorsal root ganglion.

1457. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the epidymal fat.

1458. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the diaphragm.

1459. The method of embodiment 1397, wherein the disease or disorder is a disease or disorder of the colon.

1460. A method of screening a library of oligomeric compounds for activity against a target RNA, wherein the library of oligomeric compounds comprises a plurality of oligomeric compounds of any of embodiments 887-1281.

1461. An oligomeric compound comprising a modified oligonucleotide consisting of 12-21 linked nucleosides, wherein the modified oligonucleotide has the formula A-B-C, wherein A is a 5'-region, B is a central region, and C is a 3'-region; wherein:

the 5'-region consists of 1-5 linked nucleosides, wherein at least one nucleoside of the 5'-region is a modified nucleoside comprising a modified sugar;

the 3'-region consists of 1-5 linked nucleosides wherein at least one nucleoside of the 3'-region is a modified nucleoside comprising a modified sugar; and

the central region consists of 7-11 linked nucleosides, wherein

the 5'-most portion of the central region has the following formula:



wherein one of N_x , N_y , and N_z is a safety-enhancing nucleoside;

5 the other two of N_x , N_y , and N_z are independently selected from an unmodified 2'-β-D-deoxyribosyl sugar moiety, a DNA isomer, a modified DNA isomer, and a DNA mimic; and N_{da} and N_{db} are each independently selected from an unmodified 2'-β-D-deoxyribosyl sugar moiety, a DNA isomer, a modified DNA isomer, and a DNA mimic.

10 1462. The oligomeric compound of embodiment 1461, wherein the 5'-region consists of one nucleoside.

1463. The oligomeric compound of embodiment 1461, wherein the 5'-region consists of 2-5 linked nucleosides.

15 1464. The oligomeric compound of embodiment 1461, wherein the 5'-region consists of 2-4 linked nucleosides.

1465. The oligomeric compound of embodiment 1461, wherein the 5'-region consists of 2 linked nucleosides.

20 1466. The oligomeric compound of embodiment 1461, wherein the 5'-region consists of 3 linked nucleosides.

25 1467. The oligomeric compound of embodiment 1461, wherein the 5'-region consists of 4 linked nucleosides.

1468. The oligomeric compound of embodiment 1461, wherein the 5'-region consists of 5 linked nucleosides.

30 1469. The oligomeric compound of any of embodiments 1461-1468, wherein each nucleoside of the 5'-region is a modified nucleoside.

1470. The oligomeric compound of any of embodiments 1461-1469, wherein each nucleoside of the 5'-region is a modified nucleoside comprising a modified sugar.

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1471. The oligomeric compound of any of embodiments 1461-1470, wherein each modified nucleoside of the 5'-region has the same modification.

1472. The oligomeric compound of any of embodiments 1461-1470, wherein at least two nucleosides of the 5'-region are modified nucleosides having different modifications.

1473. The oligomeric compound of any of embodiments 1461-1472, wherein each nucleoside of the 5'-region comprises a 2'-modified ribosyl sugar moiety.

1474. The oligomeric compound of any of embodiments 1461-1473, wherein at least one nucleoside of the 5'-region comprises a bicyclic furanosyl sugar moiety.

1475. The oligomeric compound of any of embodiments 1461-1474, wherein each nucleoside of the 5'-region comprises a bicyclic furanosyl sugar moiety.

1476. The oligomeric compound of any of embodiments 1461-1474, wherein at least one nucleoside of the 5'-region comprises a non-bicyclic sugar moiety.

1477. The oligomeric compound of embodiment 1476, wherein the non-bicyclic sugar moiety of the at least one nucleoside of the 5'-region is a 2'-substituted ribosyl sugar moiety.

1478. The oligomeric compound of any of embodiments 1461-1474 or 1476-1477, wherein each nucleoside of the 5'-region comprises a non-bicyclic sugar moiety.

1479. The oligomeric compound of embodiment 1478, wherein each nucleoside of the 5'-region comprises a 2'-substituted furanosyl sugar moiety.

1480. The oligomeric compound of any of embodiments 1461-1474 or 1476-1477, wherein each nucleoside of the 5'-region comprises a 2'-modified furanosyl sugar moiety independently selected from a bicyclic sugar moiety and a non-bicyclic 2'-substituted ribosyl sugar moiety.

1481. The oligomeric compound of any of embodiments 1461-1477 or 1480, wherein each nucleoside of the 5'-region comprises a bicyclic sugar moiety.

1482. The oligomeric compound of any of embodiments 1461-1474 or 1476-1480, wherein each nucleoside of the 5'-region comprises a non-bicyclic 2'-substituted ribosyl sugar moiety.

1483. The oligomeric compound of any of embodiments 1461-1477 or 1480-1481, wherein each bicyclic sugar moiety of the 5'-region is selected from among cEt, LNA, and ENA.

1484. The oligomeric compound of any of embodiments 1461-1477 or 1480-1481, wherein each bicyclic sugar moiety of the 5'-region is a cEt sugar moiety.

1485. The oligomeric compound of any of embodiments 1461-1477 or 1480-1481, wherein each bicyclic sugar moiety of the 5'-region is an LNA sugar moiety.

1486. The oligomeric compound of any of embodiments 1461-1474, 1476-1480, or 1482-1485, wherein each non-bicyclic sugar moiety of the 5'-region has a 2'-substituent selected from among 2'-MOE, 2'-OMe, and 2'-NMA.

1487. The oligomeric compound of any of embodiments 1461-1486, wherein none of the nucleosides of the 5'-region comprise a sugar moiety having a 2'-F substituent.

1488. The oligomeric compound of any of embodiments 1461-1487, wherein none of the nucleosides of the 5'-region comprise a sugar moiety having a 2'-MOE substituent.

1489. The oligomeric compound of any of embodiments 1461-1488, wherein none of the nucleosides of the 5'-region comprise a sugar moiety having a 2'-OMe substituent.

1490. The oligomeric compound of any of embodiments 1461-1489, wherein none of the nucleosides of the 5'-region comprise a cEt sugar moiety.

1491. The oligomeric compound of any of embodiments 1461-1490, wherein none of the nucleosides of the 5'-region comprise a LNA sugar moiety.

1492. The oligomeric compound of any of embodiments 1461-1491, wherein each nucleobase of the 5'-region is independently selected from among thymine, uracil, guanine, cytosine, 5-methylcytosine, and adenine.

1493. The oligomeric compound of any of embodiments 1461-1492, wherein each internucleoside linkage of the 5'-region is independently selected from among phosphodiester and phosphorothioate internucleoside linkages.

1494. The oligomeric compound of any of embodiments 1461-1493, wherein the 3'-region consists of one nucleoside.

1495. The oligomeric compound of any of embodiments 1461-1493, wherein the 3'-region consists of 2-5 linked nucleosides.

1496. The oligomeric compound of any of embodiments 1461-1493, wherein the 3'-region consists of 2-4 linked nucleosides.

1497. The oligomeric compound of any of embodiments 1461-1493, wherein the 3'-region consists of 2 linked nucleosides.

1498. The oligomeric compound of any of embodiments 1461-1493, wherein the 3'-region consists of 3 linked nucleosides.

1499. The oligomeric compound of any of embodiments 1461-1493, wherein the 3'-region consists of 4 linked nucleosides.

1500. The oligomeric compound of any of embodiments 1461-1493, wherein the 3'-region consists of 5 linked nucleosides.

1501. The oligomeric compound of any of embodiments 1461-1500, wherein each nucleoside of the 3'-region is a modified nucleoside.

1502. The oligomeric compound of any of embodiments 1461-1501, wherein each nucleoside of the 3'-region is a modified nucleoside comprising a modified sugar moiety.

1503. The oligomeric compound of any of embodiments 1461-1502, wherein each modified nucleoside of the 3'-region has the same modification.

1504. The oligomeric compound of any of embodiments 1461-1502, wherein at least two nucleosides of the 3'-region are modified nucleosides having different modifications.

1505. The oligomeric compound of any of embodiments 1461-1504, wherein each nucleoside of the 3'-region comprises a 2'-modified ribosyl sugar moiety.

1506. The oligomeric compound of any of embodiments 1461-1505, wherein at least one nucleoside of the 3'-region comprises a bicyclic furanosyl sugar moiety.

1507. The oligomeric compound of any of embodiments 1461-1506, wherein each nucleoside of the 3'-region comprises a bicyclic furanosyl sugar moiety.

1508. The oligomeric compound of any of embodiments 1461-1506, wherein at least one nucleoside of the 3'-region comprises a non-bicyclic sugar moiety.

1509. The oligomeric compound of embodiment 1508, wherein the non-bicyclic sugar moiety of the at least one nucleoside of the 3'-region is a 2'-substituted ribosyl sugar moiety.

1510. The oligomeric compound of any of embodiments 1461-1509, wherein each nucleoside of the 3'-region comprises a non-bicyclic sugar moiety.

1511. The oligomeric compound of embodiment 1510, wherein each nucleoside of the 3'-region comprises a 2'-substituted furanosyl sugar moiety.

1512. The oligomeric compound of any of embodiments 1461-1511, wherein each nucleoside of the 3'-region comprises a 2'-modified furanosyl sugar moiety independently selected from a bicyclic sugar moiety and a non-bicyclic 2'-substituted ribosyl sugar moiety.

1513. The oligomeric compound of any of embodiments 1461-1512, wherein each nucleoside of the 3'-region comprises a bicyclic sugar moiety.

1514. The oligomeric compound of any of embodiments 1461-1512, wherein each nucleoside of the 3'-region comprises a non-bicyclic 2'-substituted ribosyl sugar moiety.

1515. The oligomeric compound of any of embodiments 1461-1509 or 1512-1513, wherein each bicyclic sugar moiety of the 3'-region is selected from among cEt, LNA, and ENA.

1516. The oligomeric compound of any of embodiments 1461-1509, 1512-1513, or 1515, wherein each
5 bicyclic sugar moiety of the 3'-region is a cEt sugar moiety.

1517. The oligomeric compound of any of embodiments 1461-1509, 1512-1513, or 1515, wherein each bicyclic sugar moiety of the 3'-region is an LNA sugar moiety.

10 1518. The oligomeric compound of any of embodiments 1461-1506, 1508-1512 or 1514, wherein each non-bicyclic sugar moiety of the 3'-region has a 2'-substituent selected from among 2'-MOE, 2'-OMe, and 2'-NMA.

1519. The oligomeric compound of any of embodiments 1461-1518, wherein none of the nucleosides of the
15 3'-region comprise a sugar moiety having a 2'-F substituent.

1520. The oligomeric compound of any of embodiments 1461-1519, wherein none of the nucleosides of the 3'-region comprise a sugar moiety having a 2'-MOE substituent.

20 1521. The oligomeric compound of any of embodiments 1461-1520, wherein none of the nucleosides of the 3'-region comprise a sugar moiety having a 2'-OMe substituent.

1522. The oligomeric compound of any of embodiments 1461-1521, wherein none of the nucleosides of the 3'-region comprise a cEt sugar moiety.

25 1523. The oligomeric compound of any of embodiments 1461-1522, wherein none of the nucleosides of the 3'-region comprise a LNA sugar moiety.

1524. The oligomeric compound of any of embodiments 1461-1523, wherein each nucleobase of the 3'-
30 region is independently selected from among thymine, uracil, guanine, cytosine, 5-methylcytosine, and adenine.

1525. The oligomeric compound of any of embodiments 1461-1524, wherein each internucleoside linkage
35 of the 3'-region is independently selected from among phosphodiester and phosphorothioate internucleoside linkages.

1526. The oligomeric compound of any of embodiments 1461-1525, wherein the modified nucleosides of the 5'-region have the same modifications as the modifications of the modified nucleosides of the 3'-region.

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1527. The oligomeric compound of any of embodiments 1461-1525, wherein at least one modified nucleoside of the 5'-region and one modified nucleoside of the 3'-region comprise modifications that differ from one another.

10 1528. The oligomeric compound of any of embodiments 1461-1474, 1476-1477, 1480, 1483-1506, 1508-1509, 1512, 1515-1527, wherein the 5'-region and the 3'-region together include at least one non-bicyclic 2'-substituted modified nucleoside and at least one bicyclic nucleoside.

1529. The oligomeric compound of any of embodiment 1528, where the bicyclic nucleoside is a cEt
15 nucleoside.

1530. The oligomeric compound of embodiment 1528, where the bicyclic nucleoside is an LNA nucleoside.

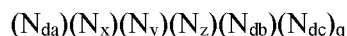
1531. The oligomeric compound of any of embodiments 1528-1530, wherein the non-bicyclic 2'-modified
20 nucleoside is a 2'-MOE nucleoside.

1532. The oligomeric compound of any of embodiments 1528-1530, wherein the non-bicyclic 2'-modified nucleoside is a 2'-OMe nucleoside.

25 1533. The oligomeric compound of any of embodiments 1528-1532, wherein at least one nucleoside of the 5'-region or the 3'-region is an unmodified 2'-β-D-deoxyribosyl sugar moiety.

1534. The oligomeric compound of any of embodiments 1461-1533, wherein the central region has the formula:

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wherein each N_{dc} is independently selected from an unmodified 2'-β-D-deoxyribosyl sugar moiety, a DNA isomer, a modified DNA isomer, and a DNA mimic; and q is 2-6.

1535. The oligomeric compound of any of embodiments 1461-1534, wherein the central region consists of
35 7 linked nucleosides.

1536. The oligomeric compound of any of embodiments 1461-1534, wherein the central region consists of 8 linked nucleosides.

1537. The oligomeric compound of any of embodiments 1461-1534, wherein the central region consists of 9 linked nucleosides.

1538. The oligomeric compound of any of embodiments 1461-1534, wherein the central region consists of 10 linked nucleosides.

1539. The oligomeric compound of any of embodiments 1461-1534, wherein the central region consists of 11 linked nucleosides.

1540. The oligomeric compound of any of embodiments 1461-1539, wherein Nx is the safety-enhancing nucleoside.

1541. The oligomeric compound of any of embodiments 1461-1539, wherein Ny is the safety-enhancing nucleoside.

1542. The oligomeric compound of any of embodiments 1461-1539, wherein Nz is the safety-enhancing nucleoside.

1543. The oligomeric compound of any of embodiments 1461-1542, wherein the safety enhancing nucleoside is a DNA isomer or a modified DNA isomer, or a modified nucleoside comprising either a sugar surrogate, a bicyclic furanosyl sugar moiety, or a non-bicyclic modified furanosyl sugar moiety.

1544. The oligomeric compound of any of embodiments 1461-1543, wherein the safety enhancing nucleoside is a DNA isomer or a modified DNA isomer, or comprises either a sugar surrogate, a bicyclic furanosyl sugar moiety, a non-bicyclic, 2'-modified furanosyl sugar moiety, a non-bicyclic 3'-modified furanosyl sugar moiety, a non-bicyclic, 4'-modified furanosyl sugar moiety, or a non-bicyclic 5'-modified furanosyl sugar moiety.

1545. The oligomeric compound of any of embodiments 1461-1544, wherein the safety enhancing nucleoside comprises a sugar surrogate selected from a morpholino, a modified morpholino, a modified cyclohexenyl, or a modified tetrahydropyran.

1546. The oligomeric compound of any of embodiments 1461-1544, wherein the safety enhancing nucleoside comprises a sugar surrogate selected from a morpholino, a modified morpholino, 2'-fluoroarabinose, 2'-fluororibose, CeNA, F-CeNA, HNA, OMe-HNA or F-HNA.

1547. The oligomeric compound of any of embodiments 1461-1544, wherein the safety enhancing nucleoside is a DNA isomer comprising a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 2'-α-D-deoxyribosyl, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl.

1548. The oligomeric compound of any of embodiments 1461-1544 or 1547, wherein the safety enhancing nucleoside is a DNA isomer comprising a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, and 2'-β-L-deoxyribosyl.

1549. The oligomeric compound of any of embodiments 1461-1544, wherein the safety enhancing nucleoside is a modified DNA isomer comprising a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a hydroxyl, a fluoro, or O-C₁-C₁₀ alkoxy substituent.

1550. The oligomeric compound of any of embodiments 1461-1544 or 1549, wherein the safety enhancing nucleoside is a modified DNA isomer comprising a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a hydroxyl, a fluoro, or OMe substituent.

1551. The oligomeric compound of any of embodiments 1461-1544 or 1549-1550, wherein the safety enhancing nucleoside is a modified DNA isomer comprising a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a fluoro or OMe substituent.

1552. The oligomeric compound of any of embodiments 1461-1544 or 1549-1551, wherein the safety enhancing nucleoside is a modified DNA isomer comprising a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, and 2'-β-L-deoxyribosyl and the 2' position is further substituted with a hydroxyl, fluoro, or OMe substituent.

1553. The oligomeric compound of any of embodiments 1461-1544, wherein the safety enhancing nucleoside is a modified nucleoside comprising a bicyclic furanosyl sugar moiety.

5 1554. The oligomeric compound of any of embodiments 1461-1544, wherein the safety enhancing nucleoside is selected from among cEt, LNA, α -L-LNA, and ENA.

1555. The oligomeric compound of any of embodiments 1461-1544, wherein the safety enhancing nucleoside comprises a 2'-substituted furanosyl sugar moiety.

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1556. The oligomeric compound of embodiment 1555, wherein the 2'-substituted furanosyl sugar moiety of the safety enhancing nucleoside has a 2' substituent selected from: halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, 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-alkylenyl-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.

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1557. The oligomeric compound of embodiment 1555, wherein the 2'-substituted furanosyl sugar moiety of the safety enhancing nucleoside has a 2' substituent selected from: halo, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, S-alkyl, N(R_m)-alkyl, 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.

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25 1558. The oligomeric compound of embodiment 1555, wherein the 2'-substituted furanosyl sugar moiety of the safety enhancing nucleoside has a 2' substituent selected from: fluoro, OMe, MOE, NMA.

1559. The oligomeric compound of any of embodiments 1461-1558, wherein the safety enhancing nucleoside comprises a 2'-substituted furanosyl sugar moiety comprising a 2'-OMe or 2'-MOE.

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1560. The oligomeric compound of any of embodiments 1461-1559, wherein the safety enhancing nucleoside comprises a 2'-substituted furanosyl sugar moiety comprising a 2'-OMe.

1561. The oligomeric compound of any of embodiments 1461-1560, wherein the safety enhancing nucleoside comprises a 2'-OMe modified 2'- β -D-deoxyribose sugar moiety.

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1562. The oligomeric compound of any of embodiments 1461-1544, wherein the safety enhancing nucleoside comprises a 3'-modified furanosyl sugar moiety having a 3' substituent selected from: halo, allyl, amino, azido, SH, CN, CF₃, OCF₃, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, S-alkyl, N(R_m)-alkyl, N(R_m)-alkenyl, N(R_m)-alkynyl, O-alkylenyl-O-alkyl, alkynyl, alkaryl, or aralkyl.

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1563. The oligomeric compound of any of embodiments 1461-1544 or embodiment 1562, wherein the safety enhancing nucleoside comprises a 3'-modified furanosyl sugar moiety having a 3' substituent selected from: C₁-C₁₀ alkyl, or C₁-C₁₀ substituted alkyl.

10 1564. The oligomeric compound of any of embodiments 1461-1544 or 1562-1563, wherein the safety enhancing nucleoside comprises a 3'-methyl furanosyl sugar moiety.

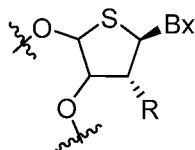
1565. The oligomeric compound of any of embodiments 1461-1544, wherein the safety enhancing nucleoside comprises a 4'-modified furanosyl sugar moiety having a 4' substituent selected from: halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, C₁-C₁₀ 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-alkylenyl-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.

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1566. The oligomeric compound of any of embodiments 1461-1544 or 1565, wherein the safety enhancing nucleoside comprises a 4'-modified furanosyl sugar moiety having a 4'-methyl.

1567. The oligomeric compound of any of embodiments 1461-1544, wherein the safety enhancing nucleoside has the structure shown below, wherein R represents an optional 2' substituent group and Bx is a heterocyclic base moiety:

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1568. The oligomeric compound of embodiment 1567, wherein in R is selected from among H, OH, OMe, F, or MOE.

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1569. The oligomeric compound of any of embodiments 1461-1544, wherein the safety enhancing nucleoside comprises a 5'-modified furanosyl sugar moiety having a 5' substituent selected from: halo,

allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, 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-alkylenyl-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.

1570. The oligomeric compound of any of embodiments 1461-1544 or 1569, wherein the safety enhancing nucleoside comprises a 5'-modified furanosyl sugar moiety with a 5' substituent selected from: 5'-methyl, 5'-ethyl or a 5'-allyl.

1571. The oligomeric compound of any of embodiments 1461-1544 or 1569-1570, wherein the safety enhancing nucleoside comprises a 5'-modified furanosyl sugar moiety with a 5' substituent selected from: 5'-(*R*)-methyl- or 5'-(*R*)-ethyl.

1572. The oligomeric compound of any of embodiments 1461-1544 or 1569-1571, wherein the safety enhancing nucleoside comprises a 5'-(*R*)-methyl-2'-β-D-deoxyribose sugar moiety.

1573. The oligomeric compound of any of embodiments 1461-154 or 1569-1572, wherein the safety enhancing nucleoside comprises a 5'-(*R*)-ethyl-2'-β-D-deoxyribose sugar moiety.

1574. The oligomeric compound of any of embodiments 1461-1573, wherein the safety enhancing nucleoside does not comprise a 2'-F modified sugar moiety.

1575. The oligomeric compound of any of embodiments 1461-1574, wherein the safety enhancing nucleoside does not comprise a cEt modified sugar moiety.

1576. The oligomeric compound of any of embodiments 1461-1575, wherein the safety enhancing nucleoside does not comprise a 2'-MOE modified sugar moiety.

1577. The oligomeric compound of any of embodiments 1461-1576, wherein the safety enhancing nucleoside comprises a hypoxanthine nucleobase.

1578. The oligomeric compound of any of embodiments 1461-1577, wherein the safety enhancing nucleoside comprises a nucleobase selected from among thymine, uracil, guanine, cytosine, 5-methylcytosine, and adenine.

1579. The oligomeric compound of any of embodiments 1461-1578, wherein the safety enhancing nucleoside is a modified nucleoside other than cEt, MOE, LNA, or FANA.

5 1580. The oligomeric compound of any of embodiments 1461-1579, wherein each Nd is independently selected from among an unmodified 2'-β-D-deoxyribosyl sugar moiety, a DNA isomer, a 2'-modified DNA isomer, and a DNA mimic.

10 1581. The oligomeric compound of embodiment 1580, wherein each DNA isomer comprises a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 2'-α-D-deoxyribosyl, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl.

1582. The oligomeric compound of embodiment 1581, wherein each DNA isomer comprises a sugar moiety selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, and 2'-β-L-deoxyribosyl.

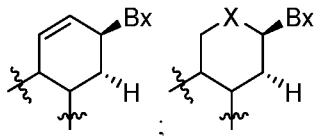
15 1583. The oligomeric compound of embodiment 1580, wherein each modified DNA isomer comprises a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a hydroxyl, a fluoro, or O-C₁-C₁₀ alkoxy substituent.

20 1584. The oligomeric compound of embodiment 1583, wherein each modified DNA isomer comprises a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a hydroxyl, a fluoro, or OMe substituent.

25 1585. The oligomeric compound of embodiment 1584, wherein each modified DNA isomer comprises a 2'-modified sugar moiety, wherein the sugar moiety has the conformation 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, 2'-β-L-deoxyribosyl, 2'-α-D-deoxyxylosyl, 1, 2'-α-L-deoxyxylosyl, and 2'-β-L-deoxyxylosyl and the 2' position is further substituted with a fluoro or OMe substituent.

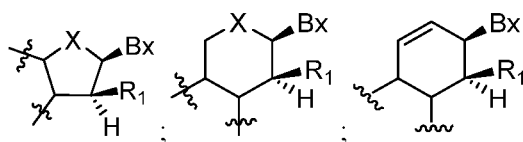
30 1586. The oligomeric compound of embodiment 1585, wherein each modified DNA isomer comprises a 2'-modified sugar moiety, wherein the sugar moiety is selected from among 2'-β-D-deoxyxylosyl, 2'-α-L-deoxyribosyl, and 2'-β-L-deoxyribosyl and the 2' position is further substituted with a hydroxyl, fluoro, or OMe substituent.

1587. The oligomeric compound of embodiment 1580, wherein each DNA mimic comprises a structure represented by one of the formulas below:



5 wherein X is O or S and Bx represents a heterocyclic base moiety.

1588. The oligomeric compound of embodiment 1580, wherein each DNA mimic comprises a structure represented by one of the formulas below:

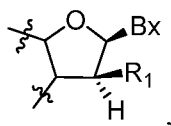


10 wherein X is O or S;

Bx represents a heterocyclic base moiety; and

R₁ is selected from among H, OH, halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, 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-alkylenyl-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;

wherein if the DNA mimic comprises the structure:

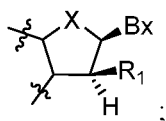


20 R₁ is other than H.

1589. The oligomeric compound of embodiment 1588, wherein R₁ is H, OH, OMe, or F.

1590. The oligomeric compound of embodiment 1588, wherein R₁ is not F.

1591. The oligomeric compound of embodiment 1580, wherein each DNA mimic comprises a structure represented by the formula below:



wherein X is S, B_x represents a heterocyclic base moiety, and R₁ is H.

1592. The oligomeric compound of embodiment 1580, wherein the DNA mimic has a sugar moiety selected from among: 5'-methyl-2'-β-D-deoxyribosyl, 5'-ethyl-2'-β-D-deoxyribosyl, and 5'-allyl-2'-β-D-deoxyribosyl.

1593. The oligomeric compound of embodiment 1580, wherein the DNA mimic comprises a 2'-fluoro-β-D-arabinofuranosyl sugar moiety.

1594. The oligomeric compound of embodiment 1580, wherein the DNA mimic does not comprise a 2'-fluoro-β-D-arabinofuranosyl sugar moiety.

1595. The oligomeric compound of any of embodiments 1461-1594, wherein each N_d is an unmodified 2'-β-D-deoxyribosyl sugar moiety.

1596. The oligomeric compound of any of embodiments 1461-1595, wherein the central region comprises no more than four nucleosides selected from among DNA isomers, modified DNA isomers, and DNA mimics.

1597. The oligomeric compound of any of embodiments 1461-1595, wherein the central region comprises no more than three nucleosides selected from among DNA isomers, modified DNA isomers, and DNA mimics.

1598. The oligomeric compound of any of embodiments 1461-1595, wherein the central region comprises no more than two nucleosides selected from among DNA isomers, modified DNA isomers, and DNA mimics.

1599. The oligomeric compound of any of embodiments 1461-1595, wherein the central region comprises no more than one nucleoside selected from among DNA isomers, modified DNA isomers, and DNA mimics.

1600. The oligomeric compound of any of embodiments 1461-1599, wherein the central region contains exactly one safety enhancing nucleoside and the remainder of nucleosides in the central region are unmodified 2'-β-D-deoxyribosyl sugar moieties.

1601. The oligomeric compound of any of embodiments 1461-1600, wherein at least one internucleoside linkage of the central region selected from among: the internucleoside Nda to Nx, Nx to Ny, Ny to Nz, or Nz to the adjacent Ndb is a neutral internucleoside linkage.

1602. The oligomeric compound of embodiment 1601, wherein the neutral linkage is a phosphonate internucleoside linkage.

1603. The oligomeric compound of embodiment 1601, wherein the neutral linkage is a methoxypropyl internucleoside linkage.

1604. The oligomeric compound of embodiment 1601, wherein each remaining internucleoside linkage is a phosphodiester or phosphorothioate internucleoside linkage.

1605. The oligomeric compound of any of embodiments 1461-1600, wherein at least one internucleoside linkage of the central region is a 2'-5' internucleoside linkage.

1606. The oligomeric compound of any of embodiments 1461-1600, wherein exactly one internucleoside linkage of the central region is a 2'-5' internucleoside linkage.

1607. The oligomeric compound of any of embodiments 1461-1600, wherein at least one internucleoside linkage of the central region selected from among: the internucleoside Nda to Nx, Nx to Ny, Ny to Nz, or Nz to the adjacent Ndb is a 2'-5' internucleoside linkage.

1608. A chirally enriched population of modified oligonucleotides of any of embodiments 1461-1607, wherein the central region has at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

1609. The chirally enriched population of embodiment 1608, wherein the central region has at least one phosphorothioate internucleoside linkage having the (*Sp*) configuration.

1610. The chirally enriched population of embodiment 1608, wherein central region has at least one phosphorothioate internucleoside linkage having the (*Rp*) configuration.

1611. The chirally enriched population of embodiment 1608, wherein the central region has a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

1612. The chirally enriched population of embodiment 1608, wherein the each phosphorothioate internucleoside linkage of the central region has the (Sp) configuration.

1613. The chirally enriched population of embodiment 1608, wherein the central region has one phosphorothioate internucleoside linkage having the (Rp) configuration and wherein each remaining central region phosphorothioate internucleoside linkage has the (Sp) configuration.

1614. The chirally enriched population of embodiment 1608, wherein the central region has an (Rp) phosphorothioate internucleoside linkage adjacent to an (Sp) phosphorothioate internucleoside linkage.

1615. The chirally enriched population of embodiment 1608, wherein the central region has an (Rp) phosphorothioate internucleoside linkage adjacent to a second (Rp) phosphorothioate internucleoside linkage.

1616. The chirally enriched population of embodiment 1608, wherein the central region has an (Rp) phosphorothioate internucleoside linkage adjacent to a second (Rp) phosphorothioate internucleoside linkage, and wherein each remaining central region phosphorothioate internucleoside linkage has the (Sp) configuration.

1617. The chirally enriched population of any of embodiments 1609, 1610, 1614, or 1615 wherein each phosphorothioate internucleoside linkage that does not have the (Rp) or (Sp) configuration is stereorandom.

1618. The oligomeric compound of any of embodiments 1461-1617 comprising a conjugate group.

1619. The oligomeric compound of embodiment 1618, wherein the conjugate group comprises a linking group attaching the remainder of the conjugate group to the modified oligonucleotide, wherein the linking group comprises 1-5 nucleosides.

1620. The oligomeric compound of any of embodiments 1461-1618, wherein the oligomeric compound does not comprise additional nucleosides beyond those of the modified oligonucleotide.

1621. The oligomeric compound of any of embodiments 1461-1620, wherein the nucleobase sequence of the modified oligonucleotide is complementary to a target RNA.

1622. The oligomeric compound of embodiment 1621, wherein the nucleobase sequence of the modified oligonucleotide is at least 85% complementary to the target RNA.

1623. The oligomeric compound of embodiment 1621, wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to the target RNA.

5 1624. The oligomeric compound of embodiment 1621, wherein the nucleobase sequence of the modified oligonucleotide is at least 95% complementary to the target RNA.

1625. The oligomeric compound of embodiment 1621, wherein the nucleobase sequence of the modified oligonucleotide is 100% complementary to the target RNA.

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1626. The oligomeric compound of any of embodiments 1621-1625, wherein the target RNA is a target mRNA or a target pre-mRNA.

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1627. The oligomeric compound of embodiment 1626, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human PTEN RNA.

1628. The oligomeric compound of embodiment 1626 or 1627, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human SRB-1 RNA.

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1629. The oligomeric compound of any of embodiments 1626-1628, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human MYD88 RNA.

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1630. The oligomeric compound of any of embodiments 1626-1629, wherein the target mRNA or target pre-mRNA is not a mouse, rat, monkey, or human HTT RNA, is not a mouse, rat, monkey, or human SOD1 RNA, and is not a mouse, rat, monkey, or human alpha-synuclein RNA.

1631. The oligomeric compound of any of embodiments 1621-1630, wherein the target RNA is a human RNA.

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1632. The oligomeric compound of any of embodiments 1621-1631, wherein the target RNA is expressed in the liver.

1633. The oligomeric compound of any of embodiments 1621-1632, wherein the target RNA is a liver target.

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1634. The oligomeric compound of any of embodiments 1621-1631, wherein the target RNA is not expressed in the liver.

1635. The oligomeric compound of any of embodiments 1621-1631 or 1634, wherein the target RNA is not a liver target.

1636. The oligomeric compound of any of embodiments 1621-1635, wherein modulation of the expression of the target RNA in the liver is associated with treating a disorder or condition.

1637. The oligomeric compound of embodiment 1636, wherein the disorder or condition is a liver disorder or condition.

1638. The oligomeric compound of any of embodiments 1621-1637, wherein the target RNA is expressed in the central nervous system.

1639. The oligomeric compound of any of embodiments 1621-1637, wherein the target RNA is not expressed in the central nervous system.

1640. The oligomeric compound of any of embodiments 1621-1638, wherein the target RNA is a central nervous system target.

1641. The oligomeric compound of any of embodiments 1621-1639, wherein the target RNA is not a central nervous system target.

1642. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in white fat cells.

1643. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in brown fat cells.

1644. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in adipocytes.

1645. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in macrophages.

1646. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in cancer cells.

1647. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in tumor cells.

1648. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in smooth muscle cells.

1649. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in lymphocytes.

1650. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in pulmonary cells.

1651. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in heart muscle cells.

1652. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in cardiomyocytes.

1653. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in endothelial cells.

1654. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in fibroblasts.

1655. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in glial cells.

1656. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in Schwann cells.

1657. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in pancreatic cells.

1658. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in kidney cells.

1659. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in beta cells.

1660. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in non-parenchymal cells.

1661. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in hepatocytes.

1662. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in oligodendrocytes.

1663. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in astrocytes.

1664. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in microglia.

1665. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in ependymal cells.

1666. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in sensory neurons.

1667. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in motor neurons.

1668. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in skeletal muscle.

1669. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in cardiac muscle.

1670. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in smooth muscle.

1671. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in adipose tissue.

1672. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in white adipose tissue.

1673. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the spleen.

1674. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the bone.

1675. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the bone marrow.

1676. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the intestine.

1677. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the adrenal glands.

1678. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the testes.

1679. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the ovaries.

1680. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the pancreas.

1681. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the pituitary gland.

1682. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the prostate gland.

1683. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the skin.

1684. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the epidermis.

1685. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the uterus.

1686. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the bladder.

1687. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the brain.

1688. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the glomerulus.

1689. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the distal tubular epithelium.

1690. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in breast tissue.

1691. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the lung.

1692. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the heart.

1693. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the kidney.

1694. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the ganglion.

1695. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the frontal cortex.

1696. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the spinal cord.

1697. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the trigeminal ganglion.

1698. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the sciatic nerve.

1699. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the dorsal root ganglion.

1700. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the epidymal fat.

1701. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the diaphragm.

1702. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is expressed in the colon.

1703. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a white fat cell target.

1704. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a brown fat cell target.

1705. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is an adipocyte target.

1706. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a macrophage target.

1707. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a cancer cell target.

1708. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a tumor cell target.

1709. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a smooth muscle cell target.

1710. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a lymphocyte target.

1711. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a pulmonary cell target.

1712. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a heart muscle cell target.

1713. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a cardiomyocyte target.

1714. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a endothelial cell target.

1715. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a fibroblast target.

1716. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a glial cell target.

1717. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a Schwann cell target.

1718. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a pancreatic cell target.

1719. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a kidney cell target.

1720. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a beta cell target.

1721. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a non-parenchymal cell target.

1722. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a hepatocyte target.

1723. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is an oligodendrocyte target.

1724. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is an astrocyte target.

1725. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a microglia target.

1726. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is an ependymal cell target.

1727. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a sensory neuron target.

1728. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a motor neuron target.

1729. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a skeletal muscle target.

1730. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a cardiac muscle target.

1731. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a smooth muscle target.

1732. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is an adipose tissue target.

1733. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a white adipose tissue target.

1734. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a spleen target.

1735. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a bone target.

1736. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a bone marrow target.

1737. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is an intestinal target.

1738. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is an adrenal gland target.

1739. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a testicular target.

1740. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is an ovarian target.

1741. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a pancreatic target.

1742. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a pituitary gland target.

1743. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a prostate gland target.

1744. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a skin target.

1745. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is an epidermal target.

1746. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a uterine target.

1747. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a bladder target.

1748. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a brain target.

1749. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a glomerulus target.

1750. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a distal tubular epithelium target.

1751. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a breast tissue target.

1752. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a lung target.

1753. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a heart target.

1754. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a kidney target.

1755. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a ganglion target.

1756. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a frontal cortex target.

1757. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a spinal cord target.

1758. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a trigeminal ganglion target.

1759. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a sciatic nerve target.

1760. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a dorsal root ganglion target.

1761. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is an epidymal fat target.

1762. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a diaphragm target.

1763. The oligomeric compound of any of embodiments 1621-1641, wherein the target RNA is a colon target.

1764. The oligomeric compound of any of embodiments 1621-1763, wherein the target RNA is a MeCP2, DUX4, HDAC2, APP, Ataxin 1, Ataxin 2, Ataxin 3, Ataxin 6, Ataxin 7, C9ORF72, UBE3A, Prion, PMP22, Tau, LRRK2, LINGO2, GYS1, KCNT1, IRF8, Progranulin, or GFAP RNA.

1765. The oligomeric compound of any of embodiments 1621-1763, wherein the target RNA is a HTT RNA.

1766. The oligomeric compound of embodiment 1764, wherein the target RNA is a MeCP2 RNA.

1767. The oligomeric compound of embodiment 1764, wherein the target RNA is a DUX4 RNA.

1768. The oligomeric compound of embodiment 1764, wherein the target RNA is a HDAC2 RNA.

1769. The oligomeric compound of embodiment 1764, wherein the target RNA is a Ataxin 1 RNA.

1770. The oligomeric compound of embodiment 1764, wherein the target RNA is a Ataxin 2 RNA.

1771. The oligomeric compound of embodiment 1764, wherein the target RNA is a Ataxin 3 RNA.

1772. The oligomeric compound of embodiment 1764, wherein the target RNA is a Ataxin 6 RNA.

1773. The oligomeric compound of embodiment 1764, wherein the target RNA is a Ataxin 7 RNA.

1774. The oligomeric compound of embodiment 1764, wherein the target RNA is a C9ORF72 RNA.

1775. The oligomeric compound of embodiment 1621-1763, wherein the target RNA is an alpha-synuclein RNA.

1776. The oligomeric compound of embodiment 1764, wherein the target RNA is an UBE3A RNA.

1777. The oligomeric compound of any of embodiments 1621-1763, wherein the target RNA is a SOD1
5 RNA.

1778. The oligomeric compound of embodiment 1764, wherein the target RNA is a Prion RNA.

1779. The oligomeric compound of embodiment 1764, wherein the target RNA is a PMP22 RNA.

1780. The oligomeric compound of any of embodiments 1621-1764, wherein the target RNA is a Tau
10 RNA.

1781. The oligomeric compound of embodiment 1764, wherein the target RNA is a LRRK2 RNA.

1782. The oligomeric compound of embodiment 1764, wherein the target RNA is an APP RNA.

1783. The oligomeric compound of 1764, wherein the target RNA is a LINGO2 RNA.

1784. The oligomeric compound of any of embodiments 1764, wherein the target RNA is a GYS1 RNA.

1785. The oligomeric compound of any of embodiments 1764, wherein the target RNA is a KCNT1 RNA.

1786. The oligomeric compound of any of embodiments 1764, wherein the target RNA is a IRF8 RNA.

1787. The oligomeric compound of any of embodiments 1764, wherein the target RNA is a Progranulin
25 RNA.

1788. The oligomeric compound of any of embodiments 1764, wherein the target RNA is a GFAP RNA.

1789. The oligomeric compound of any of embodiments 1621-1788, wherein modulation of the expression
30 of the target RNA is associated with treating a disorder or condition.

1790. The oligomeric compound of embodiment 1789, wherein the disorder or condition is Alzheimer's
35 Disease, Amyotrophic Lateral Sclerosis, Parkinson's Disease, a Spinocerebellar ataxia, Angelman
Syndrome, Alexander's Disease, Lafora Disease, Charcot-Marie Tooth Disease, Prion Disease, a

dementia, neurodegeneration, MeCP2 Duplication Syndrome, encephalopathy, neuroinflammation, or multiple sclerosis.

1791. The oligomeric compound of embodiment 1790, wherein the disorder or condition is Alzheimer's Disease.

1792. The oligomeric compound of embodiment 1790, wherein the disorder or condition is Amyotrophic Lateral Sclerosis.

1793. The oligomeric compound of embodiment 1790, wherein the disorder or condition is Parkinson's Disease.

1794. The oligomeric compound of embodiment 1790 wherein the disorder or condition is a Spinocerebellar ataxia.

1795. The oligomeric compound of embodiment 1790 wherein the disorder or condition is Angelman Syndrome.

1796. The oligomeric compound of embodiment 1790, wherein the disorder or condition is Alexander's Disease.

1797. The oligomeric compound of embodiment 1790, wherein the disorder or condition is Lafora Disease.

1798. The oligomeric compound of embodiment 1790, wherein the disorder or condition is Charcot-Marie Tooth Disease.

1799. The oligomeric compound of embodiment 1790, wherein the disorder or condition is Prion Disease.

1800. The oligomeric compound of embodiment 1790, wherein the disorder or condition is a dementia.

1801. The oligomeric compound of embodiment 1790, wherein the disorder or condition is neurodegeneration.

1802. The oligomeric compound of embodiment 1790, wherein the disorder or condition is MeCP2 Duplication Syndrome.

1803. The oligomeric compound of embodiment 1790, wherein the disorder or condition is encephalopathy.

1804. The oligomeric compound of embodiment 1790, wherein the disorder or condition is
5 neuroinflammation.

1805. The oligomeric compound of embodiment 1790, wherein the disorder or condition is multiple
sclerosis.

10 1806. The oligomeric compound of any of embodiments 1461-1805, wherein the parent oligomeric
compound of the oligomeric compound of any of embodiments 1461-1805 is cytotoxic in vitro.

1807. The oligomeric compound of embodiment 1806, wherein the parent oligomeric compound is
cytotoxic in a standard in vitro cytotoxicity assay.

15 1808. The oligomeric compound of any of embodiments 1461-1805 wherein administration to a mouse of
the parent oligomeric compound of the oligomeric compound of any of embodiments 1461-1805 is
hepatotoxic to the mouse.

20 1809. The oligomeric compound of embodiment 1808, wherein the administration of the parent oligomeric
compound to the mouse is systemic administration.

1810. The oligomeric compound of embodiment 1809, wherein the systemic administration is subcutaneous
administration.

25 1811. The oligomeric compound of any of embodiments 1808-1810, wherein the mouse is a CD-1 mouse.

1812. The oligomeric compound of any of embodiments 1808-1810, wherein the mouse is a C57BL/6 mouse.

30 1813. The oligomeric compound of any of embodiments 1808-1810, wherein the mouse is a BALB/c mouse.

1814. The oligomeric compound of any of embodiments 1807-1813, wherein the plasma ALT level in the
mouse is higher than 500 units per liter following the administration of the parent oligomeric compound.

1815. The oligomeric compound of any of embodiments 1807-1814, wherein the plasma AST level in the mouse is higher than 500 units per liter following the administration of the parent oligomeric compound.

1816. The oligomeric compound of any of embodiments 1807-1815, wherein the plasma ALT level in the mouse is higher than 1000 units per liter following the administration of the parent oligomeric compound.

1817. The oligomeric compound of any of embodiments 1807-1816, wherein the plasma AST level in the mouse is higher than 1000 units per liter following the administration of the parent oligomeric compound.

1818. The oligomeric compound of any of embodiments 1807-1817, wherein the hepatotoxicity is measured 24-48 hours following the administration of the parent oligomeric compound.

1819. The oligomeric compound of any of embodiments 1807-1817, wherein the hepatotoxicity is measured 72 hours following the administration of the parent oligomeric compound.

1820. The oligomeric compound of any of embodiments 1807-1817, wherein the hepatotoxicity is measured 3 days following the administration of the parent oligomeric compound.

1821. The oligomeric compound of any of embodiments 1807-1817, wherein the hepatotoxicity is measured 5 days following the administration of the parent oligomeric compound.

1822. The oligomeric compound of any of embodiments 1807-1817, wherein the hepatotoxicity is measured 7 days following the administration of the parent oligomeric compound.

1823. The oligomeric compound of any of embodiments 1807-1817, wherein the hepatotoxicity is measured 10 days following the administration of the parent oligomeric compound.

1824. The oligomeric compound of any of embodiments 1807-1817, wherein the hepatotoxicity is measured 14 days following the administration of the parent oligomeric compound.

1825. The oligomeric compound of any of embodiments 1807-1817, wherein 1-10 mg/kg of the parent oligomeric compound is administered to the mouse.

1826. The oligomeric compound of any of embodiments 1807-1817, wherein 10-25 mg/kg of the parent oligomeric compound is administered to the mouse.

1827. The oligomeric compound of any of embodiments 1807-1817, wherein 25-50 mg/kg of the parent oligomeric compound is administered to the mouse.

5 1828. The oligomeric compound of any of embodiments 1807-1817, wherein 50-100 mg/kg of the parent oligomeric compound is administered to the mouse.

1829. The oligomeric compound of any of embodiments 1807-1817, wherein 100-150 mg/kg of the parent oligomeric compound is administered to the mouse.

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1830. The oligomeric compound of any of embodiments 1807-1817, wherein the mouse is a BALB/c mouse, wherein 150 mg/kg of the parent oligomeric compound is administered to the mouse, and wherein the plasma ALT level in the mouse is measured 72 hours following the administration of the parent oligomeric compound.

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1831. The oligomeric compound of any of embodiments 1461-1830, wherein administration of 50 mg/kg of the oligomeric compound of any of embodiments 1461-1830 to a mouse is not hepatotoxic to the mouse.

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1832. The oligomeric compound of embodiment 1831, wherein plasma ALT level in the mouse is lower than 100 units per liter following the administration of the oligomeric compound of embodiment 1831.

25

1833. The oligomeric compound of embodiment 1831 or 1832, wherein plasma ALT level in the mouse is at least 10-fold lower than plasma ALT level in a mouse administered the parent oligomeric compound of the oligomeric compound of embodiment 1831 or 1832, wherein the administrations and plasma ALT measurements of both the oligomeric compound of embodiment 1831 or 1832 and the parent oligomeric compound are completed in the same way.

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1834. The oligomeric compound of embodiment 1833, wherein the plasma ALT level in the mouse is at least 100-fold lower than the plasma ALT level in the mouse administered the parent oligomeric compound.

1835. The oligomeric compound of embodiment 1833, wherein the plasma ALT level in the mouse is at least 500-fold lower than the plasma ALT level in the mouse administered the parent oligomeric compound.

1836. The oligomeric compound of any of embodiments 1807-1835, wherein the therapeutic index in a mouse of the oligomeric compound of any of embodiments 1807-1835 is increased relative to the therapeutic index of the parent oligomeric compound.

1837. The oligomeric compound of embodiment 1836, wherein the therapeutic index in a mouse of the oligomeric compound of embodiment 1836 is at least two-fold greater than the therapeutic index of the parent oligomeric compound.

1838. The oligomeric compound of any of embodiments 1461-1805, wherein an otherwise identical oligomeric compound lacking the at least one modified internucleoside linkage other than phosphorothioate and/or at least one modified nucleoside comprising a modified nucleobase other than 5-methylcytosine and/or a modified sugar moiety in the central region is hepatotoxic following administration to a mouse; and wherein the otherwise identical oligomeric compound has a central region consisting of phosphorothioate internucleoside linkages, unmodified 2'-β-D-deoxyribosyl sugar moieties, and nucleobases selected from thymine, uracil, adenine, guanine, cytosine, and 5-methylcytosine.

1839. The oligomeric compound of embodiment 1838, wherein the at least one modified internucleoside linkage other than phosphorothioate and/or at least one modified nucleoside comprising a modified nucleobase other than 5-methylcytosine and/or a modified sugar moiety in the central region is a 2'-O-methyl modified sugar moiety.

1840. The oligomeric compound of embodiment 1839, wherein the 2'-O-methyl modified sugar moiety is at position 2 of the central region.

1841. The oligomeric compound of embodiment 1838-1840, wherein the otherwise identical oligomeric compound lacks a 2'-O-methyl modified sugar moiety, and wherein the otherwise identical oligomeric compound comprises an unmodified 2'-β-D-deoxyribosyl sugar moiety in place of the 2'-O-methyl modified sugar moiety.

1842. The oligomeric compound of any of embodiments 1838-1841, wherein the nucleobase sequence of the otherwise identical oligomeric compound is 100% complementary to the target RNA.

1843. The oligomeric compound of any of embodiments 1838-1842, wherein the otherwise identical oligomeric compound is a parent oligomeric compound of the oligomeric compound of any of embodiments 1838-1842.

1844. The oligomeric compound of any of embodiments 1621-1843, wherein the oligomeric compound inhibits the target RNA with an IC_{50} lower than 100 nM in a standard in vitro activity assay.
- 5 1845. The oligomeric compound of any of embodiments 1621-1843, wherein the parent oligomeric compound of the oligomeric compound of any of embodiments 1621-1843 inhibits the target RNA with an IC_{50} lower than 100 nM in a standard in vitro activity assay.
- 10 1846. The oligomeric compound of any of embodiments 1621-1845, wherein the difference between the IC_{50} of the parent oligomeric compound measured in a standard in vitro activity assay and the IC_{50} of the oligomeric compound of any of embodiments 1621-1845 measured in a standard in vitro activity assay is less than 4-fold.
- 15 1847. The oligomeric compound of any of embodiments 1621-1845, wherein the difference between the IC_{50} of the parent oligomeric compound measured in a standard in vitro activity assay and the IC_{50} of the oligomeric compound of any of embodiments 1621-1845 measured in a standard in vitro activity assay is less than 3-fold.
- 20 1848. The oligomeric compound of any of embodiments 1621-1845, wherein the difference between the IC_{50} of the parent oligomeric compound measured in a standard in vitro activity assay and the IC_{50} of the oligomeric compound of any of embodiments 1621-1845 measured in a standard in vitro activity assay is less than 2-fold.
- 25 1849. The oligomeric compound of any of embodiments 1621-1848, wherein each sugar moiety of the central region of the parent oligomeric compound is an unmodified 2'- β -D-deoxyribosyl sugar moiety, and wherein each internucleoside linkage of the central region of the parent oligomeric compound is a phosphorothioate internucleoside linkage.
- 30 1850. The oligomeric compound of any of embodiments 1621-1849, wherein the nucleobase sequence of the parent oligomeric compound is 100% complementary to the target RNA.
1851. The oligomeric compound of any of embodiments 1461-1850, wherein administration of 10-50 mg of the oligomeric compound to a human is not hepatotoxic to the human.

1852. The oligomeric compound of any of embodiments 1461-1850, wherein administration of 50-100 mg of the oligomeric compound to a human is not hepatotoxic to the human.

1853. The oligomeric compound of any of embodiments 1461-1850, wherein administration of 100-300 mg of the oligomeric compound to a human is not hepatotoxic to the human.

1854. The oligomeric compound of any of embodiments 1851-1853, wherein the administration is systemic administration.

1855. A composition comprising the oligomeric compound of any of embodiments 1461-1854, and a second oligomeric compound, wherein the second oligomeric compound is complementary to the oligomeric compound of any of embodiments 1461-1854.

1856. The composition of embodiment 1855, wherein the second oligomeric compound comprises at least 14 contiguous linked nucleosides that are at least 90% complementary to the oligomeric compound of any of embodiments 1851-1853.

1857. The composition of embodiment 1855, wherein the second oligomeric compound comprises at least 14 contiguous linked nucleosides that are 100% complementary to the oligomeric compound of any of embodiments 1461-1854.

1858. A pharmaceutical composition comprising the oligomeric compound of any of embodiments 1461-1854 or the composition of any of embodiments 1855-1857, comprising a pharmaceutically acceptable carrier or diluent.

1859. A method comprising administering the oligomeric compound or composition of any of embodiments 1461-1858 to a human subject.

1860. A method of treating a disease or disorder comprising administering the oligomeric compound or composition of any of embodiments 1461-1858 to a human subject.

1861. A method of modulating the amount or activity of a target RNA in a human subject comprising administering the oligomeric compound or composition of any of embodiments 1461-1858 to the human subject; and thereby modulating the amount or activity of the target RNA in the human subject.

1862. A method of treating a disease or disorder in a human subject comprising administering the oligomeric compound or composition of any of embodiments 1461-1858 to the human subject having the disease or disorder; and thereby treating the disease or disorder in the human subject.

5 1863. The method of embodiment 1861 or 1862, wherein the disease or disorder is a liver disease, and wherein the oligomeric compound modulates the amount or activity of a liver target RNA.

1864. The method of embodiment 1861 or 1862, wherein the disease or disorder is a central nervous system disease, and wherein the oligomeric compound modulates the amount or activity of a central nervous
10 system target RNA.

1865. The method of any of embodiments 1861-1864, wherein the disease or disorder is a cancer, a neurodegenerative disease, a cardiovascular disease, an immunological disease, a hereditary disease, a repeat expansion disease, a muscle-wasting disease, or a metabolic disease.

15 1866. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a white fat cell target.

1867. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount
20 or activity of a brown fat cell target.

1868. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of an adipocyte target.

25 1869. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a macrophage target.

1870. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a cancer cell target.

30 1871. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a tumor cell target.

1872. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount
35 or activity of a smooth muscle cell target.

1873. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a lymphocyte target.

1874. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a pulmonary cell target.

5 1875. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a heart muscle cell target.

1876. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a cardiomyocyte target.

10 1877. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of an endothelial cell target.

1878. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a fibroblast target.

1879. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a glial cell target.

20 1880. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a Schwann cell target.

1881. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a pancreatic cell target.

25 1882. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a kidney cell target.

1883. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a beta cell target.

1884. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a non-parenchymal cell target.

35 1885. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a hepatocyte target.

40 1886. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of an oligodendrocyte target.

1887. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of an astrocyte target.

5 1888. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a microglia target.

1889. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of an ependymal cell target.

10 1890. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a sensory neuron target.

1891. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a motor neuron target.

1892. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a skeletal muscle target.

20 1893. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a cardiac muscle target.

1894. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a smooth muscle target.

25 1895. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of an adipose tissue target.

1896. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a white adipose tissue target.

1897. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a spleen target.

35 1898. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a bone target.

1899. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a bone marrow target.

1900. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of an intestinal target.

1901. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of an adrenal gland target.

1902. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a testicular target.

1903. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of an ovarian target.

1904. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a pancreatic target.

1905. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a pituitary gland target.

1906. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a prostate gland target.

1907. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a skin target.

1908. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of an epidermal target.

1909. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a uterine target.

1910. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a bladder target.

1911. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a brain target.

1912. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a glomerulus target.

5 1913. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a distal tubular epithelium target.

1914. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a breast tissue target.

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1915. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a lung target.

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1916. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a heart target.

1917. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a kidney target.

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1918. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a ganglion target.

1919. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a frontal cortex target.

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1920. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a spinal cord target.

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1921. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a trigeminal ganglion target.

1922. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a sciatic nerve target.

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1923. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a dorsal root ganglion target.

1924. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of an epididymal fat target.

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1925. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a diaphragm target.

1926. The method of embodiment 1861 or 1862, wherein the oligomeric compound modulates the amount or activity of a colon target.

1927. The method of any of embodiments 1802-1926, wherein the plasma ALT level of the human subject after the administration is not more than three times higher than it was prior to the administration.

1928. The method of any of embodiments 1802-1926, wherein the plasma ALT level of the human subject after the administration is not more than 150 units per liter.

1929. The method of any of embodiments 1802-1928, wherein the human subject is susceptible to liver damage.

1930. The method of any of embodiments 1802-1928, wherein the human subject is susceptible to liver degeneration.

1931. The method of any of embodiments 1802-1930, wherein the human subject is susceptible to elevated apoptosis in the liver.

1932. The method of any of embodiments 1802-1931, wherein the human subject has a liver disease.

1933. The method of any of embodiments 1802-1932, wherein the human subject has kidney disease.

1934. The method of any of embodiments 1802-1933, wherein the human subject is susceptible to kidney damage.

1935. The method of any of embodiments 1802-1934, wherein the human subject has heart disease.

1936. The method of any of embodiments 1802-1935, wherein the human subject is susceptible to heart damage.

1937. The method of any of embodiments 1802-1936, wherein the human subject has pancreatitis.

1938. The method of any of embodiments 1802-1937, wherein the human subject is susceptible to pancreatic damage.

1939. The method of any of embodiments 1802-1938, wherein the human subject has a neurological disease.

1940. The method of any of embodiments 1802-1939, wherein the human subject is susceptible to neurological damage.

1941. The method of any of embodiments 1859-1940, comprising administering the parent oligomeric compound of the oligomeric compound of any of embodiments 1461-1858 to a mouse.

1942. The method of any of embodiments 1859-1940, comprising contacting a cell with the parent oligomeric compound of the oligomeric compound of any of embodiments 1461-1858.

1943. The method of embodiment 1941 or 1942, wherein each sugar moiety of the central region of the parent oligomeric compound is an unmodified 2'- β -D-deoxyribosyl sugar moiety, and wherein each internucleoside linkage of the central region of the parent oligomeric compound is a phosphorothioate internucleoside linkage.

1944. A method of designing an oligomeric compound comprising starting with a parent oligomeric compound and changing the design of that compound in order to arrive at an oligomeric compound of any one of embodiments 1461-1858.

1945. A method of designing an oligomeric compound comprising identifying a parent oligomeric compound and changing the design of that parent oligomeric compound to arrive at a second oligomeric compound, wherein the second oligomeric compound is an oligomeric compound of any one of embodiments 1461-1858.

1946. A method of improving hepatotoxicity of an oligomeric compound comprising the steps of (i) identifying a parent oligomeric compound that has plasma ALT levels above 300 units per liter in a mouse, and (ii) providing an oligomeric compound according to any one of embodiments 1461-1858.

1947. The method of embodiment 1945 or 1946, wherein the method designs an oligomeric compound with improved therapeutic index relative to the parent oligomeric compound.

1948. The method of embodiment 1945 or 1946, wherein the method designs an oligomeric compound with lower hepatotoxicity relative to the parent oligomeric compound.

1949. The method of embodiment 1945, wherein the second oligomeric compound has an improved therapeutic index relative to the parent oligomeric compound.

1950. The method of embodiment 1945 or 1946, wherein the second oligomeric compound has reduced
5 hepatotoxicity in a mouse relative to the parent oligomeric compound.

1951. The method of embodiment 1945, wherein the oligomeric compound according to any one of
embodiments 1461-1858 has reduced hepatotoxicity relative to the parent oligomeric compound.

10 1952. A method comprising administering an oligomeric compound of any of embodiments 1461-1858 to a
mouse and separately administering the parent oligomeric compound of the oligomeric compound of any
of embodiments 1461-1858 to a second mouse, wherein the therapeutic index of the oligomeric
compound of any of embodiments 1461-1858 is improved relative to the therapeutic index of the parent
oligomeric compound.

15 1953. The method of any of embodiments 1859-1952, wherein the level of p21 RNA is measured in the
mouse, the cell, and/or the human subject.

1954. A method comprising administering an oligomeric compound of any of embodiments 1461-1858 to a
20 subject and measuring the level of p21 RNA in the subject.

1955. The method of embodiment 1954, wherein the subject is a mouse.

1956. The method of embodiment 1954, wherein the subject is a human.

25 1957. The method of any of embodiments 1954-1956, wherein the p21 RNA level is measured within 24
hours of the administration.

1958. The method of any of embodiments 1954-1956, wherein the p21 RNA level is measured 24-48 hours
30 following the administration.

1959. An oligomeric compound or composition of any one of embodiments 1461-1858, for use in medical
therapy.

35 1960. The oligomeric compound of any of embodiments 1461-1858, wherein the oligomeric compound is
not toxic.

1961. The oligomeric compound of any of embodiment 1461-1858, wherein a comparator compound is toxic; wherein the comparator compound is identical to the oligomeric compound except that each nucleoside of the central region of the comparator compound is a nucleoside comprising 2'-β-D-deoxyribosyl sugar moiety.

1962. The oligomeric compound of embodiment 1961, wherein administering a dose of the oligomeric compound to an animal results in a circulating ALT level that is at least 3-fold lower than the ALT level that results from administering the same dose of the comparator compound to an animal for at least one matched dose.

1963. The oligomeric compound of embodiment 1961 or 1962, wherein the lowest dose of the oligomeric compound that raises circulating ALT to over 300 units per liter is at least three-fold higher than the lowest dose of the comparator compound that raises circulating ALT to over 300 units per liter.

1964. The oligomeric compound of any of embodiments 1961-1963, wherein the oligomeric compound is capable of reducing the target RNA in a cell.

1965. The oligomeric compound of embodiment 1964, wherein the oligomeric compound has RNA-reducing activity comparable to a comparator compound, wherein the comparator compound is identical to the oligomeric compound except that each nucleoside of the central region of the comparator compound is a nucleoside comprising 2'-β-D-deoxyribosyl sugar moiety.

1966. The oligomeric compound of embodiment 1965 having RNA-reducing activity that is no more than 2-fold worse than the RNA-reducing activity of the comparator compound.

1967. A method of modulating the amount or activity of a target RNA in a human subject comprising administering the oligomeric compound or composition of any of embodiments 1461-1858 to the human subject; and thereby modulating the amount or activity of the target RNA in the human subject.

1968. A method of treating a disease or disorder in a human subject comprising administering the oligomeric compound or composition of any of embodiments 1461-1858 to the human subject having the disease or disorder; and thereby treating the disease or disorder in the human subject.

1969. The method of embodiment 1967 or 1968, wherein the disease or disorder is a liver disease, and wherein the oligomeric compound modulates the amount or activity of a liver target RNA.

1970. The method of embodiment 1967 or 1968, wherein the disease or disorder is a central nervous system disease, and wherein the oligomeric compound modulates the amount or activity of a central nervous system target RNA.

1971. The method of any of embodiments 1967-1970, wherein the disease or disorder is a cancer, a neurodegenerative disease, a cardiovascular disease, an immunological disease, a hereditary disease, a repeat expansion disease, a muscle-wasting disease, or a metabolic disease.

1972. The method of any of embodiments 1967-1971, wherein the plasma ALT level of the human subject after the administration is not more than three times higher than it was prior to the administration.

1973. The method of any of embodiments 1967-1972, wherein the plasma ALT level of the human subject after the administration is not more than 150 units per liter.

1974. A method of treating a disease or disorder in a human subject comprising administering the oligomeric compound or composition of any of embodiments 1461-1858 to the human subject having the disease or disorder; and thereby treating the disease or disorder in the human subject.

1975. The method of embodiment 1974, wherein the disease or disorder is not a CNS disease or disorder.

1976. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the white fat cells.

1977. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the brown fat cells.

1978. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the adipocytes.

1979. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the macrophages.

1980. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the cancer cells.

1981. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the tumor cells.

5 1982. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the smooth muscle cells.

1983. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the lymphocytes.

10 1984. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the pulmonary cells.

1985. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the heart muscle cells.

1986. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the cardiomyocytes.

20 1987. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the endothelial cells.

1988. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the fibroblasts.

25 1989. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the glial cells.

1990. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the Schwann cells.

1991. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the pancreatic cells.

35 1992. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the kidney cells.

1993. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the beta cells.

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1994. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the non-parenchymal cells.

1995. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the hepatocytes.

1996. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the oligodendrocytes.

1997. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the astrocytes.

1998. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the microglia.

1999. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the ependymal cells.

2000. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the sensory neurons.

2001. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the motor neurons.

2002. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the skeletal muscle.

2003. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the cardiac muscle.

2004. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the smooth muscle.

2005. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the adipose tissue.

2006. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the white adipose tissue.

2007. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the spleen.
2008. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the bone.
- 5 2009. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the bone marrow.
2010. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the intestine.
- 10 2011. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the adrenal glands.
2012. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the testes.
- 15 2013. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the ovaries.
- 20 2014. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the pancreas.
2015. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the pituitary gland.
- 25 2016. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the prostate gland.
2017. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the skin.
2018. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the epidermis.
- 35 2019. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the uterus.

2020. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the bladder.

2021. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the brain.

2022. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the glomerulus.

2023. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the distal tubular epithelium.

2024. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the breast tissue.

2025. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the lung.

2026. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the heart.

2027. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the kidney.

2028. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the ganglion.

2029. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the frontal cortex.

2030. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the spinal cord.

2031. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the trigeminal ganglion.

2032. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the sciatic nerve.

2033. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the dorsal root ganglion.

2034. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the epidymal fat.

2035. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the diaphragm.

2036. The method of embodiment 1974, wherein the disease or disorder is a disease or disorder of the colon.

2037. A method of screening a library of oligomeric compounds for activity against a target RNA, wherein the library of oligomeric compounds comprises a plurality of oligomeric compounds of any of
 5 embodiments 1461-1858.

Certain Compounds

In certain embodiments, compounds described herein are oligomeric compounds comprising or consisting of oligonucleotides consisting of linked nucleosides. Oligonucleotides may be unmodified
 10 oligonucleotides or may be modified oligonucleotides. Modified oligonucleotides comprise at least one modification relative to an unmodified oligonucleotide (i.e., comprise at least one modified nucleoside (comprising a modified sugar moiety and/or a modified nucleobase) and/or at least one modified internucleoside linkage).

I. Modifications

A. Modified Nucleosides

Modified nucleosides comprise a modified sugar moiety, a modified nucleobase, or both a modified sugar moiety and a modified nucleobase.

1. Certain Modified Sugar Moieties

In certain embodiments, sugar moieties are non-bicyclic, modified furanosyl sugar moieties. In certain
 20 embodiments, modified sugar moieties are bicyclic or tricyclic furanosyl 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 furanosyl sugar moieties comprising one or more acyclic substituent, including but not limited to substituents at the 2', 3', 4', and/or 5'
 25 positions. In certain embodiments, the furanosyl sugar moiety is a ribosyl sugar moiety. In certain embodiments, the furanosyl sugar moiety is a β -D-ribofuranosyl sugar moiety. In certain embodiments one or more acyclic 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 ("2'-OMe" or "2'-O-methyl"), and 2'-O(CH₂)₂OCH₃ ("2'-MOE"). In certain embodiments, 2'-substituent groups
 30 are selected from among: halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, C₁-C₁₀ alkyl, 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-alkylenyl-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
 35 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 3'-substituent groups include 3'-methyl (see Frier, et al., The ups and downs of nucleic acid duplex stability: structure-stability studies on chemically-modified DNA:RNA duplexes. *Nucleic Acids Res.*, 25, 4429-4443, 1997.) 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'-allyl, 5'-ethyl, 5'-vinyl, and 5'-methoxy. In certain embodiments, non-bicyclic modified sugars 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. 2',4'-difluoro modified sugar moieties have been described in Martinez-Montero, et al., Rigid 2',4'-difluororibonucleosides: synthesis, conformational analysis, and incorporation into nascent RNA by HCV polymerase. *J. Org. Chem.*, 2014, 79:5627-5635. Modified sugar moieties comprising a 2'-modification (OMe or F) and a 4'-modification (OMe or F) have also been described in Malek-Adamian, et al., *J. Org. Chem.*, 2018, 83: 9839-9849.

In certain embodiments, a 2'-substituted nucleoside or non-bicyclic 2'-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 nucleoside or non-bicyclic 2'-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 nucleoside or non-bicyclic 2'-modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCH₃, and OCH₂CH₂OCH₃.

In certain embodiments, the 4' O of 2'-deoxyribose can be substituted with a S to generate 4'-thio DNA (see Takahashi, et al., *Nucleic Acids Research* 2009, 37: 1353-1362). This modification can be combined with other modifications detailed herein. In certain such embodiments, the sugar moiety is further modified at the 2' position. In certain embodiments the sugar moiety comprises a 2'-fluoro. A thymidine with this sugar moiety has been described in Watts, et al., *J. Org. Chem.* 2006, 71(3): 921-925 (4'-S-fluoro5-methylarauridine or FAMU).

Certain modified sugar moieties comprise a bridging sugar substituent that forms a second ring resulting in a bicyclic sugar moiety. 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 sugar moieties comprising such 4' to 2' bridging sugar substituents include but are not limited to bicyclic sugars comprising: 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), 4'-C(=O)-N(CH₃)₂-2', 4'-C(=O)-N(R)₂-2', 4'-C(=S)-N(R)₂-2' and analogs thereof (see, e.g., Obika et al., WO2011052436A1, Yusuke, WO2017018360A1).

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;

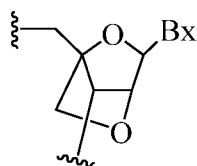
each R_a and R_b is, independently, H, a protecting group, hydroxyl, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₅-C₂₀ aryl, substituted C₅-C₂₀ aryl, heterocycle radical, substituted heterocycle radical, heteroaryl,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

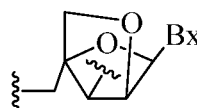
Additional bicyclic sugar moieties are known in the art, see, for example: Freier *et al.*, *Nucleic Acids Research*, 1997, 25(22), 4429-4443, Albaek *et al.*, *J. Org. Chem.*, 2006, 71, 7731-7740, Singh *et al.*, *Chem. Commun.*, 1998, 4, 455-456; Koshkin *et al.*, *Tetrahedron*, 1998, 54, 3607-3630; 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., 2017, 129, 8362-8379; Elayadi *et al.*; Christiansen, *et al.*, *J. Am. Chem. Soc.* 1998, 120, 5458-5463; 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; and U.S. Patent Publication Nos. 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'



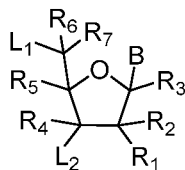
α -L-LNA (α -L-configuration)
bridge = 4'-CH₂-O-2'

α -L-methyleneoxy (4'-CH₂-O-2') or α -L-LNA bicyclic nucleosides have been incorporated into antisense 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) 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).

Nucleosides comprising modified furanosyl sugar moieties and modified furanosyl sugar moieties may be referred to by the position(s) of the substitution(s) on the sugar moiety of the nucleoside. The term "modified" following a position of the furanosyl ring, such as "2'-modified", indicates that the sugar moiety comprises the indicated modification at the 2' position and may comprise additional modifications and/or substituents. A 4'-2' bridged sugar moiety is 2'-modified and 4'-modified, or, alternatively, "2', 4'-modified". The term "substituted" following a position of the furanosyl ring, such as "2'-substituted" or "2'-4'-substituted", indicates that is the only position(s) having a substituent other than those found in unmodified sugar moieties in oligonucleotides. Accordingly, the following sugar moieties are represented by the following formulas.

In the context of a nucleoside and/or an oligonucleotide, a non-bicyclic, modified furanosyl sugar moiety is represented by formula I:

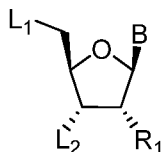


I

wherein B is a nucleobase; and L_1 and L_2 are each, independently, an internucleoside linkage, a terminal group, a conjugate group, or a hydroxyl group. Among the R groups, at least one of R_{3-7} is not H and/or at least one of R_1 and R_2 is not H or OH. In a 2'-modified furanosyl sugar moiety, at least one of R_1 and R_2 is not H or OH and each of R_{3-7} is independently selected from H or a substituent other than H. In a 4'-modified furanosyl sugar moiety, R_5 is not H and each of $R_{1-4, 6, 7}$ are independently selected from H and a substituent other than H; and so on for each position of the furanosyl ring. The stereochemistry is not defined unless otherwise noted.

In the context of a nucleoside and/or an oligonucleotide, a non-bicyclic, modified, substituted furanosyl sugar moiety is represented by formula I, wherein B is a nucleobase; and L_1 and L_2 are each, independently, an internucleoside linkage, a terminal group, a conjugate group, or a hydroxyl group. Among the R groups, *either* one (and no more than one) of R_{3-7} is a substituent other than H *or* one of R_1 or R_2 is a substituent other than H or OH. The stereochemistry is not defined unless otherwise noted. Examples of non-bicyclic, modified, substituted furanosyl sugar moieties include 2'-substituted ribosyl, 4'-substituted ribosyl, and 5'-substituted ribosyl sugar moieties, as well as substituted 2'-deoxyfuranosyl sugar moieties, such as 4'-substituted 2'-deoxyribosyl and 5'-substituted 2'-deoxyribosyl sugar moieties.

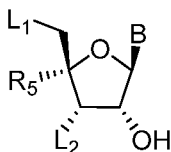
In the context of a nucleoside and/or an oligonucleotide, a 2'-substituted ribosyl sugar moiety is represented by formula II:



II

wherein B is a nucleobase; and L_1 and L_2 are each, independently, an internucleoside linkage, a terminal group, a conjugate group, or a hydroxyl group. R_1 is a substituent other than H or OH. The stereochemistry is defined as shown.

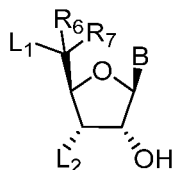
In the context of a nucleoside and/or an oligonucleotide, a 4'-substituted ribosyl sugar moiety is represented by formula III:



III

wherein B is a nucleobase; and L₁ and L₂ are each, independently, an internucleoside linkage, a terminal group, a conjugate group, or a hydroxyl group. R₅ is a substituent other than H. The stereochemistry is defined as shown.

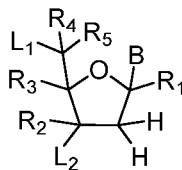
In the context of a nucleoside and/or an oligonucleotide, a 5'-substituted ribosyl sugar moiety is represented by formula IV:



IV

wherein B is a nucleobase; and L₁ and L₂ are each, independently, an internucleoside linkage, a terminal group, a conjugate group, or a hydroxyl group. R₆ or R₇ is a substituent other than H. The stereochemistry is defined as shown.

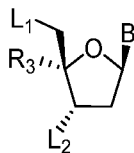
In the context of a nucleoside and/or an oligonucleotide, a 2'-deoxyfuranosyl sugar moiety is represented by formula V:



V

wherein B is a nucleobase; and L₁ and L₂ are each, independently, an internucleoside linkage, a terminal group, a conjugate group, or a hydroxyl group. Each of R₁₋₅ are independently selected from H and a non-H substituent. If all of R₁₋₅ are each H, the sugar moiety is an unsubstituted 2'-deoxyfuranosyl sugar moiety. The stereochemistry is not defined unless otherwise noted.

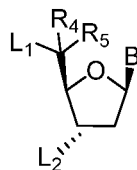
In the context of a nucleoside and/or an oligonucleotide, a 4'-substituted 2'-deoxyribosyl sugar moiety is represented by formula VI:



VI

wherein B is a nucleobase; and L₁ and L₂ are each, independently, an internucleoside linkage, a terminal group, a conjugate group, or a hydroxyl group. R₃ is a substituent other than H. The stereochemistry is defined as shown.

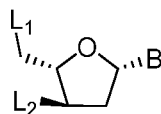
In the context of a nucleoside and/or an oligonucleotide, a 5'-substituted 2'-deoxyribosyl sugar moiety is represented by formula VII:



VII

wherein B is a nucleobase; and L₁ and L₂ are each, independently, an internucleoside linkage, a terminal group, a conjugate group, or a hydroxyl group. R₄ or R₅ is a substituent other than H. The stereochemistry is defined as shown.

Unsubstituted 2'-deoxyfuranosyl sugar moieties may be unmodified (β-D-2'-deoxyribose) or modified. Examples of modified, unsubstituted 2'-deoxyfuranosyl sugar moieties include β-L-2'-deoxyribose, α-L-2'-deoxyribose, α-D-2'-deoxyribose, and β-D-xylose sugar moieties. For example, in the context of a nucleoside and/or an oligonucleotide, a β-L-2'-deoxyribose sugar moiety is represented by formula VIII:



VIII

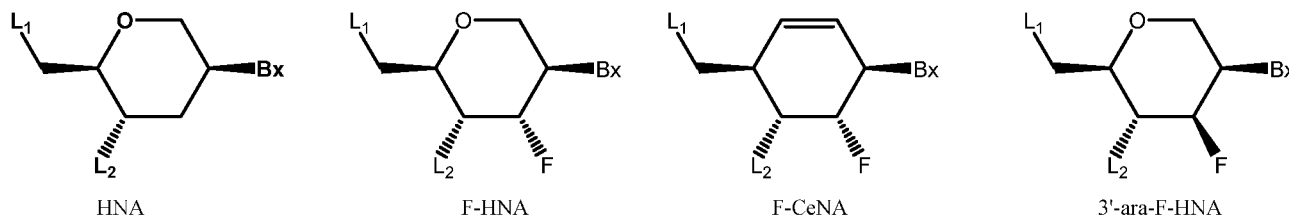
wherein B is a nucleobase; and L₁ and L₂ are each, independently, an internucleoside linkage, a terminal group, a conjugate group, or a hydroxyl group. The stereochemistry is defined as shown. Synthesis of α-L-ribose nucleotides and β-D-xylose nucleotides has been described by Gaubert, et al., *Tetrahedron* 2006, 62: 2278-2294. Additional isomers of DNA and RNA nucleosides are described by Vester, et. al., "Chemically modified oligonucleotides with efficient RNase H response," *Bioorg. Med. Chem. Letters*, 2008, 18: 2296-2300.

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"), altritol nucleic acid ("ANA"), mannitol nucleic acid ("MNA") (see, e.g., Leumann, *CJ. Bioorg. & Med. Chem.* 2002, 10, 841-854), fluoro HNA

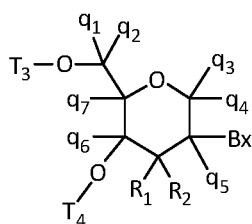
("F-HNA", *see e.g.* Swayze et al., U.S. 8,088,904; Swayze et al., U.S. 8,440,803; Swayze et al., U.S. 8,796,437; and Swayze et al., U.S. 9,005,906; F-HNA can also be referred to as a F-THP or 3'-fluoro tetrahydropyran), F-CeNA, and 3'-ara-HNA, having the formulas below, where L_1 and L_2 are each,

5 independently, an internucleoside linkage linking the modified THP nucleoside to the remainder of an oligonucleotide or one of L_1 and L_2 is an internucleoside linkage linking the modified THP nucleoside to the remainder of an oligonucleotide and the other of L_1 and L_2 is H, a hydroxyl protecting group, a linked conjugate group, or a 5' or 3'-terminal group.



Additional sugar surrogates comprise THP compounds having the formula:

10



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

Bx is a nucleobase moiety;

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

15

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

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

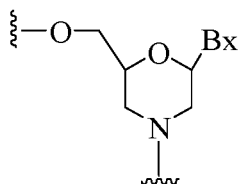
20

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

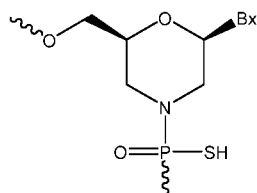
25

In certain embodiments, sugar surrogates comprise rings having no heteroatoms. For example, nucleosides comprising bicyclo [3.1.0]-hexane have been described (see, e.g., Marquez, et al., *J. Med. Chem.* 1996, 39:3739-3749).

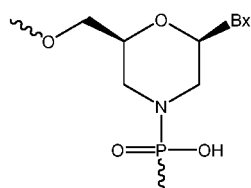
In certain embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example, nucleosides comprising morpholino sugar moieties and their use in oligonucleotides have been reported (see, e.g., Braasch et al., *Biochemistry*, 2002, 41, 4503-4510 and Summerton 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 comprising 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, morpholino residues replace a full nucleotide, including the internucleoside linkage, and have the structures shown below, wherein Bx is a heterocyclic base moiety.



morpholino PS



morpholino PO

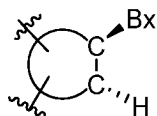
In certain embodiments, sugar surrogates comprise acyclic moieties. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include but are not limited to: peptide nucleic acid (“PNA”), acyclic butyl nucleic acid (see, e.g., Kumar et al., *Org. Biomol. Chem.*, 2013, 11, 5853-5865), glycol nucleic acid (“GNA”, see Schlegel, et al., *J. Am. Chem. Soc.* 2017, 139:8537-8546) 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. Certain such ring systems are described in Hanessian, et al., *J. Org. Chem.*, 2013, 78: 9051-9063 and include bcDNA and tcDNA. Modifications to bcDNA and tcDNA, such as 6'-fluoro, have also been described (Dogovic and Leumann, *J. Org. Chem.*, 2014, 79: 1271-1279).

In certain embodiments, modified nucleosides are DNA mimics. “DNA mimic” means a nucleoside other than a DNA nucleoside wherein the nucleobase is directly linked to a carbon atom of a ring bound to a second carbon atom within the ring, wherein the second carbon atom comprises a bond to at least one

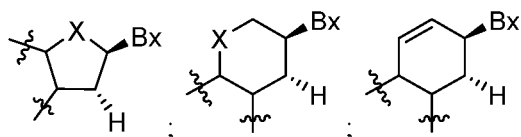
hydrogen atom, wherein the nucleobase and at least one hydrogen atom are trans to one another relative to the bond between the two carbon atoms.

In certain embodiments, a DNA mimic comprises a structure represented by the formula below:



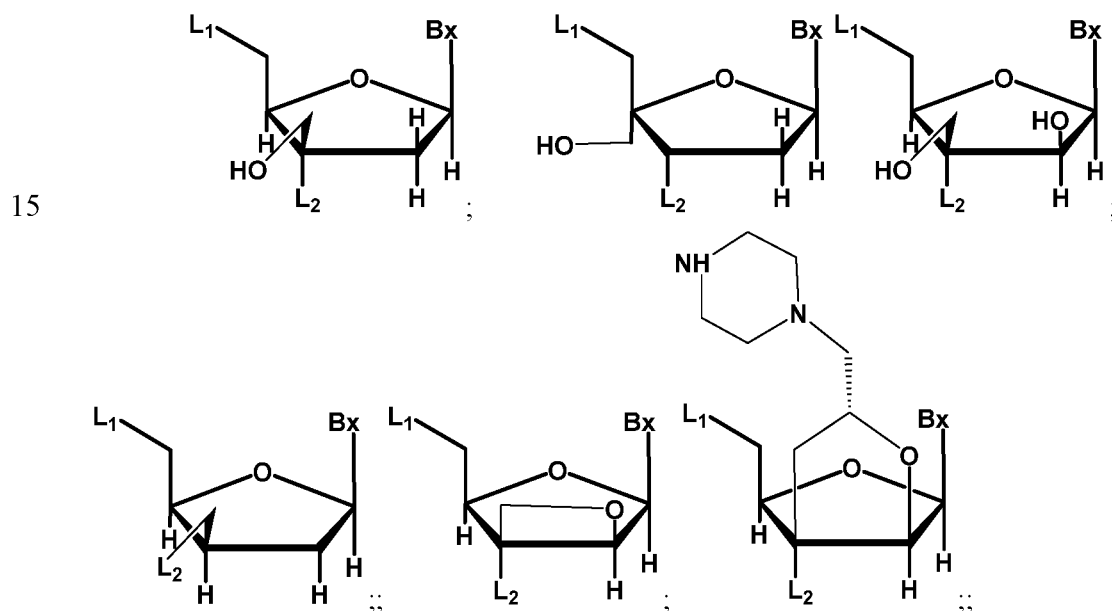
5 Wherein Bx represents a heterocyclic base moiety.

In certain embodiments, a DNA mimic comprises a structure represented by one of the formulas below:



wherein X is O or S and Bx represents a heterocyclic base moiety.

10 In certain embodiments, a DNA mimic is a sugar surrogate. In certain embodiments, a DNA mimic is a cyclohexenyl or hexitol nucleic acid. In certain embodiments, a DNA mimic is described in Figure 1 of Vester, et. al., "Chemically modified oligonucleotides with efficient RNase H response," *Bioorg. Med. Chem. Letters*, 2008, 18: 2296-2300, incorporated by reference herein. In certain embodiments, a DNA mimic nucleoside has a formula selected from:



wherein Bx is a heterocyclic base moiety, and L₁ and L₂ are each, independently, an internucleoside linkage linking the modified THP nucleoside to the remainder of an oligonucleotide or one of L₁ and L₂ is an
 20 internucleoside linkage linking the modified nucleoside to the remainder of an oligonucleotide and the other

of L₁ and L₂ is H, a hydroxyl protecting group, a linked conjugate group, or a 5' or 3'-terminal group. In certain embodiments, a DNA mimic is α,β -constrained nucleic acid (CAN), 2',4'-carbocyclic-LNA, or 2',4'-carbocyclic-ENA. In certain embodiments, a DNA mimic has a sugar moiety selected from among: 4'-C-hydroxymethyl-2'-deoxyribosyl, 3'-C-hydroxymethyl-2'-deoxyribosyl, 3'-C-hydroxymethyl-arabinosyl, 3'-C-2'-O-arabinosyl, 3'-C-methylene-extended-xylosyl, 3'-C-2'-O-piperazino-arabinosyl. In certain
 5 embodiments, a DNA mimic has a sugar moiety selected from among: 2'-methylribosyl, 2'-S-methylribosyl, 2'-aminoribosyl, 2'-NH(CH₂)-ribosyl, 2'-NH(CH₂)₂-ribosyl, 2'-CH₂-F-ribosyl, 2'-CHF₂-ribosyl, 2'-CF₃-ribosyl, 2'=CF₂ ribosyl, 2'-ethylribosyl, 2'-alkenylribosyl, 2'-alkynylribosyl, 2'-O-4'-C-methyleneribosyl, 2'-cyanoarabinosyl, 2'-chloroarabinosyl, 2'-fluoroarabinosyl, 2'-bromoarabinosyl, 2'-azidoarabinosyl, 2'-methoxyarabinosyl, and 2'-arabinosyl. In certain embodiments, a DNA mimic has a sugar moiety selected
 10 from 4'-methyl-modified deoxyfuranosyl, 4'-F-deoxyfuranosyl, 4'-OMe-deoxyfuranosyl. In certain embodiments, a DNA mimic has a sugar moiety selected from among: 5'-methyl-2'- β -D-deoxyribosyl, 5'-ethyl-2'- β -D-deoxyribosyl, 5'-allyl-2'- β -D-deoxyribosyl, 2'-fluoro- β -D-arabinofuranosyl. In certain embodiments, DNA mimics are listed on page 32-33 of PCT/US00/267929 as B-form nucleotides,
 15 incorporated by reference herein in its entirety.

2. Modified Nucleobases

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
 20 substituted purines. In certain embodiments, modified nucleobases are selected from: 2-aminopropyladenine, 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (-C $\equiv$ C-CH₃) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo,
 25 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 bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as
 30 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one and 9-(2-aminoethoxy)-1,3-diazaphenoxazine-2-one (G-clamp). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in Merigan et al., U.S. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, Kroschwitz, J.I., Ed., John Wiley & Sons,
 35 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. In certain embodiments, modified nucleosides comprise double-headed nucleosides having two nucleobases. Such compounds are described in detail in Sorinaset al., *J. Org. Chem*, 2014 79: 8020-8030.

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

In certain embodiments, compounds comprise or consist of a modified oligonucleotide complementary to an target nucleic acid comprising one or more modified nucleobases. In certain embodiments, the modified nucleobase is 5-methylcytosine. In certain embodiments, each cytosine is a 5-methylcytosine.

B. Modified Internucleoside Linkages

In certain embodiments, compounds described herein having one or more modified internucleoside linkages are selected over compounds having only phosphodiester internucleoside linkages because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for target nucleic acids, and increased stability in the presence of nucleases.

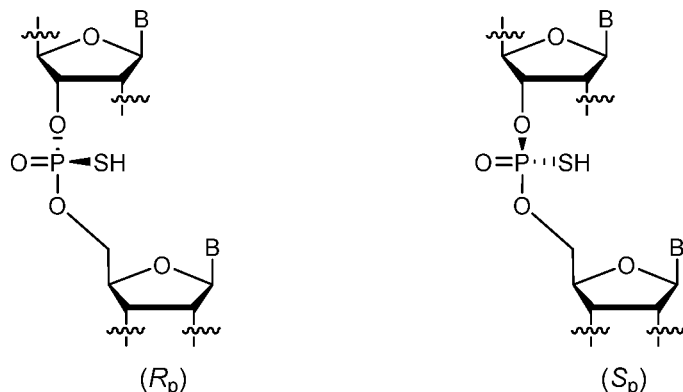
In certain embodiments, compounds comprise or consist of a modified oligonucleotide complementary to a target nucleic acid comprising one or more modified internucleoside linkages. In certain embodiments, the modified internucleoside linkages are phosphorothioate linkages. In certain embodiments, each internucleoside linkage of an antisense compound is a phosphorothioate internucleoside linkage.

In certain embodiments, nucleosides of modified oligonucleotides may be linked together using any internucleoside linkage. The two main classes of internucleoside linkages are defined by the presence or absence of a phosphorus atom. Representative phosphorus-containing internucleoside linkages include unmodified phosphodiester internucleoside linkages, modified phosphotriesters such as THP phosphotriester and isopropyl phosphotriester, phosphonates such as methylphosphonate, isopropyl phosphonate, isobutyl

phosphonate, and phosphonoacetate, phosphoramidates, phosphorothioate, and phosphorodithioate ("HS-P=S"). Representative non-phosphorus containing internucleoside linkages include but are not limited to methylenemethylimino (-CH₂-N(CH₃)-O-CH₂-), thiodiester, thionocarbamate (-O-C(=O)(NH)-S-); siloxane (-O-SiH₂-O-); formacetal, thioacetamido (TANA), alt-thioformacetal, glycine amide, and N,N'-dimethylhydrazine (-CH₂-N(CH₃)-N(CH₃)-). Modified internucleoside linkages, compared to naturally occurring phosphate linkages, can be used to alter, typically increase, nuclease resistance of the oligonucleotide. Methods of preparation of phosphorous-containing and non-phosphorous-containing internucleoside linkages are well known to those skilled in the art.

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

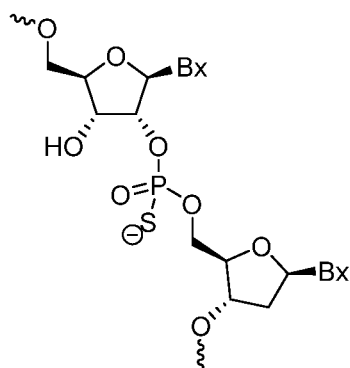
phosphorothioates comprise one or more of the following formulas, respectively, wherein "B" indicates a nucleobase:



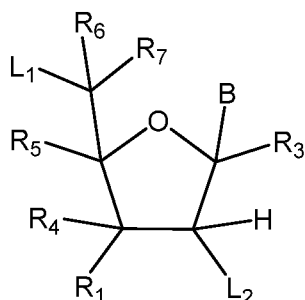
Unless otherwise indicated, chiral internucleoside linkages of modified oligonucleotides described herein can be stereorandom or in a particular stereochemical configuration.

Neutral internucleoside linkages include, without limitation, phosphotriesters, phosphonates, 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, 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.

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



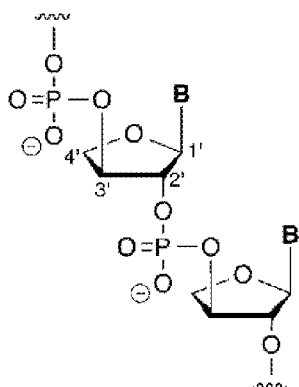
In the context of a nucleoside and/or an oligonucleotide, a non-bicyclic, 2'-linked modified furanosyl sugar moiety is represented by formula IX:



IX

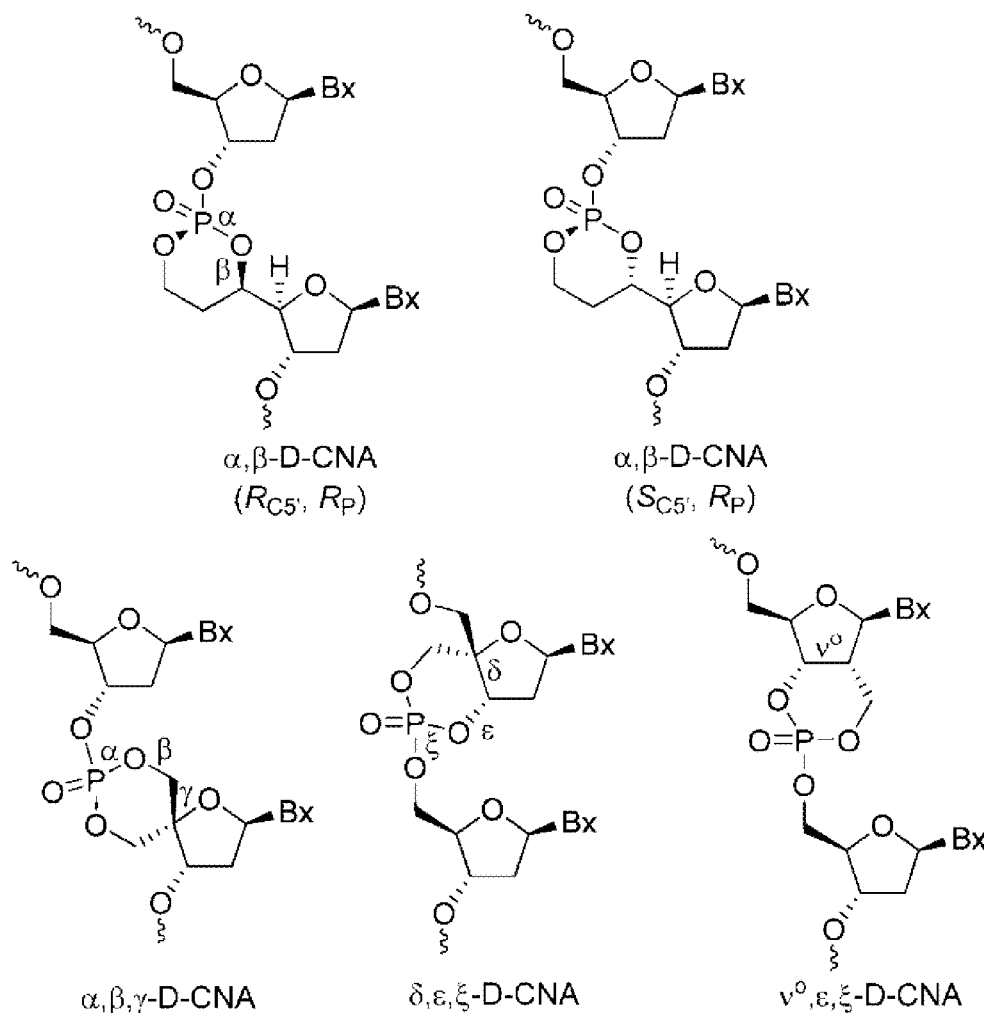
wherein B is a nucleobase; L₁ is an internucleoside linkage, a terminal group, a conjugate group, or a hydroxyl group and L₂ is an internucleoside linkage. The stereochemistry is not defined unless otherwise noted.

In certain embodiments, nucleosides can be linked by vicinal 2', 3'-phosphodiester bonds. In certain such embodiments, the nucleosides are threofuranosyl nucleosides (TNA; see Bala, et al., *J Org. Chem.* 2017, 82:5910-5916). A TNA linkage is shown below.



**threose nucleic acid
(TNA)**

Additional modified linkages include α,β -D-CNA type linkages and related conformationally-constrained linkages, shown below. Synthesis of such molecules has been described previously (see Dupouy, et al., *Angew. Chem. Int. Ed. Engl.*, 2014, 45: 3623-3627; Borsting, et al. *Tetrahedron*, 2004, 60:10955-10966; Ostergaard, et al., *ACS Chem. Biol.* 2014, 9: 1975-1979; Dupouy, et al., *Eur. J. Org. Chem.*, 2008, 1285-1294; Martinez, et al., *PLoS One*, 2011, 6:e25510; Dupouy, et al., *Eur. J. Org. Chem.*, 2007, 5256-5264; Boissonnet, et al., *New J. Chem.*, 2011, 35: 1528-1533.)



II. Certain Motifs

In certain embodiments, oligomeric compounds described herein comprise or consist of oligonucleotides. Oligonucleotides can have a motif, *e.g.* a pattern of unmodified and/or modified sugar moieties, nucleobases, and/or internucleoside linkages. In certain embodiments, modified oligonucleotides comprise one or more modified nucleoside comprising a modified sugar. 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 or motifs 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).

A. Certain Sugar Motifs

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

In certain embodiments, a modified oligonucleotide comprises or consists of a gapmer. The sugar motif of a gapmer defines the regions of the gapmer: 5'-region, central region, and 3'-region. The positions of
 10 the nucleosides within each region are counted beginning at the 5'-end of each region. Each region of a gapmer is connected by an internucleoside linkage, as are the nucleosides within each region. Each nucleoside of the 5'-region and each nucleoside of the 3'-region comprise a 2'-modified furanosyl sugar moiety. The nucleoside at the first position (position 1) of the central region and the nucleoside at the last position of the central region are adjacent to the 5'-region and 3'-region, respectively, and each comprise a
 15 sugar moiety independently selected from a 2'-deoxyfuranosyl sugar moiety or a sugar surrogate. Unlike the nucleosides at the first and last positions of the central region, the nucleosides at the other positions within the central region may comprise a 2'-modified furanosyl sugar moiety. In certain embodiments, the 2'-modified furanosyl sugar moiety in the 5' and 3'-regions is a 4'-2'-bicyclic sugar moiety. In certain embodiments, the 2'-modified furanosyl sugar moiety in the 5' and 3' regions is a cEt. In certain embodiments, the 2'-modified
 20 furanosyl sugar moiety is a 2'-MOE furanosyl sugar moiety. In certain embodiments, each nucleoside within the gap supports RNase H cleavage. In certain embodiments, a plurality of nucleosides within the gap support RNase H cleavage. In certain embodiments, the nucleoside at the first and last positions of the central region adjacent to the 5' and 3' regions are DNA nucleosides.

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

In certain embodiments, modified oligonucleotides are 5-10-5 MOE gapmers. In certain
 35 embodiments, modified oligonucleotides are 3-10-3 BNA gapmers. In certain embodiments, modified

oligonucleotides are 3-10-3 cEt gapmers. In certain embodiments, modified oligonucleotides are 3-10-3 LNA gapmers.

The sugar motif of a 3-10-3 cEt gapmer may also be denoted by the notation kkk-d(10)-kkk, wherein each “k” represents a cEt and each “d” represents a 2’-β-D-deoxyribosyl sugar moiety. This sugar motif is independent of the nucleobase sequence, the internucleoside linkage motif, and any nucleobase modifications. A 5-10-5 MOE gapmer may be denoted by the notation eeeee-d(10)-eeee or e(5)-d(10)-e(5), wherein each “e” represents a 2’-MOE-β-D-ribofuranosyl sugar moiety, and each “d” represents a 2’-β-D-deoxyribosyl sugar moiety.

B. Certain Nucleobase Motifs

In certain embodiments, oligomeric compounds described herein comprise or consist of oligonucleotides. In certain embodiments, oligonucleotides comprise modified and/or unmodified nucleobases arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each nucleobase is modified. In certain embodiments, none of the nucleobases are modified. In certain embodiments, each purine or each pyrimidine is modified. In certain embodiments, each adenine is modified. In certain embodiments, each guanine is modified. In certain embodiments, each thymine is modified. In certain embodiments, each uracil is modified. In certain embodiments, each cytosine is modified. In certain embodiments, some or all of the cytosine nucleobases in a modified oligonucleotide are 5-methylcytosines.

In certain embodiments, 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, one nucleoside comprising a modified nucleobase is in the central region of a modified oligonucleotide. In certain such embodiments, the sugar moiety of said nucleoside is a 2’-β-D-deoxyribosyl moiety. In certain such embodiments, the modified nucleobase is selected from: 5-methyl cytosine, 2-thiopyrimidine, 2-thiothymine, 6-methyladenine, inosine, pseudouracil, or 5-propynepyrimidine.

C. Certain Internucleoside Linkage Motifs

In certain embodiments, oligomeric compounds described herein comprise or consist of oligonucleotides. In certain embodiments, oligonucleotides comprise modified and/or unmodified internucleoside linkages arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each internucleoside linkage is a phosphodiester internucleoside linkage (P=O). In certain embodiments, each internucleoside linkage 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 internucleoside linkages within the central region of a modified oligonucleotide are all modified. In certain such embodiments, some or all of the internucleoside linkages in the 5'-region and 3'-region are unmodified phosphate linkages. In certain embodiments, the terminal internucleoside linkages are modified. In certain embodiments, the internucleoside linkage motif comprises at least one phosphodiester internucleoside linkage in at least one of the 5'-region and the 3'-region, wherein the at least one phosphodiester linkage is not a terminal internucleoside linkage, and the remaining internucleoside linkages are phosphorothioate internucleoside linkages. In certain such embodiments, all of the phosphorothioate linkages are stereorandom. In certain embodiments, all of the phosphorothioate linkages in the 5'-region and 3'-region are (*Sp*) phosphorothioates, and the central region 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, oligonucleotides comprise a region having an alternating internucleoside linkage motif. In certain embodiments, oligonucleotides comprise a region of uniformly modified internucleoside linkages. In certain such embodiments, the internucleoside linkages are phosphorothioate internucleoside linkages. In certain embodiments, all of the internucleoside linkages of the oligonucleotide are phosphorothioate internucleoside linkages. In certain embodiments, each internucleoside linkage of the oligonucleotide is selected from phosphodiester or phosphate and phosphorothioate. In certain embodiments, each internucleoside linkage of the oligonucleotide is selected from phosphodiester or phosphate and phosphorothioate and at least one internucleoside linkage is phosphorothioate.

In certain embodiments, the oligonucleotide comprises at least 6 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 8 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 10 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 6 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 8 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 10 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least one 12 consecutive phosphorothioate internucleoside linkages. In certain such embodiments, at least one such block is located at the 3' end of the oligonucleotide. In certain such embodiments, at least one such block is located within 3 nucleosides of the 3' end of the oligonucleotide.

In certain embodiments, oligonucleotides comprise one or more methylphosphonate linkages. In certain embodiments, modified oligonucleotides comprise a linkage motif comprising all phosphorothioate

linkages except for one or two methylphosphonate linkages. In certain embodiments, one methylphosphonate linkage is in the central region of an oligonucleotide.

In certain embodiments, it is desirable to arrange the number of phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages to maintain nuclease resistance. In certain
5 embodiments, it is desirable to arrange the number and position of phosphorothioate internucleoside linkages and the number and position of phosphodiester internucleoside linkages to maintain nuclease resistance. In certain embodiments, the number of phosphorothioate internucleoside linkages may be decreased and the number of phosphodiester internucleoside linkages may be increased. In certain embodiments, the number of phosphorothioate internucleoside linkages may be decreased and the number of phosphodiester
10 internucleoside linkages may be increased while still maintaining nuclease resistance. In certain embodiments it is desirable to decrease the number of phosphorothioate internucleoside linkages while retaining nuclease resistance. In certain embodiments it is desirable to increase the number of phosphodiester internucleoside linkages while retaining nuclease resistance.

III. Certain Modified Oligonucleotides

15 In certain embodiments, oligomeric compounds described herein comprise or consist of 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 modifications, motifs, and overall lengths. In certain embodiments, such parameters are each independent of one another. Thus, unless otherwise indicated, each internucleoside linkage of a
20 modified oligonucleotide may be modified or unmodified and may or may not follow the modification pattern of the sugar moieties. Likewise, such modified oligonucleotides may comprise one or more modified nucleobase independent of the pattern of the sugar modifications. Furthermore, in certain instances, a modified oligonucleotide is described by an overall length or range and by lengths or length ranges of two or more regions (*e.g.*, a region of nucleosides having specified sugar modifications), in such circumstances it
25 may be possible to select numbers for each range that result in an oligonucleotide having an overall length falling outside the specified range. In such circumstances, both elements must be satisfied. For example, in certain embodiments, a modified oligonucleotide consists of 15-20 linked nucleosides and has a sugar motif consisting of three regions or segments, A, B, and C, wherein region or segment A consists of 2-6 linked nucleosides having a specified sugar moiety, region or segment B consists of 6-10 linked nucleosides having
30 a specified sugar moiety, and region or segment C consists of 2-6 linked nucleosides having a specified sugar moiety. Such embodiments do not include modified oligonucleotides where A and C each consist of 6 linked nucleosides and B consists of 10 linked nucleosides (even though those numbers of nucleosides are permitted within the requirements for A, B, and C) because the overall length of such oligonucleotide is 22, which exceeds the upper limit of 20 for the overall length of the modified oligonucleotide. Unless otherwise
35 indicated, all modifications are independent of nucleobase sequence except that the modified nucleobase 5-

methylecytosine is necessarily a “C” in an oligonucleotide sequence. In certain embodiments, when a DNA nucleoside or DNA-like nucleoside that comprises a T in a DNA sequence is replaced with a RNA-like nucleoside, including a nucleoside comprising a 2'-OMe modified sugar moiety, the nucleobase T is replaced with the nucleobase U. Each of these compounds has an identical target RNA.

5 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
 10 12 to 13, 12 to 14, 12 to 15, 12 to 16, 12 to 17, 12 to 18, 12 to 19, 12 to 20, 12 to 21, 12 to 22, 12 to 23, 12 to 24, 12 to 25, 12 to 26, 12 to 27, 12 to 28, 12 to 29, 12 to 30, 13 to 14, 13 to 15, 13 to 16, 13 to 17, 13 to 18, 13 to 19, 13 to 20, 13 to 21, 13 to 22, 13 to 23, 13 to 24, 13 to 25, 13 to 26, 13 to 27, 13 to 28, 13 to 29, 13 to 30, 14 to 15, 14 to 16, 14 to 17, 14 to 18, 14 to 19, 14 to 20, 14 to 21, 14 to 22, 14 to 23, 14 to 24, 14 to 25, 14 to 26, 14 to 27, 14 to 28, 14 to 29, 14 to 30, 15 to 16, 15 to 17, 15 to 18, 15 to 19, 15 to 20, 15 to 21, 15 to 22, 15 to 23, 15 to 24, 15 to 25, 15 to 26, 15 to 27, 15 to 28, 15 to 29, 15 to 30, 16 to 17, 16 to 18, 16 to 19, 16 to 20, 16 to 21, 16 to 22, 16 to 23, 16 to 24, 16 to 25, 16 to 26, 16 to 27, 16 to 28, 16 to 29, 16 to 30, 17 to 18, 17 to 19, 17 to 20, 17 to 21, 17 to 22, 17 to 23, 17 to 24, 17 to 25, 17 to 26, 17 to 27, 17 to 28, 17 to 29, 17 to 30, 18 to 19, 18 to 20, 18 to 21, 18 to 22, 18 to 23, 18 to 24, 18 to 25, 18 to 26, 18 to 27, 18 to 28, 18 to 29, 18 to 30, 19 to 20, 19 to 21, 19 to 22, 19 to 23, 19 to 24, 19 to 25, 19 to 26, 19 to 27, 19 to 28, 19 to 29, 19 to 30, 20 to 21, 20 to 22, 20 to 23, 20 to 24, 20 to 25, 20 to 26, 20 to 27, 20 to 28, 20 to 29, 20 to 30, 21 to 22, 21 to 23, 21 to 24, 21 to 25, 21 to 26, 21 to 27, 21 to 28, 21 to 29, 21 to 30, 22 to 23, 22 to 24, 22 to 25, 22 to 26, 22 to 27, 22 to 28, 22 to 29, 22 to 30, 23 to 24, 23 to 25, 23 to 26, 23 to 27, 23 to 28, 23 to 29, 23 to 30, 24 to 25, 24 to 26, 24 to 27, 24 to 28, 24 to 29, 24 to 30, 25 to 26, 25 to 27, 25 to 28, 25 to 29, 25 to 30, 26 to 27, 26 to 28, 26 to 29, 26 to 30, 27 to 28, 27 to 29, 27 to 30, 28 to 29, 28 to 30, or 29 to 30 linked
 25 nucleosides.

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 embodiments, a region of an oligonucleotide has a nucleobase sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain embodiments,
 30 the nucleobase sequence of a region or entire length of an oligonucleotide is at least 70%, at least 80%, at least 90%, at least 95%, or 100% complementary to the second oligonucleotide or nucleic acid, such as a target nucleic acid.

IV. Certain Conjugated Compounds

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

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

A. Certain Conjugate Groups

In certain embodiments, oligonucleotides are covalently attached to one or more conjugate groups. In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge and clearance. In certain embodiments, 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, a palmityl moiety (Mishra et al., *Biochim. Biophys. Acta*, 1995, 1264, 229-237), an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., *J. Pharmacol. Exp. Ther.*, 1996, i, 923-937), a tocopherol group (Nishina et al., *Molecular Therapy Nucleic Acids*, 2015, 4, e220; doi:10.1038/mtna.2014.72 and Nishina et al., *Molecular Therapy*, 2008, 16, 734-740), or a GalNAc cluster (*e.g.*, WO2014/179620).

1. *Conjugate Moieties*

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

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

2. *Conjugate linkers*

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

In certain embodiments, a conjugate linker comprises 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 oligomeric 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 an oligomeric compound and the other is selected to bind to a conjugate group. Examples of functional groups used in a bifunctional linking moiety include but are not limited to electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In certain embodiments, bifunctional linking moieties comprise one or more groups selected from amino, hydroxyl, carboxylic acid, thiol, alkyl, alkenyl, and alkynyl.

Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic

acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) and 6-aminohexanoic acid (AHEX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted 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, such linker-nucleosides are modified nucleosides. In certain embodiments such linker-nucleosides comprise a modified sugar moiety. In certain embodiments, linker-nucleosides are unmodified. In certain embodiments, linker-nucleosides comprise an optionally protected heterocyclic base selected from a purine, substituted purine, pyrimidine or substituted pyrimidine. In certain embodiments, a cleavable moiety is a nucleoside selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methylcytosine, 4-N-benzoyl-5-methylcytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. It is typically desirable for linker-nucleosides to be cleaved from the oligomeric compound after it reaches a target tissue.

Accordingly, linker-nucleosides are typically linked to one another and to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are phosphodiester bonds.

Herein, linker-nucleosides are not considered to be part of the oligonucleotide. Accordingly, in embodiments in which an oligomeric compound comprises an oligonucleotide consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid and the oligomeric compound also comprises a conjugate group comprising a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid. For example, an oligomeric compound may comprise (1) a modified oligonucleotide consisting of 8-30 nucleosides and (2) a conjugate group comprising 1-10 linker-nucleosides that are contiguous with the nucleosides of the modified oligonucleotide. The total number of contiguous linked nucleosides in such a 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 a 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 compound has been taken up, it is desirable that the conjugate group be cleaved to release the unconjugated oligonucleotide. Thus, certain conjugate may

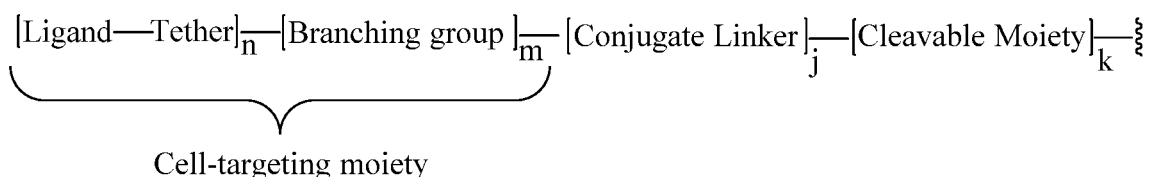
comprise one or more cleavable moieties, typically within the conjugate linker. In certain embodiments, a cleavable moiety is a cleavable bond. In certain embodiments, a cleavable moiety is a group of atoms comprising at least one cleavable bond. In certain embodiments, a cleavable moiety comprises a 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, 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 a nucleoside comprising a 2'-deoxyfuranosyl 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 phosphodiester or phosphorothioate linkage. In certain such embodiments, the cleavable moiety is a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety. In certain such embodiments, the cleavable moiety is 2'-deoxyadenosine.

3. Certain Cell-Targeting Conjugate Moieties

In certain embodiments, a conjugate group comprises a cell-targeting conjugate 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.

5 In certain embodiments, the cell-targeting moiety comprises a branching group comprising one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether and hydroxylamino groups. In certain embodiments, the branching group comprises a branched aliphatic group comprising groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether and hydroxylamino groups. In certain such embodiments, the branched aliphatic group comprises groups selected from alkyl, amino, oxo, amide and ether groups. In certain such embodiments, the branched aliphatic group comprises groups selected from alkyl, amino and ether groups. In certain such embodiments, the branched aliphatic group comprises groups selected from alkyl and ether groups. In certain embodiments, the branching group comprises a mono or polycyclic ring system.

15 In certain embodiments, each tether of a cell-targeting moiety comprises one or more groups selected from alkyl, substituted alkyl, ether, thioether, disulfide, amino, oxo, amide, phosphodiester, and polyethylene glycol, in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, ether, thioether, disulfide, amino, oxo, amide, and polyethylene glycol, in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, phosphodiester, ether, amino, oxo, and amide, in any combination. In certain
20 embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, ether, amino, oxo, and amid, in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, amino, and oxo, in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl and oxo, in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or
25 more groups selected from alkyl and phosphodiester, in any combination. In certain embodiments, each tether comprises at least one phosphorus linking group or neutral linking group. In certain embodiments, each tether comprises a chain from about 6 to about 20 atoms in length. In certain embodiments, each tether comprises a chain from about 10 to about 18 atoms in length. In certain embodiments, each tether comprises about 10 atoms in chain length.

30 In certain embodiments, each ligand of a cell-targeting moiety has an affinity for at least one type of receptor on a target cell. In certain embodiments, each ligand has an affinity for at least one type of receptor on the surface of a mammalian lung cell.

In certain embodiments, each ligand of a cell-targeting moiety is a carbohydrate, carbohydrate derivative, modified carbohydrate, polysaccharide, modified polysaccharide, or polysaccharide derivative. In
35 certain such embodiments, the conjugate group comprises a carbohydrate cluster (*see, e.g.,* Maier et al.,

“Synthesis of Antisense Oligonucleotides Conjugated to a Multivalent Carbohydrate Cluster for Cellular Targeting,” *Bioconjugate Chemistry*, 2003, 14, 18-29, or Rensen et al., “Design and Synthesis of Novel *N*-Acetylgalactosamine-Terminated Glycolipids for Targeting of Lipoproteins to the Hepatic Asialoglycoprotein Receptor,” *J. Med. Chem.* 2004, 47, 5798-5808, which are incorporated herein by reference in their entirety).

In certain such embodiments, each ligand is an amino sugar or a thio sugar. For example, amino sugars may be selected from any number of compounds known in the art, such as sialic acid, α -D-galactosamine, β -muramic acid, 2-deoxy-2-methylamino-L-glucopyranose, 4,6-dideoxy-4-formamido-2,3-di-*O*-methyl-D-mannopyranose, 2-deoxy-2-sulfoamino-D-glucopyranose and *N*-sulfo-D-glucosamine, and *N*-glycoloyl- α -neuraminic acid. For example, thio sugars may be selected from 5-Thio- β -D-glucopyranose, methyl 2,3,4-tri-*O*-acetyl-1-thio-6-*O*-trityl- α -D-glucopyranoside, 4-thio- β -D-galactopyranose, and ethyl 3,4,6,7-tetra-*O*-acetyl-2-deoxy-1,5-dithio- α -D-*gluco*-heptopyranoside.

In certain embodiments, oligomeric compounds described herein comprise a conjugate group found in any of the following references: Lee, *Carbohydr Res*, 1978, 67, 509-514; Connolly et al., *J Biol Chem*, 1982, 257, 939-945; Pavia et al., *Int J Pep Protein Res*, 1983, 22, 539-548; Lee et al., *Biochem*, 1984, 23, 4255-4261; Lee et al., *Glycoconjugate J*, 1987, 4, 317-328; Toyokuni et al., *Tetrahedron Lett*, 1990, 31, 2673-2676; Biessen et al., *J Med Chem*, 1995, 38, 1538-1546; Valentijn et al., *Tetrahedron*, 1997, 53, 759-770; Kim et al., *Tetrahedron Lett*, 1997, 38, 3487-3490; Lee et al., *Bioconjug Chem*, 1997, 8, 762-765; Kato et al., *Glycobiol*, 2001, 11, 821-829; Rensen et al., *J Biol Chem*, 2001, 276, 37577-37584; Lee et al., *Methods Enzymol*, 2003, 362, 38-43; Westerlind et al., *Glycoconj J*, 2004, 21, 227-241; Lee et al., *Bioorg Med Chem Lett*, 2006, 16(19), 5132-5135; Maierhofer et al., *Bioorg Med Chem*, 2007, 15, 7661-7676; Khorev et al., *Bioorg Med Chem*, 2008, 16, 5216-5231; Lee et al., *Bioorg Med Chem*, 2011, 19, 2494-2500; Kornilova et al., *Analyt Biochem*, 2012, 425, 43-46; Pujol et al., *Angew Chemie Int Ed Engl*, 2012, 51, 7445-7448; Biessen et al., *J Med Chem*, 1995, 38, 1846-1852; Slidregt et al., *J Med Chem*, 1999, 42, 609-618; Rensen et al., *J Med Chem*, 2004, 47, 5798-5808; Rensen et al., *Arterioscler Thromb Vasc Biol*, 2006, 26, 169-175; van Rossenberg et al., *Gene Ther*, 2004, 11, 457-464; Sato et al., *J Am Chem Soc*, 2004, 126, 14013-14022; Lee et al., *J Org Chem*, 2012, 77, 7564-7571; Biessen et al., *FASEB J*, 2000, 14, 1784-1792; Rajur et al., *Bioconjug Chem*, 1997, 8, 935-940; Duff et al., *Methods Enzymol*, 2000, 313, 297-321; Maier et al., *Bioconjug Chem*, 2003, 14, 18-29; Jayaprakash et al., *Org Lett*, 2010, 12, 5410-5413; Manoharan, *Antisense Nucleic Acid Drug Dev*, 2002, 12, 103-128; Merwin et al., *Bioconjug Chem*, 1994, 5, 612-620; Tomiya et al., *Bioorg Med Chem*, 2013, 21, 5275-5281; International applications WO1998/013381; WO2011/038356; WO1997/046098; WO2008/098788; WO2004/101619; WO2012/037254; WO2011/120053; WO2011/100131; WO2011/163121; WO2012/177947; WO2013/033230; WO2013/075035; WO2012/083185; WO2012/083046; WO2009/082607; WO2009/134487; WO2010/144740; WO2010/148013; WO1997/020563; WO2010/088537; WO2002/043771; WO2010/129709; WO2012/068187; WO2009/126933; WO2004/024757; WO2010/054406; WO2012/089352;

WO2012/089602; WO2013/166121; WO2013/165816; U.S. Patents 4,751,219; 8,552,163; 6,908,903; 7,262,177; 5,994,517; 6,300,319; 8,106,022; 7,491,805; 7,491,805; 7,582,744; 8,137,695; 6,383,812; 6,525,031; 6,660,720; 7,723,509; 8,541,548; 8,344,125; 8,313,772; 8,349,308; 8,450,467; 8,501,930; 8,158,601; 7,262,177; 6,906,182; 6,620,916; 8,435,491; 8,404,862; 7,851,615; Published U.S. Patent
5 Application Publications US2011/0097264; US2011/0097265; US2013/0004427; US2005/0164235; US2006/0148740; US2008/0281044; US2010/0240730; US2003/0119724; US2006/0183886; US2008/0206869; US2011/0269814; US2009/0286973; US2011/0207799; US2012/0136042; US2012/0165393; US2008/0281041; US2009/0203135; US2012/0035115; US2012/0095075; US2012/0101148; US2012/0128760; US2012/0157509; US2012/0230938; US2013/0109817;
10 US2013/0121954; US2013/0178512; US2013/0236968; US2011/0123520; US2003/0077829; US2008/0108801; and US2009/0203132.

Compositions and Methods for Formulating Pharmaceutical Compositions

Oligomeric compounds described herein may be admixed with pharmaceutically acceptable active or inert substances for the preparation of pharmaceutical compositions. Compositions and methods for the
15 formulation of pharmaceutical compositions are dependent upon a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

Certain embodiments provide pharmaceutical compositions comprising one or more oligomeric compounds or a salt thereof. In certain embodiments, the oligomeric compounds comprise or consist of a modified oligonucleotide. In certain such embodiments, the pharmaceutical composition comprises a suitable
20 pharmaceutically acceptable diluent or carrier. In certain embodiments, a pharmaceutical composition comprises a sterile saline solution and one or more oligomeric compound. In certain embodiments, such pharmaceutical composition 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 one or more oligomeric compound and sterile water. In certain
25 embodiments, a pharmaceutical composition consists of one 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, a pharmaceutical composition consists of one or more oligomeric compound and sterile PBS. In certain embodiments, the sterile PBS is pharmaceutical grade PBS.
30 Compositions and methods for the formulation of pharmaceutical compositions are dependent upon a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

An oligomeric compound described herein complementary to a target nucleic acid can be utilized in pharmaceutical compositions by combining the oligomeric compound with a suitable pharmaceutically acceptable diluent or carrier and/or additional components such that the pharmaceutical composition is
35 suitable for injection. In certain embodiments, a pharmaceutically acceptable diluent is phosphate buffered

saline. Accordingly, in one embodiment, employed in the methods described herein is a pharmaceutical composition comprising an oligomeric compound complementary to a target nucleic acid and a pharmaceutically acceptable diluent. In certain embodiments, the pharmaceutically acceptable diluent is phosphate buffered saline. In certain embodiments, the oligomeric compound comprises or consists of a modified oligonucleotide provided herein.

Pharmaceutical compositions comprising oligomeric compounds provided herein encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other oligonucleotide which, upon administration to an animal, including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. In certain embodiments, the oligomeric compound comprises or consists of a modified oligonucleotide. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of 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.

Certain Mechanisms

In certain embodiments, oligomeric compounds described herein comprise or consist of modified oligonucleotides. In certain such embodiments, the oligomeric compounds described herein are capable of hybridizing to a target nucleic acid, resulting in at least one antisense activity. In certain embodiments, compounds described herein selectively affect one or more target nucleic acid. Such 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 a significant undesired antisense activity.

In certain antisense activities, hybridization of a compound described herein to a target nucleic acid results in recruitment of a protein that cleaves the target nucleic acid. For example, certain compounds described herein 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, compounds described herein are sufficiently “DNA-like” to elicit RNase H activity. Nucleosides that are sufficiently “DNA-like” to elicit RNase H activity are referred to as DNA mimics herein. Further, in certain embodiments, one or more non-DNA-like nucleoside in the RNA:DNA duplex is tolerated.

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

Antisense activities may be observed directly or indirectly. In certain embodiments, observation or

detection of an antisense activity involves observation or detection of a change in an amount of a target nucleic acid or protein encoded by such target nucleic acid, a change in the ratio of splice variants of a nucleic acid or protein, and/or a phenotypic change in a cell or animal.

5 *Certain Toxicities*

For a compound to be a viable therapeutic agent, it must be safe at therapeutically relevant doses. It has become clear that toxicity of oligonucleotides can arise from one or more of several mechanisms. For example, some oligonucleotides hybridize an unintended RNA (or “off-target RNA”) resulting in reduction of the off-target RNA and the protein encoded by that off-target RNA. Such unintended protein reduction
10 may have toxic consequences. The data disclosed herein demonstrate that toxicity can result from oligonucleotides binding certain proteins and subsequent sub-cellular localization of the oligonucleotide/protein complex. Other mechanisms of toxicity may also contribute. Of course, for an oligonucleotide to be a suitable drug for use in therapy, all of the forms or mechanisms of toxicity must be acceptably low.

15 Since toxicity can result from multiple mechanisms, the observed toxicity for a particular compound will typically be the most toxic mechanism or the mechanism that results in toxicity at the lowest dose for that particular compound (the “limiting toxicity”). Changes to a compound that reduce the limiting toxicity will result in a compound having an observable improvement in toxic profile. Changes that reduce a form of toxicity that is not the limiting toxicity may not result in an observable improvement in toxicity, because the
20 improvement may be masked by the limiting toxicity. In such instances, the improvement to a non-limiting toxicity can nonetheless have value. For example, the limiting toxicity might be controlled through additional changes to the compound or through changes in dose or dose frequency or through use of a separate therapy that mitigates the limiting toxicity; at that point, a previously masked toxicity would become limiting. Alternatively, in certain circumstances, the limiting toxicity might be less relevant (for example, if the drug is
25 intended for delivery to specific tissues not affected by the limiting toxicity or if the compound is for the treatment of severe or life-threatening indications where a certain degree of the limiting toxicity may be acceptable). In such instances, improvements to a non-limiting toxicity can have significant benefit. Further, the various forms and mechanisms of toxicity may have a cumulative effect, particularly over time. Accordingly, the beneficial effects of improvements to a particular mechanism of toxicity might be masked at
30 an early time point where another mechanism is the limiting toxicity, but over time such masked toxicity may contribute or even predominate the overall safety profile.

In certain embodiments, oligomeric compounds of the invention have improved toxicity profiles compared to standard gapmer compounds having a gap comprising only nucleosides having 2'-β-D-deoxyribose sugar moieties and the same nucleobase sequence. It should be noted that some standard gapmers
35 are suitable therapeutic agents. Toxicity is driven in part by nucleobase sequence (oligonucleotides having

identical chemical modification patterns but different sequences can have vastly different safety profiles). When one attempts to modulate a particular target RNA, one might find an antisense oligonucleotide that has an acceptable safety profile at therapeutic doses. On other occasions, however, the most active/potent oligonucleotides have unacceptable toxicity. In such instances, it is desirable to modify such compounds to
5 reduce their toxicity, ideally with no loss or only modest loss in activity/potency. In certain embodiments, modification motifs described herein reduce toxicity with little or no loss in activity/potency.

Without limitation to any particular mechanism, it is believed that certain modification motifs described herein may reduce interactions between an oligomeric compound and certain proteins. In certain
10 embodiments, such interactions result in the limiting toxicity and so disruption of these interactions results in observable improvements in the toxicity profile. In certain embodiments, the motifs described herein may alter off-target cleavage. In certain embodiments, the disclosed motifs improve toxicity through an undefined mechanism. In certain embodiments, the motifs may improve toxicity through multiple mechanisms, including, but not limited to those described here.

Disclosed herein for comparison are certain gapmer oligonucleotides that are notably more toxic than
15 other gapmers. These toxic gapmer oligonucleotides cause rapid delocalization of paraspeckle proteins, including p54nrb, to nucleoli, possibly due to the binding of these toxic oligonucleotides to the p54nrb protein and/or other paraspeckle proteins. Certain such toxic oligonucleotides have both more global protein binding than their nontoxic (or less toxic) counterparts (Figures 1-5) and have higher binding affinities (i.e., lower K_d values) for key paraspeckle proteins, including p54nrb and RNase H1. Certain such toxic
20 oligonucleotides, but not nontoxic (or less toxic) oligonucleotides, cause the paraspeckle proteins PSF, PSPC1, and FUS to localize to the nucleoli as well, as observed across a number of mouse and human cell types. In certain instances, the nucleolar delocalization of paraspeckle proteins is mediated by RNase H1. Importantly, in some instances, nontoxic (or less toxic) modified oligonucleotides with the same chemical modification pattern (gapmer motif) and a different sequence do not cause the delocalization of p54nrb to
25 nucleoli. This early event leads to nucleolar stress, p53 activation, and apoptotic cell death, both *in vitro* across a number of mammalian cell types and *in vivo* in mice. These results were consistent for gapmers with toxic sequences and containing several different commonly-used chemical modifications of modified oligonucleotides, including LNA, cEt, and 2'-MOE.

In certain embodiments, the instant invention is directed towards modified oligonucleotides having
30 chemical modifications that can alleviate the observed toxicity. In certain embodiments, such toxicity is related to protein binding and the resulting nucleolar mislocalization of proteins, such as paraspeckle proteins described above. In certain embodiments, the incorporation of a safety-enhancing nucleoside at position 2, 3 or 4 of the central region (or "gap") of the modified oligonucleotide can reduce both global protein binding and the associated toxicity. In certain embodiments, the safety-enhancing nucleoside is a nucleoside
35 comprising a 2'-OMe β-D-deoxyribsyl sugar moiety at position 2 of the central region. Incorporation of a

nucleoside comprising a 2'-OMe- β -D-deoxyribosyl sugar moiety at position 2 of the central region in a toxic 3-10-3, 3-10-4, 4-10-3 cEt gapmer, a 3-10-3 LNA gapmer, a 5-10-5 MOE gapmer, or several cEt/MOE mixed wing gapmers reduced cellular toxicity and apoptosis *in vitro* and hepatotoxicity *in vivo* across a wide variety of sequences, while having only a modest effect, if any, on antisense activity. In certain

5 embodiments, incorporation of a nucleoside comprising a 2'-OMe- β -D-deoxyribosyl sugar moiety at position 2 of the central region also reduced delayed neurotoxicity, suggesting a common mechanism for delayed neurotoxicity and hepatotoxicity. In certain embodiments, the safety-enhancing nucleoside is a nucleoside comprising a 5'-alkyl or 5'-allyl modified β -D-deoxyribosyl sugar moiety at position 3 or position 4 of the central region. In certain instances, incorporation of a nucleoside comprising a 5'-alkyl β -D-deoxyribosyl

10 sugar moiety at position 3 or position 4 of the central region of a 3-10-3 cEt gapmer reduces cellular toxicity and apoptosis *in vitro* and hepatotoxicity *in vivo* across a variety of sequences, while having a modest effect, if any, on antisense activity. In certain embodiments, the incorporation of a safety-enhancing internucleoside linkage between the nucleosides at positions 2-3 or positions 3-4 of the central region can reduce toxicity. In certain embodiments, one or more of a safety-enhancing linkages linking the nucleosides from positions 2-4

15 of the central region is a neutral linkage. In certain embodiments, one or more of a safety-enhancing linkages linking the nucleosides from positions 2-4 of the central region is a 2'-5' internucleoside linkage. The instant invention extends to any chemical modification introduced at positions 2, 3 or 4 of the central region, including modifications to nucleosides and to internucleoside linkages. In certain embodiments, such modification reduces *in vitro* toxicity (compared to the modified oligonucleotide lacking the safety enhancing

20 nucleoside at positions 2, 3 or 4 of the central region or lacking the safety enhancing internucleoside linkage between positions 2-3 or 3-4 of the central region) as measured by the caspase 3/7 assay and/or *in vivo* hepatotoxicity, as measured by ALT or AST, and/or *in vivo* neurotoxicity, as measured by an FOB score or accumulation of markers of glial inflammation, Aif1 and GFAP.

In certain embodiments, introducing chemical modifications at positions 2, 3 or 4 of the central region

25 can significantly reduce toxicity with only a modest loss in potency, if any. This leads to an improvement in therapeutic index for a given target sequence. In certain cases, such improvements in therapeutic index are large enough to allow further drug development based on a compound targeted to a previously-toxic (but potent) sequence.

Target Nucleic Acids, Target Regions and Nucleotide Sequences

30 In certain embodiments, compounds described herein comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid. In certain embodiments, the target nucleic acid is an endogenous RNA molecule. In certain embodiments, the target nucleic acid encodes a protein. In certain such embodiments, the target nucleic acid is selected from: an mRNA and a pre-mRNA, including intronic, exonic and untranslated regions. In certain embodiments, the target RNA is an mRNA. In certain

35 embodiments, the target nucleic acid is a pre-mRNA. In certain embodiments, a pre-mRNA and corresponding

mRNA are both target nucleic acids of a single compound. In certain such embodiments, the target region is entirely within an intron of a target pre-mRNA. In certain embodiments, the target region spans an intron/exon junction. In certain embodiments, the target region is at least 50% within an intron.

Certain Compounds Having Central Region Modifications

5 In certain embodiments, the oligomeric compounds herein comprise a gapmer comprising one or more altered nucleotides in the central region of the gapmer. Each of such oligomeric compounds has a corresponding parent oligomeric compound that is identical to the first oligomeric compound except that is lacking the one or more altered nucleotides in the central region of the gapmer. Examples of such parent oligomeric compounds and their corresponding identical oligomeric compounds lacking the altered
10 nucleotide are found in Tables 1 and 2 of Example 1 as well as throughout the Examples section. In Example 1, 558807 is the parent oligonucleotide. In certain embodiments, the central region of a parent oligomeric compound comprises only phosphodiester and/or phosphorothioate internucleoside linkages, unmodified nucleobases and/or 5-methylcytosine, and unmodified, 2'- β -D-deoxyribose sugar moieties.

In certain embodiments, the present disclosure provides oligomeric compounds that comprise a
15 gapmer comprising one or more altered nucleotides in the central region of the gapmer that have an increased therapeutic index and/or increased tolerability compared to the corresponding parent oligomeric compounds. In certain such embodiments, the modification or modifications of the central region of the oligomeric compounds with increased therapeutic index and/or increased tolerability are particularly useful in providing oligomeric compounds having reduced toxicity without significantly altering the potency. The modifications
20 in the central region described herein can be at any position in the central region, and examples of embodiments comprising modifications at such positions are disclosed in the numbered embodiments and Examples. In certain embodiments, the altered nucleotide is an altered nucleoside attached to a phosphorothioate or phosphodiester internucleoside linkage. In a preferred embodiment, the altered nucleotide is at positions 1-4 of the central region of the modified oligonucleotide. In another preferred
25 embodiment, the altered nucleotide comprises a nucleoside comprising a 2'-modified sugar moiety at position 2 of the central region of the modified oligonucleotide. In another preferred embodiment, the altered nucleotide comprises a nucleoside comprising a 5'-modified sugar moiety at positions 3 or 4 of the central region of the modified oligonucleotide. In another preferred embodiment, the altered nucleotide comprises a neutral internucleoside linkage between positions 2-3 or positions 3-4 of the central region of the modified
30 oligonucleotide.

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
35 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. All tautomeric forms of the compounds provided herein are included unless otherwise indicated.

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 , ^{13}C or ^{14}C in place of ^{12}C , ^{15}N in place of ^{14}N , ^{17}O or ^{18}O in place of ^{16}O , and ^{33}S , ^{34}S , ^{35}S , or ^{36}S in place of ^{32}S . In certain embodiments, non-radioactive isotopic substitutions may impart new properties on the oligomeric compound that are beneficial for use as a therapeutic or research tool. In certain embodiments, radioactive isotopic substitutions may make the compound suitable for research or diagnostic purposes such as imaging.

EXAMPLES

Non-limiting disclosure and incorporation by reference

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 nucleobase could be described as a DNA having an RNA sugar, or as an RNA having a DNA nucleobase.

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 unmodified 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 oligonucleotide having the nucleobase sequence “ATCGATCG” encompasses any oligonucleotides 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 compounds having other modified nucleobases, such as “AT^mCGAUCG,” wherein ^mC indicates a cytosine base comprising a methyl group at the 5-position. In certain cases, compounds comprising a uridine nucleobase and a 2'-OMe sugar moiety are compared to compounds comprising a thymidine nucleobase with a 2'-β-D-deoxyribose sugar moiety at the same position. While these compounds have different SEQ ID NOs, they are not considered distinct sequences, and they have identical target RNA. In certain cases, compounds comprising a cytosine nucleobase and a 2'-OMe sugar moiety are compared to compounds comprising a 5-methylcytosine nucleobase and a 2'-β-D-deoxyribose sugar moiety at the same position.

In the Examples below, modified oligonucleotides are represented by a chemistry notation, always shown in the 5'-to-3' direction, of the format B_sB_s^mB_s, where "B" or "mB" represents the nucleobase, with a superscript "m" before "B" representing a 5-methyl modification, the subscript in position "s" represents the sugar moiety, and the subscript in position "l" represents the 5'-to-3' internucleoside linkage.

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 recited in the present application is incorporated herein by reference in its entirety.

Example 1 Effect of position-specific 2'-modifications on *in vitro* activity and *in vivo* liver toxicity of modified oligonucleotides complementary to CXCL12

Modified oligonucleotides were synthesized with kkk-x-d(9)-kkk, kkk-d-x-d(8)-kkk, kkk-dd-x-d(7)-kkk or kkk-d(3)-x-d(6)-kkk sugar motifs, respectively, where "x" represents a sugar moiety having the modification indicated in the table below, "k" represents a cEt, and "d" represents an unmodified, 2'-β-D-deoxyribose sugar moiety. These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking an altered nucleotide in the central region, a 3-10-3 cEt gapmer, having three cEt nucleosides in each of the 5' and 3' regions and 10 DNA nucleosides in the central region. Each internucleoside linkage is a phosphorothioate. The compounds in the table below are 100% complementary to mouse CXCL12, GENBANK NT_039353.7 truncated from 69430515 to 69445350 (SEQ ID NO: 1), at position 6877 to 6892.

Table 1 Modified oligonucleotides complementary to CXCL12

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	Chemistry Notation (5'-3')	SEQ ID NO
558807	n/a	n/a	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
936049	1	2'-OMe	G _{ks} ^m C _{ks} A _{ks} U _{ms} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	19
828910	1	2'-MOE	G _{ks} ^m C _{ks} A _{ks} T _{es} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
936050	1	cEt	G _{ks} ^m C _{ks} A _{ks} T _{ks} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
936054	1	2'-FANA	G _{ks} ^m C _{ks} A _{ks} U _{(FANA)s} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	19
936048	1	2'-ribo-F	G _{ks} ^m C _{ks} A _{ks} U _{fs} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	19
936053	2	2'-OMe	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ms} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
828911	2	2'-MOE	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{es} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
1070041	2	cEt	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ks} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
1061314	2	2'-OH (RNA)	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{rs} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
936051	2	2'-FANA	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{(FANA)s} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18

936052	2	2'-ribo-F	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{fs} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
892826	3	2'-OMe	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} U_{ms} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	20
828912	3	2'-MOE	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{es} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
892816	3	cEt	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ks} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
895596	3	2'-FANA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} U_{(FANA)s} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	20
892821	3	2'-ribo-F	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} U_{fs} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	20
892819	4	2'-OMe	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} U_{ms}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	21
828913	4	2'-MOE	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{es}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
892817	4	cEt	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ks}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
895595	4	2'-FANA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} U_{(FANA)s}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	21
892822	4	2'-ribo-F	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} U_{fs}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	21

A subscript “d” indicates an unmodified, 2'-β-D-deoxyribosyl sugar moiety. A subscript “e” indicates a 2'-MOE-β-D-ribofuranosyl sugar moiety. A subscript “m” indicates a 2'-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A subscript “f” indicates a 2'-F-β-D-2'-deoxyribosyl sugar moiety. A subscript “(FANA)” indicates a 2'-F-β-D-arabinofuranosyl modified sugar moiety. A superscript “m” before a C indicates 5-methyl Cytosine.

For *in vitro* activity studies, approximately 20,000 mouse 3T3-L1 cells were electroporated with 0, 27 nM, 82 nM, 247 nM, 740 nM, 2,220 nM, 6,660 nM or 20,000 nM antisense oligonucleotide. mRNA was harvested and analyzed by RT-qPCR. CXCL12 mRNA was detected with primer probe

set RTS2605 (forward sequence CCAGAGCCAACGTCAAGCAT, SEQ ID NO: 9; reverse sequence:

CAGCCGTGCAACAATCTGAA, SEQ ID NO: 10; probe sequence:

TGAAAATCCTCAACACTCCAACTGTGCC, SEQ ID NO: 11) and RAPTOR mRNA was detected with primer probe set RTS3420 (forward sequence GCCCTCAGAAAGCTCTGGAA, SEQ ID NO: 12; reverse sequence: TAGGGTCGAGGCTCTGCTTGT, SEQ ID NO: 13; probe sequence:

CCATCGGTGCAAACCTACAGAAGCAGTATG, SEQ ID NO: 14). RAPTOR is a sentinel gene that can be indicative of toxicity, as described in US 20160160280, hereby incorporated by reference.

For acute *in vivo* toxicity studies, three BALB/C mice per group were administered 150mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. Three mice were administered an injection of saline as a control. Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

Table 2 Activity and toxicity of modified oligonucleotides complementary CXCL12

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	<i>in vitro</i> CXCL12 IC ₅₀ (μM)	<i>in vitro</i> RAPTOR IC ₅₀ (μM)	ALT @ 150mg/kg (IU/L)
PBS	n/a	n/a	n/a	n/a	23

558807	n/a	n/a	0.2	1.26	n.d.**
936049	1	2'-OMe	0.17	4.8	8622
828910	1	2'-MOE	0.12	7.2	2175
936050	1	cEt	0.15	6.5	912
936054	1	2'-FANA	0.12	9.9	5755
936048	1	2'-ribo-F	0.15	1.9	death
936053	2	2'-OMe	0.17	>>10	46
828911	2	2'-MOE	0.42	>>10	27
1070041	2	cEt	0.52	n.d.	96
1061314	2	2'-OH (RNA)	n.d.	n.d.	26
936051	2	2'-FANA	0.12	2.34	death
936052	2	2'-ribo-F	0.19	13.5	1110
892826	3	2'-OMe	0.21	7.1	10463
828912	3	2'-MOE	0.28	10	701
892816	3	cEt	0.17	11	278
895596	3	2'-FANA	0.12	7.4	17369
892821	3	2'-ribo-F	0.18	4.5	6333
892819	4	2'-OMe	0.18	>10	565
828913	4	2'-MOE	0.22	10	2474
892817	4	cEt	0.23	9	5264
895595	4	2'-FANA	0.08	8.8	22082
892822	4	2'-ribo-F	0.04	4.85	4020

**558807 treatment at 16.7 mg/kg leads to an ALT of 586 IU/L in this experiment; mice that are treated with 558807 at 150mg/kg typically experience death before 72 hours post-treatment.

- 5 For the *in vitro* study reported in the tables below, 3T3-L1 cells were electroporated with 27 nM, 80 nM, 250 nM, 740 nM, 2, 222 nM, 6,667 nM, or 20,000 nM of modified oligonucleotide and levels of P21 and Gadd45a were measured by RT-qPCR. Levels of Gadd45a were analyzed using primer probe set Mm00432802_m1 (ThermoFisher). Levels of P21 were analyzed using primer probe set Mm04207341_m1 (ThermoFisher).

10

Table 2b *in vitro* P21 Expression in 3T3-L1 cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
Expression level of P21 mRNA (% Control)							
558807	110	98	69	99	117	228	488
936049	63	116	96	93	121	151	199
936053	151	144	158	160	152	143	155
892826	140	104	104	128	138	181	177

Table 2c *in vitro* Gadd45a Expression in 3T3-L1 cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of Gadd45a mRNA (% Control)						
558807	115	120	111	136	155	237	298
936049	101	124	131	158	172	212	276
936053	144	227	175	203	197	201	193
892826	132	114	134	152	147	163	158

For the *in vitro* study reported in the tables below, b.END cells were electroporated with 27 nM, 80 nM, 250 nM, 740 nM, 2, 222 nM, 6,667 nM, or 20,000 nM of modified oligonucleotide and levels of P21 were measured by RT-qPCR using primer probe set Mm04207341_m1 (ThermoFisher).

Table 2d *in vitro* P21 Expression in b.END cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of P21 mRNA (% Control)						
558807	138	117	93	73	107	160	226
936053	108	112	96	90	111	101	118
892826	112	112	114	107	117	116	137
1061314	126	128	103	115	128	122	112
936051	114	113	109	118	117	123	178
936052	109	116	102	100	112	119	138
828911	115	108	120	113	114	115	122
1070041	101	100	109	104	104	120	132

Table 2e *in vitro* Gadd45a Expression in b.END cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of P21 mRNA (% Control)						
558807	558807	86	132	93	101	178	220
936053	936053	111	n.d.	148	150	200	215
892826	892826	134	177	160	170	177	162
1061314	1061314	135	149	150	197	199	184
936051	136	132	152	185	199	193	258
936052	125	160	146	173	210	201	228
828911	121	154	158	193	190	189	249
1070041	118	139	163	194	225	301	313

For the *in vivo* activity and toxicity study in the table below, 2 or 3 BALB/C mice per group were administered modified oligonucleotide at 1.8 mg/kg, 5.5 mg/kg, or 16.7 mg/kg by subcutaneous injection and sacrificed after 72 hours.

Table 2f *in vivo* Activity and Toxicity

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	<i>in vivo</i> CXCL12 ED50 (mg/kg)	ALT @5.5 mg/kg (IU/L)	ALT @ 16.7mg/kg (IU/L)
PBS	n/a	n/a	n/a	30 (@0mg/kg)	
558807	n/a	n/a	1.6	40	1721
936051	2	2'-FANA	0.15	44	4285
936053	2	2'-OMe	5.5	27	25
828911	2	2'-MOE	14	36	25
936052	2	2'-ribo-F	2.9	26	29

For *in vivo* activity and toxicity study in the table below, 3 BALB/C mice per group were administered modified oligonucleotide by subcutaneous injection and sacrificed after 72 hours. Compound 558807 was dosed at 1.8, 5.5, or 16.7 mg/kg, compounds 828911, 936052 and 936053 were dosed at 1.8, 5.5, 16.7 and 50 mg/kg, and compounds 1061315 and 1070041 were dosed at 1.8, 5.5, 16.7, 50 or 150 mg/kg. Tissue were collected and mRNA was isolated and levels of CXCL12 were measured by RT-qPCR with primer probe set RTS2605 as described above. Levels of Gadd45a were analyzed using primer probe set Mm00432802_m1 (ThermoFisher). Levels of P21 were analyzed using primer probe set Mm04207341_m1 (ThermoFisher). Levels of Tnfrsf10b were analyzed using primer probe set Mm00457866_m1 (ThermoFisher). Expression levels were normalized with Ribogreen® and are presented relative to levels in mice treated with PBS.

Table 2g *In Vivo* Activity and Toxicity of modified oligonucleotides complementary to CXCL12

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	<i>in vivo</i> CXCL12 ED50 (mg/kg)	ALT @50 mg/kg (IU/L)	ALT @ 150mg/kg (IU/L)
PBS	n/a	n/a	n/a	28 (@0mg/kg)	
558807	n/a	n/a	2.7	n.d.**	
936053	2	2'-OMe	4.9	23	n.d.
828911	2	2'-MOE	14	27	n.d.
1070041	2	cEt	29	25	78
1061314	2	2'-OH (RNA)	78	21	24
936052	2	2'-ribo-F	4.2	39	n.d.

**558807 treatment at 16.7 mg/kg leads to an ALT of 586 IU/L; mice that are treated with 558807 at 150mg/kg typically experience death before 72 hours post-treatment.

Table 2h *In Vivo* Dose-response of Gadd45a mRNA upon treatment with modified oligonucleotides complementary to CXCL12

Compound ID	1.8 mg/kg	5.5 mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg
	Expression level of Gadd45a mRNA (% Control)				
558807	100	172	856	n/a	n/a
936053	61	99	91	92	n/a
828911	80	100	96	100	n/a
1070041	128	225	139	177	169
1061314	112	84	89	105	180
936052	84	80	134	126	n/a

Table 2i *In Vivo* Dose-response of Tnfrsf10b mRNA upon treatment with modified oligonucleotides complementary to CXCL12

Compound ID	1.8 mg/kg	5.5 mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg
	Expression level of Tnfrsf10b mRNA (% Control)				
558807	102	267	790	n/a	n/a
936053	106	111	130	100	n/a
828911	120	116	95	102	n/a
1070041	106	139	252	483	1021
1061314	79	66	81	136	220
936052	82	101	183	138	n/a

Table 2j *In Vivo* Dose-response of P21 mRNA upon treatment with modified oligonucleotides complementary to CXCL12

Compound ID	1.8 mg/kg	5.5 mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg
	Expression level of P21 mRNA (% Control)				
558807	100	61	609	n/a	n/a
936053	104	94	104	89	n/a
828911	90	145	52	92	n/a
1070041	28	93	83	132	264
1061314	45	59	30	34	178
936052	70	71	51	101	n/a

10 For the *in vivo* activity study in the tables below, 3 BALB/C mice per group were administered 3.37, 11, 33, or 100 mg/kg doses of modified oligonucleotide, as indicated in the table below, by subcutaneous injection and sacrificed 72 hours later. Liver mRNA was isolated and analyzed by RT-PCR as described in above. Expression levels were normalized with Ribogreen® and are expressed relative to PBS-treated control mice.

Table 2k Activity and toxicity of modified oligonucleotides complementary to CXCL12

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	ALT (IU/L) at 100 mg/kg	ALT (IU/L) at 33 mg/kg
558807	n/a	n/a	death	3740
936049	1	2'-OMe	3060	612
936053	2	2'-OMe	42	21
892826	3	2'-OMe	1127	2281

Table 2l *In Vivo* Dose-response of CXCL12 mRNA upon treatment with modified oligonucleotides complementary to CXCL12

Compound ID	3.37 mg/kg	11 mg/kg	33 mg/kg	100 mg/kg
	Expression level of CXCL12 mRNA (% Control)			
558807	95	29	12	n.d.
936049	102	50	22	14
936053	100	70	40	31
892826	100	49	16	10

5

Table 2m *In Vivo* Dose-response of P21 mRNA upon treatment with modified oligonucleotides complementary to CXCL12

Compound ID	3.37 mg/kg	11 mg/kg	33 mg/kg	100 mg/kg
	Expression level of P21 mRNA (% Control)			
558807	194	186	32700	n.d.
936049	126	127	3156	21746
936053	100	49	89	185
892826	60	60	2401	12981

10 Example 2 Effect of position-specific 5'-modifications on *in vitro* activity and *in vivo* liver toxicity of modified oligonucleotides complementary CXCL12

Modified oligonucleotides containing 5'-methyl, 5'-allyl, and 5'-ethyl modifications at various positions were synthesized. Procedures for the synthesis of 5'-methyl and 5'-allyl analogs are detailed in WO2013022967. Procedures for the synthesis of 5'-ethyl analogs are detailed herein below in Example 39.

15 These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking a modified nucleoside in the central region, a 3-10-3 cEt modified oligonucleotide, containing three cEt nucleosides in each of the 5' and 3' regions and 10 unmodified DNA nucleobases in the central region. The compounds in the table below are 100% complementary to mouse CXCL12, GENBANK NT_039353.7 truncated from 69430515 to 69445350 (SEQ ID NO: 1), at position 6877 to 6892.

Table 3 Modified oligonucleotides complementary to CXCL12

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	Chemistry Notation (5'-3')	SEQ ID NO
558807	n/a	n/a	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1123320	2	5'-(S)-Me	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{[(S)-\mu]s} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1123322	2	5'-(R)-Me	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{[(R)-\mu]s} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1123479	2	5'-(R,S)-allyl	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{[\gamma]s} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
942943	3	5'-(R)-Me	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{[(R)-\mu]s} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
957908	3	5'-(S)-Me	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{[(S)-\mu]s} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
957910	3	5'-(R)-allyl	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{[(R)-\gamma]s} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
957912	3	5'-(S)-allyl	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{[(S)-\gamma]s} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1175787	3	5'-(R)-Et	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{[(R)-\epsilon]s} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1175785	3	5'-(S)-Et	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{[(S)-\epsilon]s} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
942944	4	5'-(R)-Me	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{[(R)-\mu]s}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
957909	4	5'-(S)-Me	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{[(S)-\mu]s}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
957911	4	5'-(R)-allyl	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{[(R)-\gamma]s}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
957913	4	5'-(S)-allyl	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{[(S)-\gamma]s}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1175786	4	5'-(R)-Et	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{[(R)-\epsilon]s}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1175782	4	5'-(S)-Et	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{[(S)-\epsilon]s}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18

A subscript “d” indicates an unmodified, 2'-β-D-deoxyribose sugar moiety. A subscript “k” indicates a cEt.

A subscript “s” indicates a phosphorothioate internucleoside linkage. A subscript “[μ]” indicates a 5'-(R,S)-

Me-β-D-2'-deoxyribose sugar moiety. A subscript “[(R)-μ]” indicates a 5'-(R)-Me-β-D-2'-deoxyribose

sugar moiety. A subscript “[(S)-μ]” indicates a 5'-(S)-Me-β-D-2'-deoxyribose sugar moiety. A subscript

“[γ]” indicates a 5'-(R,S)-allyl-β-D-2'-deoxyribose sugar moiety. A subscript “[(R)-γ]” indicates a 5'-(R)-

allyl-β-D-2'-deoxyribose sugar moiety. A subscript “[(S)-γ]” indicates a 5'-(S)-allyl-β-D-2'-deoxyribose

sugar moiety. A subscript “[ε]” indicates a 5'-(R,S)-ethyl-β-D-2'-deoxyribose sugar moiety. A subscript

“[(R)-ε]” indicates a 5'-(R)-ethyl-β-D-2'-deoxyribose sugar moiety. A subscript “[(S)-ε]” indicates a 5'-(S)-

ethyl-β-D-2'-deoxyribose sugar moiety.

Experimental Procedures & Results

In vitro activity and *in vivo* activity and toxicity experiments were performed essentially as described in Example 1. For *in vivo* toxicity studies, a single BALB/C mouse per modified oligonucleotide was administered 150mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. For the *in vivo* activity study in the table below, 2 BALB/C mice per group were administered 1.8 mg/kg, 5.5 mg/kg, 16.7 mg/kg, 50 mg/kg dose of modified oligonucleotide subcutaneously and sacrificed after 72 hours. For 558807, only 1.8 mg/kg, 5.5 mg/kg, and 16.7 mg/kg doses were tested for dose response, due to acute toxicity of higher doses. Tissues were collected and liver mRNA was isolated and levels of CXCL12 were measured by RT-qPCR with primer probe set RTS2605 as described above.

Table 4 Activity and toxicity of modified oligonucleotides complementary CXCL12

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	<i>In vitro</i> IC50 CXCL12 (μM)	Raptor IC50 (tox marker)	<i>in vivo</i> ED50 (mg/kg)	ALT (at 150 mg/kg)
558807	n/a	Parent	0.11	1.3	2.9	n.d.**
942943	3	5'-(<i>R</i>)-Me	0.118	23	2.8	2466
942944	4	5'-(<i>R</i>)-Me	0.169	22	3	233
957908	3	5'-(<i>S</i>)-Me	0.193	33	3.7	52
957909	4	5'-(<i>S</i>)-Me	0.159	4	2.2	1267
957910	3	5'-(<i>R</i>)-allyl	0.239	>>20	3.6	32
957911	4	5'-(<i>R</i>)-allyl	0.269	>>20	6.4	30
957912	3	5'-(<i>S</i>)-allyl	0.234	>>20	5.1	30
957913	4	5'-(<i>S</i>)-allyl	0.263	>>20	5.7	32

**Not tested in this experiment; mice that are treated with 558807 at 150mg/kg typically experience death before 72 hours post-treatment.

For the *in vivo* activity and toxicity study reported in the table below, 2 BALB/C mice per group were administered 5 mg/kg or 150 mg/kg modified oligonucleotide subcutaneously and sacrificed 72 hours later. Plasma levels of ALT were measured and liver mRNA was analyzed for target reduction as in example 1 above.

Table 5 Activity and toxicity of modified oligonucleotides complementary CXCL12

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	CXCL12 mRNA (% control) 5 mg/kg	CXCL12 mRNA (% control) 150 mg/kg	ALT 5mg/kg (IU/L)	ALT 150mg/kg (IU/L)
558807	n/a	n/a	n.d.	n.d.	n.d.	n.d.**
942943	3	5'-(<i>R</i>)-Me	28	3	27	4407
957910	3	5'-(<i>R</i>)-allyl	53	7	24	38
1175787	3	5'-(<i>R</i>)-Et	57	6	27	39

1175785	3	5'-(S)-Et	46	8	25	45
957909	4	5'-(S)-Me	30	7	22	7133
957913	4	5'-(S)-allyl	59	10	30	37
1175786	4	5'-(R)-Et	44	35	24	44
1175782	4	5'-(S)-Et	52	7	26	131

**Not tested in this experiment; mice that are treated with 558807 at 150mg/kg typically experience death before 72 hours post-treatment.

For the results in the tables below, *in vivo* activity and toxicity experiments were performed essentially as described in Example 1. For *in vivo* toxicity studies, two BALB/C mice per group was administered 50 or 150mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT were measured using an automated clinical chemistry analyzer.

For the *in vivo* activity study in the tables below, 2 BALB/C mice per group were administered 1.8 mg/kg, 5.5 mg/kg, 16.7 mg/kg, 50 mg/kg, or 150 mg/kg doses of modified oligonucleotide, as indicated in the table below, by subcutaneous injection and sacrificed 72 hours later. For 558807, only 1.8 mg/kg, 5.5 mg/kg, and 16.7 mg/kg doses were tested for dose response, due to acute toxicity of higher doses. Liver mRNA was isolated and analyzed by RT-PCR as described in Example 1 above. Expression levels were normalized with Ribogreen® and are expressed relative to PBS-treated control mice.

Table 6 Activity and toxicity of modified oligonucleotides complementary CXCL12

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	<i>in vivo</i> ED ₅₀ (mg/kg)	ALT (IU/L) at 150 mg/kg	ALT (IU/L) at 50mg/kg
558807	n/a	n/a	1.7*	n.d.**	n.d.**
1123320	2	5'-(R)-Me	2.8	7448	3987
1123322	2	5'-(S)-Me	2.1	5181	1912
1123479	2	5'-(R,S)-allyl	6.1	2562	56

*Compound 558807 was only dosed at 1.8, 5.5, and 16.7 mg/kg

**Not tested in this experiment; mice that are treated with 558807 150mg/kg typically experience death within 72 hours post-treatment.

Table 6b *In Vivo* Dose-response of Gadd45a mRNA upon treatment with modified oligonucleotides complementary to CXCL12

Compound ID	1.8 mg/kg	5.5 mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg
	Expression level of Gadd45a mRNA (% Control)				
558807	83	143	188	n/a	n/a
1123320	68	80	114	387	683
1123322	105	61	169	141	575
1123479	88	70	75	273	141

Table 6c *In Vivo* Dose-response of Tnfrsf10b mRNA upon treatment with modified oligonucleotides complementary to CXCL12

Compound ID	1.8 mg/kg	5.5 mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg
	Expression level of Tnfrsf10b mRNA (% Control)				
558807	115	119	195	n/a	n/a
1123320	78	115	77	1,802	6,928
1123322	95	75	231	1,036	8,281
1123479	174	132	125	303	1,423

Table 6d *In Vivo* Dose-response of P21 mRNA upon treatment with modified oligonucleotides complementary to CXCL12

Compound ID	1.8 mg/kg	5.5 mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg
	Expression level of P21 mRNA (% Control)				
558807	144	123	1212	n/a	n/a
1123320	109	224	114	17,332	51,431
1123322	218	92	303	10,383	75,226
1123479	271	209	295	838	12,248

Table 7 Activity and toxicity of modified oligonucleotides complementary CXCL12

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	<i>in vivo</i> EC ₅₀ (mg/kg)	ALT (IU/L) at 150 mg/kg	ALT (IU/L) at 50mg/kg
936053	2	2'-OMe	4.9	49	23
1175782	4	5'-(<i>S</i>)-Et	3.7	153	37
1175785	3	5'-(<i>S</i>)-Et	6.6	34	24
1175786	4	5'-(<i>R</i>)-Et	3.5	33	26
1175787	3	5'-(<i>R</i>)-Et	5.8	39	28

10 Example 3 Effect of position-specific 2'-modifications on *in vitro* activity and *in vivo* liver toxicity of modified oligonucleotides complementary to Factor XI

15 Modified oligonucleotides were synthesized as indicated in the table below, comprising an altered nucleotide at positions 1-3 of the central region. These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking an altered nucleotide in the central region, a 3-10-3 cEt gapmer, containing three cEt nucleosides in each of the 5' and 3' regions and 10 unmodified DNA nucleosides in the central region. Each internucleoside linkage is a phosphorothioate internucleoside linkage. The compounds in the table below are 100% complementary to the complement of mouse Factor XI, GENBANK NT_039460.6 truncated from 6086000 to 6111000 (SEQ ID NO: 2), at position 11699 to 11714.

Table 8 Modified oligonucleotides complementary to Factor XI

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	Chemistry Notation (5'-3')	SEQ ID NO
464917	n/a	n/a	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}T_{ds}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
982033	1	2'-OMe	$G_{ks}T_{ks}^mC_{ks}U_{ms}G_{ds}T_{ds}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	143
982034	2	2'-OMe	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ms}T_{ds}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
985292	2	2'-MOE	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{es}T_{ds}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
985293	2	cEt	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ks}T_{ds}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
1011274	2	2'-FANA	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{(FANA)s}T_{ds}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
604581	2	2'-ribo-F	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{fs}T_{ds}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
982035	3	2'-OMe	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}U_{ms}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	23
985294	3	2'-MOE	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}T_{es}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
985295	3	cEt	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}T_{ks}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
1011276	3	2'-FANA	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}U_{(FANA)s}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	23
605933	3	2'-ribo-F	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}U_{fs}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	23

A subscript "d" indicates an unmodified, 2'-β-D-deoxyribose sugar moiety. A subscript "e" indicates a 2'-MOE-β-D-ribofuranosyl sugar moiety. A subscript "m" indicates a 2'-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript "k" indicates a cEt. A subscript "s" indicates a phosphorothioate internucleoside linkage. A subscript "f" indicates a 2'-F-β-D-2'-deoxyribose sugar moiety. A subscript "(FANA)" indicates a 2'-F-β-D-arabinofuranosyl modified sugar moiety. A superscript "m" before a C indicates 5-methyl Cytosine.

Experimental Procedures & Results

For *in vitro* toxicity studies, 3T3-L1 cells were electroporated with 27, 80, 250, 740, 2, 222, 6,667, or 20,000 nM of modified oligonucleotide and levels of Raptor were measured by RT-qPCR as in Example 1.

For *in vivo* toxicity studies, two BALB/C mice per group were administered 100 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

Table 8b Toxicity of modified oligonucleotides complementary Factor XI

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	Raptor IC50 (μM)	ALT at 100mg/kg (IU/L)
464917	n/a	n/a	1.6	18751 *
982034	2	2'-OMe	>20	1363
985292	2	2'-MOE	15.5	2406
985293	2	cEt	9.3	15141

1011274	2	2'-FANA	2.3	death
604581	2	2'-ribo-F	6	14957
982035	3	2'-OMe	1.8	6411
985294	3	2'-MOE	6.2	2836
985295	3	cEt	5.2	3669
1011276	3	2'-FANA	>20	death
605933	3	2'-ribo-F	4.6	18570

*ALT for 464917 is for a 50mg/kg dose

For the *in vitro* study reported in the tables below, 3T3-L1 cells were electroporated with 27, 80, 250, 740, 2, 222, 6,667, or 20,000 nM of modified oligonucleotide and levels of P21 and Gadd45a were measured by RT-qPCR. Levels of Gadd45a were analyzed using primer probe set Mm00432802_m1 (ThermoFisher). Levels of P21 were analyzed using primer probe set Mm04207341_m1 (ThermoFisher).

Table 8c *in vitro* P21 Expression in 3T3-L1 cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of P21 mRNA (% Control)						
464917	108	124	122	169	228	478	749
982033	119	120	128	128	218	498	895
982034	115	121	110	102	136	266	840
982035	162	157	175	206	466	768	661

Table 8d *in vitro* Gadd45a Expression in 3T3-L1 cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of Gadd45a mRNA (% Control)						
464917	130	150	115	179	321	632	633
982033	120	117	126	203	331	767	798
982034	89	111	103	102	173	678	800
982035	161	120	140	181	557	779	497

For the *in vitro* study reported in the tables below, b.END cells were electroporated with 27, 80, 250, 740, 2, 222, 6,667, or 20,000 nM of modified oligonucleotide and levels of P21 and Gadd45a were measured by RT-qPCR. Levels of Gadd45a were analyzed using primer probe set Mm00432802_m1 (ThermoFisher). Levels of P21 were analyzed using primer probe set Mm04207341_m1 (ThermoFisher).

Table 8e *in vitro* P21 Expression in b.END cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of P21 mRNA (% Control)						
464917	111	115	124	120	139	192	446
982033	105	102	107	110	125	171	414

982034	106	102	109	112	120	132	208
982035	102	97	111	115	129	168	392

Table 8f *in vitro* Gadd45a Expression in b.END cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
Expression level of Gadd45a mRNA (% Control)							
464917	101	83	85	87	129	236	380
982033	89	76	101	91	177	347	731
982034	58	73	86	88	115	202	373
982035	68	72	81	103	166	298	620

For the *in vivo* activity study in the tables below, 3 BALB/C mice per group were administered 3.37, 11, 33, or 100 mg/kg doses of modified oligonucleotide, as indicated in the table below, by subcutaneous injection and sacrificed 72 hours later. Liver mRNA was isolated and analyzed by RT-PCR as described in Example 1 above. Expression levels were normalized with Ribogreen® and are expressed relative to PBS-treated control mice.

Table 8g Activity and toxicity of modified oligonucleotides complementary FXI

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	ALT (IU/L) at 100 mg/kg	ALT (IU/L) at 33 mg/kg
464917	n/a	n/a	11816	11682
982033	1	OMe	26992	3951
982034	2	OMe	7954	920
982035	3	OMe	28994	3848

Table 8h *In Vivo* Dose-response of FXI mRNA upon treatment with modified oligonucleotides complementary to FXI

Compound ID	3.37 mg/kg	11 mg/kg	33 mg/kg	100 mg/kg
Expression level of FXI mRNA (% Control)				
464917	47	12	8.0	1.8
982033	53	18	10	5.5
982034	53	24	9.9	3.5
982035	36	20	11	5.3

Table 8i *In Vivo* Dose-response of P21 mRNA upon treatment with modified oligonucleotides complementary to FXI

Compound ID	3.37 mg/kg	11 mg/kg	33 mg/kg	100 mg/kg
	Expression level of P21 mRNA (% Control)			
464917	230	4143	4678	5289
982033	122	1106	2926	5653
982034	93	297	1694	4294
982035	418	1283	4759	6960

Example 4 Effect of position-specific 2' and 5'-modifications on in vivo activity and liver toxicity of modified oligonucleotides complementary to Factor XI

Modified oligonucleotides were synthesized with 2' or 5' modifications as indicated in the table below. These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking a modified nucleoside in the central region, a 3-10-3 cEt modified oligonucleotide, containing three cEt nucleosides in each of the 5' and 3' regions and 10 unmodified DNA nucleobases in the central region. The compounds in the table below are 100% complementary to mouse Factor XI, the complement of GENBANK NT_039460.6 truncated from 6086000 to 6111000 (SEQ ID NO: 2), at position 11699 to 11714.

Table 9 Modified oligonucleotides complementary to Factor XI

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	Chemistry Notation (5'-3')	SEQ ID NO
464917	n/a	n/a	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}T_{ds}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
443919	n/a	n/a	$G_{es}T_{es}^mC_{es}T_{ds}G_{ds}T_{ds}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{es}^mC_{es}^mC_e$	22
465977	n/a	n/a	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}T_{ds}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{es}^mC_{es}^mC_e$	22
483706	n/a	n/a	$G_{es}T_{es}^mC_{es}T_{ds}G_{ds}T_{ds}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
1183062	2	5'-(R)-Me	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}G_{[R]}T_{[R]}-_{\mu}sT_{ds}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
1183059	2	5'-(S)-Me	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}G_{[S]}T_{[S]}-_{\mu}sT_{ds}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
1183065	2	5'-(R)-allyl	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}G_{[R]}T_{[R]}-_{\gamma}sT_{ds}G_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
1183063	3	5'-(R)-Me	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}T_{[R]}-_{\mu}sG_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
1183060	3	5'-(S)-Me	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}T_{[S]}-_{\mu}sG_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
1183066	3	5'-(R)-allyl	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}T_{[R]}-_{\gamma}sG_{ds}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
1183064	4	5'-(R)-Me	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}T_{ds}G_{[R]}T_{[R]}-_{\mu}s^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22

1183061	4	5'-(S)-Me	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}T_{ds}G_{[(S)-\mu]s}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22
1183067	4	5'-(R)-allyl	$G_{ks}T_{ks}^mC_{ks}T_{ds}G_{ds}T_{ds}G_{[(R)-\gamma]s}^mC_{ds}A_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ks}^mC_{ks}^mC_k$	22

A subscript “d” indicates an unmodified, 2'-β-D-deoxyribosyl sugar moiety. A subscript “k” indicates a cEt.

A subscript “s” indicates a phosphorothioate internucleoside linkage. A subscript “[μ]” indicates a 5'-(R,S)-

Me-β-D-2'-deoxyribosyl sugar moiety. A subscript “[(R)-μ]” indicates a 5'-(R)-Me-β-D-2'-deoxyribosyl

sugar moiety. A subscript “[(S)-μ]” indicates a 5'-(S)-Me-β-D-2'-deoxyribosyl sugar moiety. A subscript

5 “[γ]” indicates a 5'-(R,S)-allyl-β-D-2'-deoxyribosyl sugar moiety. A subscript “[(R)-γ]” indicates a 5'-(R)-

allyl-β-D-2'-deoxyribosyl sugar moiety. A subscript “[(S)-γ]” indicates a 5'-(S)-allyl-β-D-2'-deoxyribosyl

sugar moiety. A subscript “[ε]” indicates a 5'-(R,S)-ethyl-β-D-2'-deoxyribosyl sugar moiety. A subscript

“[(R)-ε]” indicates a 5'-(R)-ethyl-β-D-2'-deoxyribosyl sugar moiety. A subscript “[(S)-ε]” indicates a 5'-(S)-

ethyl-β-D-2'-deoxyribosyl sugar moiety.

10 Experimental Procedures & Results

For the *in vivo* activity and toxicity study below, two BALB/C mice per group were administered 33 or 100 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. Expression levels of FXI were measured by RT-qPCR using primer probe set RTS2898 (forward sequence:

ACATGACAGGCGGATCTCT, SEQ ID NO: 78; reverse sequence:

15 TCTAGGTTACGTACACATCTTTGC, SEQ ID NO: 79; probe sequence:

TTCCTTCAAGCAATGCCCTCAGCAAT, SEQ ID NO: 80). Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

Table 10 Toxicity and activity of modified oligonucleotides complementary Factor XI

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	FXI mRNA (% control) 33 mg/kg	FXI mRNA (% control) 100 mg/kg	ALT (IU/L) at 33 mg/kg	ALT (IU/L) at 100mg/kg
464917	n/a	n/a	11	0.9	7511	31066*
443919	n/a	n/a	27	7.9	24	57
465977	n/a	n/a	5.6	n.d.	11575	death
483706	n/a	n/a	20.3	4.9	52	732
1183062	2	5'-(R)-Me	5.7	n.d.	12083	death
1183059	2	5'-(S)-Me	4.0	2.4	662	7894
1183065	2	5'-(R)-allyl	5.2	1.5	4707	24000
1183063	3	5'-(R)-Me	4.9	2.0	2458	14891
1183060	3	5'-(S)-Me	8.2	2.1	8710	23995

1183066	3	5'-(R)-allyl	5.1	2.0	524	6473
1183064	4	5'-(R)-Me	4.0	1.5	4357	11342
1183061	4	5'-(S)-Me	4.1	2.3	1891	20557
1183067	4	5'-(R)-allyl	11	3.6	184	2536

*One of two mice died

For the *in vitro* study reported in the tables below, 3T3-L1 cells were electroporated with 27 nM, 80 nM, 250 nM, 740 nM, 2, 222 nM, 6,667 nM, or 20,000 nM of modified oligonucleotide and levels of P21 and Gadd45a were measured by RT-qPCR as described in Example 1 above. Caspase-3 and caspase-7 activation was measured using the Caspase-Glo® 3/7 Assay System (G8090, Promega). Levels of caspase activation correlate with apoptotic cell death.

Table 10b *in vitro* P21 Expression in 3T3-L1 cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of P21 mRNA (% Control)						
464917	100	100	116	139	216	496	1232
443919	122	116	99	86	114	105	184
465977	104	117	103	106	139	220	578
483706	105	92	116	125	135	165	376

Table 10c *in vitro* Gadd45a Expression in 3T3-L1 cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of Gadd45a mRNA (% Control)						
464917	89	93	106	113	157	324	599
443919	163	166	147	129	145	126	178
465977	101	110	119	100	135	150	334
483706	89	133	185	194	197	217	459

Table 10d *in vitro* Caspase Activation in 3T3-L1 cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Caspase Activation						
464917	4388	4428	4656	6208	20274	48106	82324
443919	4200	4802	4986	4605	4714	4552	9385
465977	4017	4133	4253	4465	6983	34156	61008
483706	4155	4595	4020	4476	4585	6565	16766

For the *in vivo* study in the table below, three BALB/C mice per group were administered 11 or 33 mg/kg of modified oligonucleotide and sacrificed after 72 hours.

Table 10e *in vivo* Activity and toxicity of modified oligonucleotides complementary FXI

Compound ID	2' sugar modification of nucleosides in 5' region	2' sugar modification of nucleosides in 3' region	P21 mRNA @ 33 mg/kg (% control)	Tnfrsf10b mRNA @ 33 mg/kg (% control)	FXI mRNA @ 33 mg/kg (% control)	ALT@33 mg/kg
464917	kkk	kkk	24040	108884	1.4	18316
443919	kkk	eee	109	110	16	68
465977	eee	kkk	n.d.	n.d.	n.d.	death
483706	eee	eee	1195	733	2.7	1424

Example 5 Effect of position-specific 2'-modifications on *in vitro* activity and *in vivo* liver toxicity of modified oligonucleotides complementary to PTEN

- 5 Modified oligonucleotides were synthesized with 2' modifications as indicated in the table below. These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking a modified nucleoside in the central region, a 3-10-3 cEt modified oligonucleotide, containing three cEt nucleosides in each of the 5' and 3' regions and 10 unmodified DNA nucleobases in the central region. The compounds in the table below are 100% complementary to mouse PTEN, GENBANK NC_000085.6, truncated from 32755001 to 32829000 (SEQ ID NO: 3), at position 2635 to 2650.

Table 11 Modified oligonucleotides complementary to PTEN

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	Chemistry Notation (5'-3')	SEQ ID NO
482050	n/a	n/a	A _{ks} T _{ks} ^m C _{ks} A _{ds} T _{ds} G _{ds} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	24
982036	1	2'-OMe	A _{ks} T _{ks} ^m C _{ks} A _{ms} T _{ds} G _{ds} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	24
982037	2	2'-OMe	A _{ks} T _{ks} ^m C _{ks} A _{ds} U _{ms} G _{ds} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	25
985297	2	2'-MOE	A _{ks} T _{ks} ^m C _{ks} A _{ds} T _{es} G _{ds} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	24
985298	2	cEt	A _{ks} T _{ks} ^m C _{ks} A _{ds} T _{ks} G _{ds} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	24
1011277	2	2'-FANA	A _{ks} T _{ks} ^m C _{ks} A _{ds} U _{(FANA)s} G _{ds} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	25
985296	2	2'-ribo-F	A _{ks} T _{ks} ^m C _{ks} A _{ds} U _{fs} G _{ds} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	25
982038	3	2'-OMe	A _{ks} T _{ks} ^m C _{ks} A _{ds} T _{ds} G _{ms} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	24
985301	3	2'-MOE	A _{ks} T _{ks} ^m C _{ks} A _{ds} T _{ds} G _{es} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	24
985302	3	cEt	A _{ks} T _{ks} ^m C _{ks} A _{ds} T _{ds} G _{ks} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	24
1011278	3	2'-FANA	A _{ks} T _{ks} ^m C _{ks} A _{ds} T _{ds} G _{(FANA)s} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	24
985300	3	2'-ribo-F	A _{ks} T _{ks} ^m C _{ks} A _{ds} T _{ds} G _{fs} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	24

- A subscript "d" indicates an unmodified, 2'-β-D-deoxyribosyl sugar moiety. A subscript "e" indicates a 2'-MOE-β-D-ribofuranosyl sugar moiety. A subscript "m" indicates a 2'-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript "k" indicates a cEt. A subscript "s" indicates a phosphorothioate internucleoside linkage. A subscript "f" indicates a 2'-F-β-D-2'-deoxyribosyl sugar moiety. A subscript "(FANA)" indicates a 2'-F-β-D-arabinofuranosyl modified sugar moiety. A superscript "m" before a C indicates 5-methyl Cytosine.

For *in vitro* activity studies, 3T3-L1 cells were plated and transfected with 16, 80, 400, 2,000, and 10,000 nM modified oligonucleotide by electroporation. mRNA was harvested and analyzed by RT-qPCR.

PTEN mRNA was detected and RAPTOR mRNA was detected.

For *in vivo* toxicity studies, 2-4 BALB/C mice per group were administered 200 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

Table 12 Activity and toxicity of modified oligonucleotides complementary PTEN

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	PTEN IC ₅₀ (μM)	RAPTOR IC ₅₀ (μM)	ALT @ 200 mg/kg (IU/L)
482050	n/a	n/a	3.9	2.4	2458
982037	2	2'-OMe	2.7	10	133
985297	2	2'-MOE	3	9.4	242
985298	2	cEt	1.4	2.1	890
1011277	2	2'-FANA	3.1	3.5	1488
985296	2	2'-ribo-F	2.2	6	1884
982038	3	2'-OMe	1.8	3.7	327
985301	3	2'-MOE	1.5	5	261
985302	3	cEt	2	3.3	87
1011278	3	2'-FANA	1.7	1.1	14073
985300	3	2'-ribo-F	2.2	6	107

For the *in vitro* study reported in the tables below, 3T3-L1 cells were transfected with 27, 80, 250, 740, 2, 222, 6,667, or 20,000 nM of modified oligonucleotide by electroporation and levels of P21 and Gadd45a were measured by RT-qPCR as described in example 1.

Table 12b *in vitro* P21 Expression

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of P21 mRNA (% Control)						
482050	111	107	113	124	113	130	157
982036	92	95	93	95	91	110	162
982037	112	108	99	105	112	120	113
982038	108	105	111	111	114	99	108

Table 12c *in vitro* Gadd45a Expression

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of Gadd45a mRNA (% Control)						
482050	65	64	70	67	79	176	276
982036	81	62	62	71	113	189	467
982037	107	90	79	75	79	100	165
982038	110	112	104	131	118	129	266

Example 6 Effect of position-specific 2'-modifications on in vitro activity and in vivo liver toxicity of modified oligonucleotides complementary to SOD1

Modified oligonucleotides were synthesized with 2' modifications as indicated in the table below. These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking a modified nucleoside in the central region, a 3-10-3 cEt modified oligonucleotide, containing three cEt nucleosides in each of the 5' and 3' regions and 10 unmodified DNA nucleobases in the central region. The compounds in the table below are 100% complementary to mouse SOD1, GENBANK NT_039625.7 truncated from 24924000 to 24933000 (SEQ ID NO: 4), at position 5685 to 5880.

Table 13 Modified oligonucleotides complementary to SOD1

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	Chemistry Notation (5'-3')	SEQ ID NO
508031	n/a	n/a	T _{ks} G _{ks} A _{ks} G _{ds} G _{ds} T _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	26
508034	n/a	n/a	T _{ks} G _{ks} A _{ks} G _{ds} G _{ds} T _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{es} G _{es} G _e	26
508037	n/a	n/a	T _{es} G _{es} A _{es} G _{ds} G _{ds} T _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	26
529933	n/a	n/a	T _{es} G _{es} A _{es} G _{ds} G _{ds} T _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{es} G _{es} G _e	26
895154	1	2'-OMe	T _{ks} G _{ks} A _{ks} G _{ms} G _{ds} T _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	26
895155	2	2'-OMe	T _{ks} G _{ks} A _{ks} G _{ds} G _{ms} T _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	26
985305	2	2'-MOE	T _{ks} G _{ks} A _{ks} G _{ds} G _{es} T _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	26
985306	2	cEt	T _{ks} G _{ks} A _{ks} G _{ds} G _{ks} T _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	26
1011279	2	2'-FANA	T _{ks} G _{ks} A _{ks} G _{ds} G(FANA) _s T _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	26
985304	2	2'-ribo-F	T _{ks} G _{ks} A _{ks} G _{ds} G _{fs} T _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	26
895156	3	2'-OMe	T _{ks} G _{ks} A _{ks} G _{ds} G _{ds} U _{ms} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	27
985309	3	2'-MOE	T _{ks} G _{ks} A _{ks} G _{ds} G _{ds} T _{es} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	26
985310	3	cEt	T _{ks} G _{ks} A _{ks} G _{ds} G _{ds} T _{ks} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	26
1011280	3	2'-FANA	T _{ks} G _{ks} A _{ks} G _{ds} G _{ds} U(FANA) _s ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	27
985308	3	2'-ribo-F	T _{ks} G _{ks} A _{ks} G _{ds} G _{ds} U _{fs} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	27

A subscript “d” indicates an unmodified, 2’-β-D-deoxyribosyl sugar moiety. A subscript “e” indicates a 2’-MOE-β-D-ribofuranosyl sugar moiety. A subscript “m” indicates a 2’-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A subscript “f” indicates a 2’-F-β-D-2’-deoxyribosyl sugar moiety. A subscript “(FANA)” indicates a 2’-F-β-D-arabinofuranosyl modified sugar moiety. A superscript “m” before a C indicates 5-methyl Cytosine.

For *in vitro* activity studies, 3T3-L1 cells were plated at 20,000 cells/well and transfected with 16, 80, 400, 2,000, and 10,000 nM modified oligonucleotide by electroporation. mRNA was harvested and analyzed by RT-qPCR. SOD1 mRNA was detected using primer probe set RTS3025 (forward sequence: TTTTTTGCGCGGTCCTTTC (SEQ ID NO: 119); reverse sequence: GAGGGACCAGAGAGAGCAAGAC (SEQ ID NO: 120); probe sequence: CGCCTTCCGTCCGTCGGCT (SEQ ID NO: 121)) and RAPTOR mRNA was detected as in Example 1 above.

For the *in vivo* toxicity study in the table below, two BALB/C mice per modified oligonucleotide were administered 150 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

Table 14 Activity and toxicity of modified oligonucleotides complementary SOD1

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	SOD1 IC ₅₀ (μM)	RAPTOR IC ₅₀ (μM)	ALT @ 150 mg/kg (IU/L)
508031	n/a	n/a	0.03	0.46	21934
895155	2	2’-OMe	0.04	1	112
985305	2	2’-MOE	0.21	n/a	63
985306	2	cEt	1.61	10.2	826
1011279	2	2’-FANA	0.28	1	death
985304	2	2’-ribo-F	0.04	0.8	182
895156	3	2’-OMe	0.48	4.5	1371
985309	3	2’-MOE	0.61	6	1629
985310	3	cEt	1.46	11.9	178
1011280	3	2’-FANA	0.6	4	death
985308	3	2’-ribo-F	0.24	0.92	887

For *in vitro* activity studies, 3T3-L1 cells were plated at 20,000 cells/well and transfected with 30 nM, 80 nM, 250 nM, 740 nM, 2,222 nM, 6,667 nM, or 20,000 nM modified oligonucleotide by electroporation. P21 and Gadd45a mRNA were analyzed as in Example 1 above and caspase activation was measured as in Example 4 above. Results were normalized with Ribogreen® and are presented relative to the average of untreated control cells.

Table 14b *in vitro* P21 Expression

Compound ID	30 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
Expression level of P21 mRNA (% Control)							
508031	104	96	104	91	99	180	366
895154	94	117	85	93	105	159	181
895155	98	110	92	88	88	101	137
895156	95	104	74	97	125	139	283

Table 14c *in vitro* Gadd45a Expression

Compound ID	30 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
Expression level of Gadd45a mRNA (% Control)							
508031	103	99	113	103	139	564	844
895154	110	125	114	106	130	297	669
895155	129	139	120	126	122	145	340
895156	122	132	94	125	223	490	856

Table 14d *in vitro* Caspase Activation in 3T3-L1 cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
Caspase Activation							
508031	10871	11667	12107	14458	46619	101512	177873
895154	11681	11503	11656	11422	17167	70398	124774
895155	11669	11005	11479	11156	12487	20199	77630
895156	11980	10646	10616	11178	24226	72844	153302

For the *in vivo* toxicity study in the table below, three BALB/C mice per modified oligonucleotide were administered 100 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT and AST were measured using an automated clinical chemistry analyzer. Increased ALT and AST are indicative of acute liver toxicity.

For the *in vivo* study in the table below, three BALB/C mice per group were administered 33 or 100 mg/kg of modified oligonucleotide and sacrificed after 24 hours.

Table 15 Activity and toxicity of modified oligonucleotides complementary SOD1

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	P21 mRNA @ 100 mg/kg (% control)	Tnfrsf10b mRNA @ 100 mg/kg (% control)	Gadd45a mRNA @ 100 mg/kg (% control)	SOD1 mRNA @ 100 mg/kg (% control)
508031	n/a	n/a	823	399	321	36
895154	1	2'-OMe	125	176	345	56

895155	2	2'-OMe	67	147	365	75
895156	3	2'-OMe	538	351	525	51

For the *in vivo* study in the table below, three BALB/C mice per group were administered 33 or 100 mg/kg of modified oligonucleotide and sacrificed after 72 hours.

Table 15b Activity and toxicity of modified oligonucleotides complementary SOD1

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	P21 mRNA @ 100 mg/kg (% control)	Tnfrsf10b mRNA @ 100 mg/kg (% control)	Gadd45a mRNA @ 100 mg/kg (% control)	SOD1 mRNA @ 100 mg/kg (% control)	ALT @ 100 mg/kg (IU/L)
508031	n/a	n/a	6007	9032	392	13	16,317
895154	1	2'-OMe	561	1042	129	19	206
895155	2	2'-OMe	165	233	18	26	41
895156	3	2'-OMe	3218	8189	190	9.6	1,242

5

Table 15c Activity and toxicity of modified oligonucleotides complementary to SOD1

Compound ID	2' sugar modification in 5' region	2' sugar modification in 3' region	P21 mRNA @ 100 mg/kg (% control)	Tnfrsf10b mRNA @ 100 mg/kg (% control)	SOD1 mRNA @ 100 mg/kg (% control)	ALT @ 100 mg/kg (IU/L)
508031	kkk	kkk	3478	4593	9	14526
508034	kkk	eee	11365	7288	3	22396*
508037	eee	kkk	130	225	17	20
529933	eee	eee	90	142	18	11

*2/3 animals were found dead

For the *in vitro* study reported in the tables below, 3T3-L1 cells were electroporated with 27 nM, 80 nM, 250 nM, 740 nM, 2, 222 nM, 6,667 nM, or 20,000 nM of modified oligonucleotide and levels of P21 and Gadd45a were measured by RT-qPCR as described in Example 1 above. Caspase-3 and caspase-7 activation was measured using the Caspase-Glo® 3/7 Assay System (G8090, Promega). Levels of caspase activation correlate with apoptotic cell death.

Table 15d *in vitro* Caspase Activation in 3T3-L1 cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Caspase Activation						
508031	5969	6550	5986	8376	22499	56695	91450
508034	5652	5258	6555	7590	17098	49473	73813
508037	4027	4000	4222	4104	4208	3899	7869
529933	5904	5393	5595	5677	4772	4914	11918

Table 15e *in vitro* P21 mRNA in 3T3-L1 cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of P21 mRNA (% Control)						
508031	132	116	119	108	121	185	692
508034	119	115	120	117	125	174	344
508037	120	119	121	121	117	122	149
529933	106	110	101	120	108	108	100

Table 15f *in vitro* Gadd45a mRNA in 3T3-L1 cells

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of Gadd45a mRNA (% Control)						
508031	202	132	198	137	215	570	1046
508034	132	132	167	161	185	475	842
508037	175	164	181	175	195	215	416
529933	136	136	148	167	169	130	155

5

For the *in vivo* dose-response study in the table below, three BALB/C mice per group were administered 3.7, 11.1, 33, or 100 mg/kg 508031 or 3.7, 11.1, 33, 100, or 300 mg/kg 895155 by subcutaneous injection and sacrificed. Levels of Gadd45a, P21, and Tnfrsf1b mRNA were measured by RT-PCR as described in Example 1.

10

Table 15g Activity and toxicity of modified oligonucleotides complementary to SOD1

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	ED ₅₀ (mg/kg)
508031	n/a	n/a	13.12
895155	2	2'-OMe	38.8

Table 15h *In Vivo* Dose-response of Tnfrsf10b mRNA upon treatment with modified oligonucleotides complementary to SOD1

Compound ID	3.7 mg/kg	11.1 mg/kg	33 mg/kg	100 mg/kg	300 mg/kg
	Expression level of Tnfrsf10b mRNA (% Control)				
508031	99	276	3443	6446	n/a
895155	81	105	115	193	2215

15

Table 15i *In Vivo* Dose-response of P21 mRNA upon treatment with modified oligonucleotides complementary to SOD1

Compound ID	3.7 mg/kg	11.1 mg/kg	33 mg/kg	100 mg/kg	300 mg/kg
	Expression level of P21 mRNA (% Control)				
508031	163	222	1867	3788	n/a
895155	162	167	167	199	1467

Example 7 Effect of position-specific 2'-modifications on in vitro activity and in vivo liver toxicity of modified oligonucleotides complementary to SRB1

5 Modified oligonucleotides were synthesized with 2' modifications as indicated in the table below. These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking a modified nucleoside in the central region, a 3-10-3 cEt modified oligonucleotide, containing three cEt nucleosides in each of the 5' and 3' regions and 10 unmodified DNA nucleosides in the central region. Each internucleoside linkage is a phosphorothioate. The compounds in the table below are 100% complementary
 10 to the complement of mouse SRB1, GENBANK NT_039313.7 truncated from 566000 to 632000 (SEQ ID NO: 5), at position 64840 to 64855.

Table 16 Modified oligonucleotides complementary to SRB1

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	Chemistry Notation (5'-3')	SEQ ID NO
449093	n/a	n/a	T _{ks} T _{ks} ^m C _{ks} A _{ds} G _{ds} T _{ds} ^m C _{ds} A _{ds} T _{ds} G _{ds} A _{ds} ^m C _{ds} T _{ds} T _{ks} ^m C _{ks} ^m C _k	28
982030	1	2'-OMe	T _{ks} T _{ks} ^m C _{ks} A _{ms} G _{ds} T _{ds} ^m C _{ds} A _{ds} T _{ds} G _{ds} A _{ds} ^m C _{ds} T _{ds} T _{ks} ^m C _{ks} ^m C _k	28
982031	2	2'-OMe	T _{ks} T _{ks} ^m C _{ks} A _{ds} G _{ms} T _{ds} ^m C _{ds} A _{ds} T _{ds} G _{ds} A _{ds} ^m C _{ds} T _{ds} T _{ks} ^m C _{ks} ^m C _k	28
1042573	2	2'-MOE	T _{ks} T _{ks} ^m C _{ks} A _{ds} G _{es} T _{ds} ^m C _{ds} A _{ds} T _{ds} G _{ds} A _{ds} ^m C _{ds} T _{ds} T _{ks} ^m C _{ks} ^m C _k	28
1042574	2	cEt	T _{ks} T _{ks} ^m C _{ks} A _{ds} G _{ks} T _{ds} ^m C _{ds} A _{ds} T _{ds} G _{ds} A _{ds} ^m C _{ds} T _{ds} T _{ks} ^m C _{ks} ^m C _k	28
1042575	2	2'-FANA	T _{ks} T _{ks} ^m C _{ks} A _{ds} G _{(FANA)s} T _{ds} ^m C _{ds} A _{ds} T _{ds} G _{ds} A _{ds} ^m C _{ds} T _{ds} T _{ks} ^m C _{ks} ^m C _k	28
1042572	2	2'-ribo-F	T _{ks} T _{ks} ^m C _{ks} A _{ds} G _{fs} T _{ds} ^m C _{ds} A _{ds} T _{ds} G _{ds} A _{ds} ^m C _{ds} T _{ds} T _{ks} ^m C _{ks} ^m C _k	28
982032	3	2'-OMe	T _{ks} T _{ks} ^m C _{ks} A _{ds} G _{ds} U _{ms} ^m C _{ds} A _{ds} T _{ds} G _{ds} A _{ds} ^m C _{ds} T _{ds} T _{ks} ^m C _{ks} ^m C _k	29
1042577	3	2'-MOE	T _{ks} T _{ks} ^m C _{ks} A _{ds} G _{ds} T _{es} ^m C _{ds} A _{ds} T _{ds} G _{ds} A _{ds} ^m C _{ds} T _{ds} T _{ks} ^m C _{ks} ^m C _k	28
1042578	3	cEt	T _{ks} T _{ks} ^m C _{ks} A _{ds} G _{ds} T _{ks} ^m C _{ds} A _{ds} T _{ds} G _{ds} A _{ds} ^m C _{ds} T _{ds} T _{ks} ^m C _{ks} ^m C _k	28
1042580	3	2'-FANA	T _{ks} T _{ks} ^m C _{ks} A _{ds} G _{ds} U _{(FANA)s} ^m C _{ds} A _{ds} T _{ds} G _{ds} A _{ds} ^m C _{ds} T _{ds} T _{ks} ^m C _{ks} ^m C _k	29
1042576	3	2'-ribo-F	T _{ks} T _{ks} ^m C _{ks} A _{ds} G _{ds} U _{fs} ^m C _{ds} A _{ds} T _{ds} G _{ds} A _{ds} ^m C _{ds} T _{ds} T _{ks} ^m C _{ks} ^m C _k	29

A subscript "d" indicates an unmodified, 2'-β-D-deoxyribosyl sugar moiety. A subscript "e" indicates a 2'-MOE-β-D-ribofuranosyl sugar moiety. A subscript "m" indicates a 2'-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript "k" indicates a cEt. A subscript "s" indicates a phosphorothioate internucleoside linkage.
 15 A subscript "f" indicates a 2'-F-β-D-2'-deoxyribosyl sugar moiety. A subscript "(FANA)" indicates a 2'-F-β-D-arabinofuranosyl modified sugar moiety. A superscript "m" before a C indicates 5-methyl Cytosine.

For *in vivo* toxicity studies, two BALB/C mice per modified oligonucleotide was administered 150 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

5 **Table 17 Toxicity of modified oligonucleotides complementary SRB1**

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	ALT @ 150 mg/kg (IU/L)
449093	n/a	n/a	2009
982031	2	2'-OMe	2168
1042573	2	2'-MOE	3368
1042574	2	cEt	1972
1042575	2	2'-FANA	16335
1042572	2	2'-ribo-F	3563
982032	3	2'-OMe	1630
1042577	3	2'-MOE	2965
1042578	3	cEt	3650
1042580	3	2'-FANA	6622
1042576	3	2'-ribo-F	3521

For the *in vitro* study reported in the tables below, 3T3-L1 cells were transfected with 27, 80, 250, 740, 2, 222, 6,667, or 20,000 nM of modified oligonucleotide by electroporation and levels of P21 and Gadd45a were measured by RT-qPCR as described in example 1.

10

Table 17b *in vitro* P21 Expression

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of P21 mRNA (% Control)						
449093	99	107	101	104	175	212	255
982030	102	100	108	125	172	215	288
982031	115	116	114	137	174	204	330
982032	107	97	106	112	134	183	224

Table 17c *in vitro* Gadd45a Expression

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of Gadd45a mRNA (% Control)						
449093	124	105	120	105	122	215	350
982030	105	103	107	104	126	249	551
982031	88	79	86	80	95	182	447
982032	82	69	73	76	89	172	366

15

Example 8 Effect of inosine substitution on *in vitro* activity and *in vivo* liver toxicity of modified oligonucleotides complementary to CXCL12 and Factor XI

5

Table 18 Modified oligonucleotides

Compound ID	position of altered nucleotide in central region	nucleobase of altered nucleotide	Chemistry Notation (5'-3')	SEQ ID NO
1061955	2	Inosine	G _{ks} ^m C _{ks} A _{ks} T _{ds} I _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	30
1154233	2	Inosine	G _{ks} T _{ks} ^m C _{ks} T _{ds} I _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} T _{ks} ^m C _{ks} ^m C _k	40

A subscript “d” indicates a nucleoside comprising an unmodified, 2'-β-D-deoxyribose sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before C indicates 5-methyl Cytosine. I indicates inosine.

10

For *in vitro* activity studies, 3T3-L1 cells were plated at 20,000 cells/well and transfected with 27 nM, 80 nM, 250 nM, 740 nM, 2,222 nM, 6,667 nM, or 20,000 nM modified oligonucleotide by electroporation. mRNA was harvested and analyzed by RT-qPCR. CXCL12 mRNA and P21 mRNA were analyzed as in example 1.

15

Caspase-3 and caspase-7 activation was measured using the Caspase-Glo® 3/7 Assay System (G8090, Promega). Levels of caspase activation correlate with apoptotic cell death. Results are presented relative to the caspase activation in control cells not treated with modified oligonucleotide.

20

For the *in vivo* activity and toxicity study in the table below, two BALB/C mice per group were administered 16.7, 50, or 150 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

Table 19 Effect of Inosine on activity and toxicity

Compound ID	position of altered nucleotide in central region	nucleobase of altered nucleotide	CXCL12 IC ₅₀ (μM)	<i>in vivo</i> CXCL12 ED ₅₀ (mg/kg)	ALT @ 16.7 mg/kg (IU/L)	ALT @ 50 mg/kg (IU/L)	ALT @ 150mg/kg (IU/L)
558807*	n/a	n/a	0.2	1.7	209	death	death
1061955	2	Inosine	0.3	4.2	20.5	26	86

*Data presented above in Example 4

Table 19b *in vitro* P21 Expression

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of P21 mRNA (% Control)						
558807	102	104	105	101	133	191	301
1061955	117	116	106	104	104	121	149

Table 19c *in vitro* Caspase Activation

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Relative Caspase Activation (% Control)						
558807	135	110	131	115	147	476	462
1061955	75	81	134	120	121	162	170

For the study in the tables below, two BALB/C mice per group were administered 1.8 mg/kg, 5.5 mg/kg, 16.7 mg/kg, 50 mg/kg, or 150 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed after 72 hours. 558807 was administered at 1.8 mg/kg, 5.5 mg/kg, 16.7 mg/kg due to acute toxicity at higher doses. Expression levels of Gadd45a, Tnfrsf10b, and P21 mRNA were measured as described in Example 1. Data for 558807 was also presented in Example 2, Tables 6b-6d.

Table 19d *In Vivo* Dose-response of Gadd45a mRNA upon treatment with modified oligonucleotides complementary to CXCL12

Compound ID	1.8 mg/kg	5.5 mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg
	Expression level of Gadd45a mRNA (% Control)				
558807	122	211	278	n/a	n/a
1061955	109	86	93	84	123

Table 19e *In Vivo* Dose-response of Tnfrsf10b mRNA upon treatment with modified oligonucleotides complementary to CXCL12

Compound ID	1.8 mg/kg	5.5 mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg
	Expression level of Tnfrsf10b mRNA (% Control)				
558807	160	166	271	n/a	n/a
1061955	158	77	126	134	192

Table 19f *In Vivo* Dose-response of P21 mRNA upon treatment with modified oligonucleotides complementary to CXCL12

Compound ID	1.8 mg/kg	5.5 mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg
	Expression level of P21 mRNA (% Control)				
558807	173	148	1456	n/a	n/a
1061955	36	8.6	16	33	72

For the *in vivo* activity and toxicity study in the table below, two BALB/C mice per group were administered 33 or 100 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours

later. Four mice were administered an injection of saline as a control. FXI mRNA expression was measured by RT-qPCR as described in Example 3. Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

Table 19g Effect of Inosine on activity and toxicity

Compound ID	position of altered nucleotide in central region	nucleobase of altered nucleotide	FXI mRNA @ 33 mg/kg (% control)	FXI mRNA @ 100 mg/kg (% control)	ALT @ 33 mg/kg (IU/L)	ALT @ 100 mg/kg (IU/L)
464917*	n/a	n/a	10.9	0.9	7511	31066
1154233	2	Inosine	5.0	1.2	315	4553

5 *Data presented above in Example 4

Example 9 Effect of position-specific nucleobase substitutions on in vitro activity and in vivo liver toxicity of modified oligonucleotides complementary to CXCL12

Modified oligonucleotides containing nucleobase modifications at various positions were synthesized. These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking a modified nucleoside in the central region, a 3-10-3 cEt modified oligonucleotide, containing three cEt nucleosides in each of the 5' and 3' regions and 10 unmodified DNA nucleobases in the central region. The compounds in the table below are 100% complementary to mouse CXCL12, GENBANK NT_039353.7 truncated from 69430515 to 69445350 (SEQ ID NO: 1), at position 6877 to 6892.

15 Nucleobase modifications:

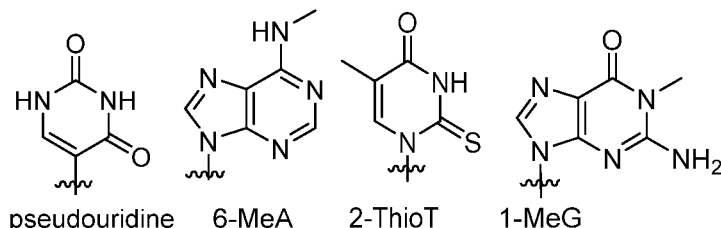


Table 20 Modified oligonucleotides

Compound ID	position of altered nucleotide in central region	nucleobase of altered nucleotide	Chemistry Notation (5'-3')	SEQ ID NO
1076587	2	6-MeA, 2'-OH	G _{ks} ^m C _{ks} A _{ks} T _{ds} ^{m6} A _{rs} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	31
1076588	3	6-MeA, 2'-OH	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} ^{m6} A _{rs} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	32
1069852	2	pseudouridine, 2'-OH	G _{ks} ^m C _{ks} A _{ks} T _{ds} Ψ _{rs} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	33
1061328	3	pseudouridine, 2'-OH	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} Ψ _{rs} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	34
1016673	1	pseudouridine, 2'-H	G _{ks} ^m C _{ks} A _{ks} Ψ _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	35
1004684	3	pseudouridine, 2'-H	G _{ks} ^m C _{ks} A _{ks} T _{ds} T _{ds} Ψ _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	36
1004685	4	pseudouridine, 2'-H	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} Ψ _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	37

1016674	6	pseudouridine, 2'-H	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} ^m C _{ds} T _{ds} Ψ _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	38
863089	1	2-thioT	G _{ks} ^m C _{ks} A _{ks} ^s T _{ds} G _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
863090	3	2-thioT	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} ^s T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
863091	4	2-thioT	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} ^s T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
863092	6	2-thioT	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} ^m C _{ds} ^s T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
1061964	2	1-MeG, 2'-OH	G _{ks} ^m C _{ks} A _{ks} T _{ds} ^m G _{rs} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18

A subscript “d” indicates an unmodified, 2'-β-D-deoxyribose sugar moiety. A subscript “r” indicates an unmodified, β-D-ribofuranosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before C indicates 5-methyl Cytosine. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a nucleobase indicator indicates that the nucleobase has a 5-methyl group, such as methyl Cytosine, methyl Adenosine, or methyl Guanosine. A superscript “m6” before a A indicates 6-methyl Adenosine. Ψ represents the nucleobase pseudouridine. ^sT represents the nucleobase 2-thiothymidine.

For *in vitro* activity studies, 3T3-L1 cells were plated at 20,000 cells/well and transfected with 10 nM, 30 nM, 250 nM, 740 nM, 2,220 nM, 6, 667 nM, or 20,000 nM modified oligonucleotide by electroporation. mRNA was harvested and analyzed by RT-qPCR. CXCL12 and RAPTOR mRNA was analyzed as in Example 1. The *in vitro* caspase assay was performed as described in Example 4.

For the *in vivo* toxicity study in the table below, two BALB/C mice per modified oligonucleotide were administered 50 or 150 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

Table 21 Effect of modified nucleobases on activity and toxicity

Compound ID	position of altered nucleotide in central region	nucleobase of altered nucleotide	CXCL12 IC ₅₀ (nM)	RAPTOR IC ₅₀ (nM)	ALT @ 50mg/kg (IU/L)	ALT @ 150 mg/kg (IU/L)
558807	n/a	n/a	47	800	6303	death
1076587	2	6-MeA	300	18	n.d.	n.d.
1076588	3	6-MeA	1400	13	n.d.	n.d.
1016673	1	pseudouridine, 2'-H	156	3600	n.d.	n.d.
1004684	2	pseudouridine, 2'-H	105	2600	n.d.	n.d.
1004685	3	pseudouridine, 2'-H	157	4100	n.d.	n.d.
1016674	4	pseudouridine, 2'-H	142	3800	n.d.	n.d.
863089	1	2-thioT	48	8800	390	3620
863090	3	2-thioT	130	1400	death	death
863091	4	2-thioT	155	1700	6237	death
863092	6	2-thioT	110	1900	14514.5	death
1061964	2	1-MeG	5200	8600	n.d.	n.d.

Table 21b *in vitro* Caspase Activation

Compound ID	27 nM	80 nM	250 nM	740 nM	2222 nM	6667 nM	20,000 nM
	Relative Caspase Activation (% Control)						
558807	100	100	100	97	110	202	298
1076587	90	86	80	82	81	77	94
1076588	91	91	96	91	96	97	114
1069852	97	87	105	100	89	79	85
1061328	92	95	96	98	102	153	199

Table 21c *in vitro* Caspase Activation

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Relative Caspase Activation (% Control)						
558807	135	110	131	115	147	476	462
1061964	107	142	140	149	135	123	125

5

Table 21d *in vitro* P21 Expression

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of P21 mRNA (% Control)						
558807	102	104	105	101	133	191	301
1061964	121	110	115	90	107	102	90

For *in vivo* activity and toxicity study in the table below, 2 BALB/C mice per group were administered modified oligonucleotide by subcutaneous injection and sacrificed after 72 hours. Compounds were dosed at 0.6, 1.8, 5.5, 16.7, 50 or 150 mg/kg. Tissue were collected and mRNA was isolated and levels of CXCL12 were measured by RT-qPCR with primer probe set RTS2605 as described above. Levels of Gadd45a were analyzed using primer probe set Mm00432802_m1 (ThermoFisher). Levels of P21 were analyzed using primer probe set Mm04207341_m1 (ThermoFisher). Levels of Tnfrsf10b were analyzed using primer probe set Mm00457866_m1 (ThermoFisher). Expression levels were normalized with Ribogreen® and are presented relative to levels in mice treated with PBS.

15

Table 21e *In Vivo* of modified oligonucleotides complementary to CXCL12 containing 2-Thio-T

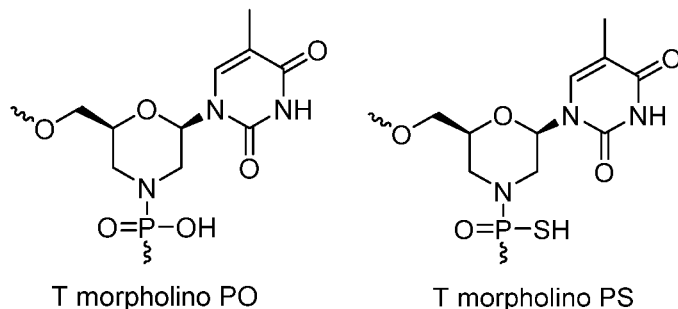
Compound ID	2-Thio-T position in central region	ALT@16.7 mg/kg (IU/L)	ALT @50 mg/kg (IU/L)	ALT @ 150mg/kg (IU/L)
PBS	n/a	27 (@0mg/kg)		
558807	n/a	2002	6303	death
863089	1	60	390	3620
863090	3	4929	death	death
863091	4	1894	6237	death
863092	6	1073	14515	death

Table 21f *In Vivo* Activity of modified oligonucleotides complementary to CXCL12 containing 2-Thio-T

Compound ID	0.6 mg/kg	1.8 mg/kg	5.5 mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg
	Expression level of CXCL12 mRNA (% Control)					
558807	65	34	14	4	7	n.d.
863089	72	51	33	16	14	8
863090	58	31	11	11	0	0
863091	66	28	24	12	12	0
863092	59	42	20	5	6	0

5 Example 10 Effect of position-specific morpholinos on in vitro activity and in vivo liver toxicity of modified oligonucleotides complementary to CXCL12

Modified oligonucleotides containing morpholinos at various positions were synthesized. These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking a modified nucleoside in the central region, a 3-10-3 cEt modified oligonucleotide, containing three cEt nucleosides in each of the 5' and 3' regions and 10 unmodified DNA nucleobases in the central region. The compounds in the table below are 100% complementary to mouse CXCL12, GENBANK NT_039353.7 truncated from 69430515 to 69445350 (SEQ ID NO: 1), at position 6877 to 6892. Morpholino residues replace a full nucleotide, including the internucleoside linkage, and have the structures shown below.



15

Table 22 Modified oligonucleotides

Compound ID	morpholino position in central region	morpholino type	Chemistry Notation (5'-3')	SEQ ID NO
1044689	1	T-PO	$G_{ks}^m C_{ks} A_{ks} (MP^T_o) G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1044690	3	T-PO	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} (MP^T_o) T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1044691	4	T-PO	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} (MP^T_o) T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1044692	6	T-PO	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} (MP^T_o) T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1048416	1	T-PS	$G_{ks}^m C_{ks} A_{ks} (MP^T_s) G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1048417	3	T-PS	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} (MP^T_s) T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18

1048418	4	T-PS	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} (MP^T_s)^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1048419	6	T-PS	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} (MP^T_s)^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18

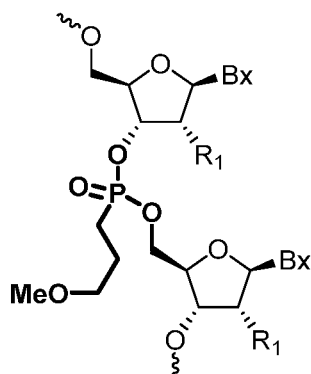
A subscript “d” indicates a nucleoside comprising an unmodified, 2’-β-D-deoxyribosyl sugar moiety. A subscript “r” indicates a nucleoside comprising an unmodified, β-D-ribofuranosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before C indicates 5-methyl Cytosine. A (MP^T_o) represents a phosphate thymidine morpholino, while (MP^T_s) represents a phosphorothioate thymidine morpholino.

Table 22 Effect of morpholinos on in vitro activity and toxicity

Compound ID	morpholino position in central region	morpholino type	CXCL12 IC ₅₀ (nM)	RAPTOR IC ₅₀ (nM)
558807	n/a	n/a	47	800
1044689	1	T-PO	405	>20000
1044690	3	T-PO	182	4100
1044691	4	T-PO	128	4400
1044692	6	T-PO	145	1900
1048416	1	T-PS	333	>20000
1048417	3	T-PS	159	3300
1048418	4	T-PS	134	5200
1048419	6	T-PS	119	1100

Example 11 Effect of position-specific MOP on *in vitro* activity and *in vivo* toxicity of modified oligonucleotides complementary CXCL12, Factor XI, PTEN, and SOD-1

Modified oligonucleotides were synthesized with MOP neutral backbone linkages at specific positions in place of phosphorothioate linkages. These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking the altered nucleotide in the central region, a 3-10-3 cEt modified oligonucleotide, containing three cEt nucleosides in each of the 5’ and 3’ regions and 10 unmodified DNA nucleosides in the central region, and phosphorothioate linkages throughout. The compounds in the table below are 100% complementary to mouse CXCL12, Factor XI, PTEN, or SOD-1, with sequences described above.



MOP
(alkyl phosphonate)

Table 23 Modified oligonucleotides containing MOP linkages

Compound ID	MOP position in central region	Target	Chemistry Notation (5'-3')	SEQ ID NO
766676	1	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{dx} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766677	2	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{dx} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766678	3	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766679	4	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{dx} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766680	5	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{dx} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766681	6	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{dx} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766682	7	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{dx} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766683	8	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{dx} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766684	9	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{dx} A _{ds} T _{ks} T _{ks} A _k	18
766685	10	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{dx} T _{ks} T _{ks} A _k	18
965605	2	FactorXI	G _{ks} T _{ks} ^m C _{ks} T _{ds} G _{dx} T _{ds} G _{ds} ^m C _{ds} A _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} T _{ks} ^m C _{ks} ^m C _k	22
965606	3	FactorXI	G _{ks} T _{ks} ^m C _{ks} T _{ds} G _{ds} T _{dx} G _{ds} ^m C _{ds} A _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} T _{ks} ^m C _{ks} ^m C _k	22
985299	2	PTEN	A _{ks} T _{ks} ^m C _{ks} A _{ds} T _{dx} G _{ds} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	24
985303	3	PTEN	A _{ks} T _{ks} ^m C _{ks} A _{ds} T _{ds} G _{dx} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	24
985307	2	SOD1	T _{ks} G _{ks} A _{ks} G _{ds} G _{dx} T _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	26
985311	3	SOD1	T _{ks} G _{ks} A _{ks} G _{ds} G _{ds} T _{dx} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	26

A subscript “d” indicates an unmodified, 2'-β-D-deoxyribose sugar moiety. A subscript “k” indicates a cEt.

A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates

5-methyl Cytosine. A subscript “x” indicates a MOP or methoxypropyl internucleoside linkage. The position of the internucleoside linkage is designated as the position of the nucleoside that is on the 5' end of the linkage.

For *in vitro* activity studies for compounds complementary to CXCL12, b.END cells were plated at 20,000 cells/well and transfected with 0, 27 nM, 82 nM, 247 nM, 740 nM, 2,220 nM, 6,660 nM or 20,000 nM

antisense oligonucleotide by electroporation. mRNA was harvested and analyzed by RT-qPCR. CXCL12 and raptor mRNA was analyzed as in previous examples.

For *in vitro* activity studies for compounds complementary to Factor XI, PTEN or SOD1, 3T3-L1 cells were plated at 20,000 cells/well and transfected with 0, 27 nM, 82 nM, 247 nM, 740 nM, 2,220 nM, 6,660 nM or 20,000 nM antisense oligonucleotide by electroporation. mRNA was harvested and analyzed by RT-qPCR. Complementary mRNA and raptor mRNA was analyzed as in previous examples.

For the *in vivo* toxicity study in the table below, one or two BALB/C mice per modified oligonucleotide were administered modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

For the *in vivo* activity study in the table below, two to four BALB/C mice per dosing group were administered modified oligonucleotide by subcutaneous injection and sacrificed 24 hours later. Mice were administered 1.9 mg/kg, 5.6 mg/kg, 16.7 mg/kg, 50 mg/kg or 150 mg/kg of compound 558807 or 766676-766685. Mice were administered 6.25 mg/kg, 12.5 mg/kg, 25 mg/kg, 50 mg/kg, or 100 mg/kg modified oligonucleotide for compounds 965605 and 965606. Mice were administered 6.25 mg/kg, 12.5 mg/kg, 25 mg/kg, or 100 mg/kg modified oligonucleotide for 464917. Mice were administered 6.25 mg/kg, 12.5 mg/kg, 25 mg/kg, or 150 mg/kg modified oligonucleotide for 482050. Mice were administered 6.25 mg/kg, 12.5 mg/kg, 25 mg/kg, 50 mg/kg or 150 mg/kg modified oligonucleotide for 985299 and 985303. Mice were administered 12.5 mg/kg, 25 mg/kg, 50 mg/kg or 150 mg/kg modified oligonucleotide for 508031, 985307, and 985311. Two animals were administered an injection of saline as a control.

Table 24 Effect of MOP backbone modifications on activity and toxicity

Compound ID	MOP position in central region	Complementary mRNA	Complementary mRNA IC ₅₀ (μM)	RAPTOR IC ₅₀ (μM)	<i>in vivo</i> Complementary mRNA ED ₅₀ (mg/kg)	ALT @ Max dose* (IU/L)
PBS	n/a	n/a	n/a	n/a	n/a	23
558807	n/a	CXCL12	0.095	1.26	2.9	death
766676	1	CXCL12	0.100	5.8	4.5	7764
766677	2	CXCL12	0.110	>>10	6.8	46
766678	3	CXCL12	0.115	>>10	6.2	44
766679	4	CXCL12	0.080	7.2	5.7	4481
766680	5	CXCL12	0.085	3.5	5.1	9139
766681	6	CXCL12	0.080	3.0	3.6	17846
766682	7	CXCL12	0.090	3.8	4.4	12510
766683	8	CXCL12	0.070	2.2	4.3	death
766684	9	CXCL12	0.090	2.2	3.1	death
766685	10	CXCL12	0.090	2.0	2.1	death
464917	n/a	Factor XI	n.d.	1.6	6.9	33848

965605	2	Factor XI	n.d.	3.7	10.2	3464
965606	3	Factor XI	n.d.	7.7	12.3	1160
482050	n/a	PTEN	3.9	2.4	67	2458
985299	2	PTEN	1.1	4	120	767
985303	3	PTEN	1.7	3.7	194	43
508031	n/a	SOD1	0.03	0.46	63	21934
985307	2	SOD1	0.17	3.6	157	57
985311	3	SOD1	0.78	5.1	173	71

*ALT at 150 mg/kg for CXCL12 oligonucleotides, 100 mg/kg for Factor XI oligonucleotides, 200 mg/kg for PTEN oligonucleotides 985299 and 985303, 100 mg/kg for PTEN oligonucleotide 482050 and 150 mg/kg for SOD1 oligonucleotides 985307 and 985311, and 100 mg/kg for SOD1 oligonucleotide 508031.

**Value represents the average of two independent experiments

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Relative caspase activation in 3T3-L1 cells was determined as described in Example 4.

For the *in vitro* study reported in the tables below, b.END cells were electroporated with 27 nM, 80 nM, 250 nM, 740 nM, 2, 222 nM, 6,667 nM, or 20,000 nM of modified oligonucleotide and levels of P21 were measured by RT-qPCR using primer probe set Mm04207341_m1 (ThermoFisher).

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Selected modified nucleotides described in above were tested for their effect on HeLa cells by microscopy. HeLa cells were transfected by lipofectamine 2000 with 200nM of modified oligonucleotide for 2 hrs and then cellular protein p54nrb was stained by mP54 antibody (Santa Cruz Biotech, sc-376865) and DAPI was used to stain for the nucleus of cells. The number of cells with nucleolar p54nrb and the total number of cells in the images were counted.

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Table 24a Effect of MOP backbone modifications on activity and toxicity

Compound ID	MOP position in central region	Complementary mRNA	Caspase (% mock)	<i>in vitro</i> p21 mRNA (% saline)	% nucleolar p54nrb
558807	n/a	CXCL12	313	243	82
766676	1	CXCL12	243	187	32
766677	2	CXCL12	121	179	25
766678	3	CXCL12	136	180	32
766679	4	CXCL12	240	195	39
766680	5	CXCL12	351	263	86
766681	6	CXCL12	315	309	79
766682	7	CXCL12	345	236	71
766683	8	CXCL12	257	260	91
766684	9	CXCL12	314	247	88
766685	10	CXCL12	308	291	90

For the *in vivo* toxicity study in the table below, two BALB/C mice per dosing group were administered modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. Mice were administered 10 mg/kg, 33 mg/kg, or 100 mg/kg modified oligonucleotide for compounds 464917, 965605, and 965606 and 10 mg/kg, 100 mg/kg, or 200 mg/kg for 482050, 985299, and 985303. Two animals were administered an injection of saline as a control. Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity. Therapeutic index was calculated as the ratio of maximum non-toxic dose (MNTD)/ED₅₀, where ED₅₀ was determined via the *in vivo* activity study reported in the table above.

Table 24b *in vivo* Toxicity improvement for modified oligonucleotides complementary to Factor XI

Compound ID	ALT @ 10 mg/kg	ALT @ 33 mg/kg	ALT @ 100mg/kg	TI (MNTD/ED50)
464917	239	8199	33848	1.4
965605	46	125	3464	3.2
965606	55	77	1160	2.7

Table 24c *in vivo* Toxicity improvement for modified oligonucleotides complementary to PTEN

Compound ID	ALT @ 10 mg/kg	ALT @ 100 mg/kg	ALT @ 200mg/kg	TI (MNTD/ED50)
482050	55	9496	5329	0.15
985299	45	164	767	0.8
985303	33	39	43	1.0

Table 24d *in vivo* Toxicity improvement for modified oligonucleotides complementary to SOD1

Compound ID	ALT @ 50 mg/kg	ALT @ 150 mg/kg	TI (MNTD/ED50)
482050	2189	n.d.	<0.8
985307	n.d.	57	>1.0
985311	n.d.	71	>0.9

Example 12 Effect of position-specific MOP in combination with 2'-modifications

Modified oligonucleotides were synthesized with MOP neutral backbone linkages at specific positions in place of phosphorothioate linkages in combination with 2'-FANA or 2'-OMe modified sugar moieties. These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking a modified nucleoside in the central region, a 3-10-3 cEt modified oligonucleotide, containing three cEt nucleosides in each of the 5' and 3' regions and 10 unmodified DNA nucleosides in the central region, and phosphorothioate linkages throughout. The compounds in the table below are 100% complementary to mouse CXCL12 or SOD1, with sequences as described above.

3'-HPPO-GalNAc refers to the structure below, wherein the phosphate group is attached to the 3'-oxygen atom of the 3' nucleoside:

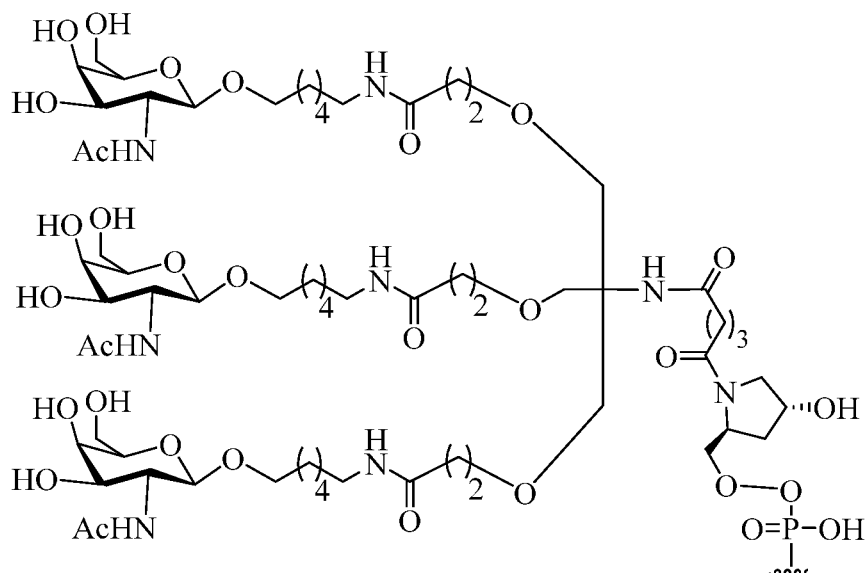


Table 25 Modified oligonucleotides containing MOP linkages and 2'-Modifications

Compound ID	MOP position in central region	2'-altered nucleotide position in central region	sugar modification of 2'-altered nucleotide	Target	Chemistry Notation (5'-3')	SEQ ID NO
1061302	1	1	2'-OMe	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{mx} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}$ $m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1061303	2	2	2'-OMe	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{mx} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}$ $m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1061304	3	3	2'-OMe	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{mx} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}$ $m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1061305	4	4	2'-OMe	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{mx}^m C_{ds} T_{ds}^m C_{ds} A_{ds}$ $m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1061306	1	1	2'-OMe	SOD1	$T_{ks} G_{ks} A_{ks} G_{mx} G_{ds} T_{ds}^m C_{ds}^m C_{ds} T_{ds} G_{ds}^m C_{ds}$ $s A_{ds}^m C_{ds} T_{ks} G_{ks} G_k$	26
1061307	2	2	2'-OMe	SOD1	$T_{ks} G_{ks} A_{ks} G_{ds} G_{mx} T_{ds}^m C_{ds}^m C_{ds} T_{ds} G_{ds}^m C_{ds}$ $s A_{ds}^m C_{ds} T_{ks} G_{ks} G_k$	26
1061308	3	3	2'-OMe	SOD1	$T_{ks} G_{ks} A_{ks} G_{ds} G_{ds} T_{mx}^m C_{ds}^m C_{ds} T_{ds} G_{ds}^m C_{ds}$ $s A_{ds}^m C_{ds} T_{ks} G_{ks} G_k$	26
955900	3	1	2'-FANA	CXCL12	$G_{ks}^m C_{ks} A_{ks} U_{(FANA)s} G_{ds} T_{dx}$ $T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	19
955901	3	2	2'-FANA	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{(FANA)s} T_{dx}$ $T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
955902	3	4	2'-FANA	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx}$ $U_{(FANA)s}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	21
955903	3	5	2'-FANA	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds} C_{(FANA)s} T_{ds}^m C_{ds}$ $A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
955904	3	6	2'-FANA	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds}^m C_{ds} U_{(FANA)s}^m$ $C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	39

955905	3	7	2'-FANA	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds}^m C_{ds} T_{ds} C_{(FANA)s} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
955906	3	8	2'-FANA	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{(FANA)s}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
955907	3	9	2'-FANA	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds} C_{(FANA)s} A_{ds} T_{ks} T_{ks} A_k$	18
955908	3	10	2'-FANA	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{(FANA)s} T_{ks} T_{ks} A_k$	18
855156	n/a	n/a	n/a	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$ -HPPO-GalNac	18
855161	3	n/a	n/a	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$ -HPPO-GalNac	18
855160	1,2	n/a	n/a	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{dx} G_{dx} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$ -HPPO-GalNac	18
895571	n/a	3	2'-MOE	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{es} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$ -HPPO-GalNac	18
978782	3	2	2'-FANA	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{(FANA)s} T_{dx} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$ -HPPO-GalNac	18
978783	3	4	2'-FANA	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} U_{(FANA)s}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$ -HPPO-GalNac	21
978784	3	5	2'-FANA	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds} C_{(FANA)s} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$ -HPPO-GalNac	18
978785	3	6	2'-FANA	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds}^m C_{ds} U_{(FANA)s}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$ -HPPO-GalNac	39
978786	3	10	2'-FANA	CXCL12	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{(FANA)s} T_{ks} T_{ks} A_k$ -HPPO-GalNac	18

A subscript “d” indicates an unmodified, 2'-β-D-deoxyribosyl sugar moiety. A subscript “e” indicates a 2'-MOE-β-D-ribofuranosyl sugar moiety. A subscript “m” indicates a 2'-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A subscript “f” indicates a 2'-F-β-D-2'-deoxyribosyl sugar moiety. A subscript “(FANA)” indicates a 2'-F-β-D-arabinofuranosyl modified sugar moiety. A superscript “m” before a C indicates 5-methyl Cytosine.

For *in vitro* activity studies, 3T3-L1 cells were plated at 20,000 cells/well and transfected with 0, 27 nM, 82 nM, 247 nM, 740 nM, 2,220 nM, 6,660 nM or 20,000 nM of modified oligonucleotide by electroporation. After X hours, mRNA was harvested and analyzed by RT-qPCR. Target and raptor mRNA was analyzed as previous examples.

Table 26 Effect of MOP backbone modifications combined with ara-F modifications on *in vitro* activity and toxicity

Compound ID	MOP position in central region	FANA position in central region	Target IC ₅₀ (nM)	RAPTOR IC ₅₀ (nM)
558807	n/a	n/a	34	1000
766678	3	n/a	67	>20,000
955900	3	1	58	>20,000
955901	3	2	43	>20,000
955902	3	4	27	>20,000
955903	3	5	27	>20,000
955904	3	6	65	>20,000
955905	3	7	93	16000
955906	3	8	99	>20,000
955907	3	9	154	>20,000
955908	3	10	171	>20,000

For the *in vivo* toxicity study in the table below, three male BALB/C mice per modified oligonucleotide were administered 0.2, 0.6, 1.8 or 50 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

Table 27 Effect of MOP backbone modifications combined with 2' modifications on *in vivo* activity and toxicity

Compound ID	MOP position in central region	position of 2' - altered nucleotide in central region	sugar modification of 2' - altered nucleotide	<i>in vivo</i> CXCL12 ED ₅₀ (mg/kg)	ALT @ 50 mg/kg
855156	n/a	n/a	n/a	0.13	2938*
855161	3	n/a	n/a	0.36	40
855160	2,3	n/a	n/a	0.37	28
895571	n/a	3	2'-MOE	0.43	319
978782	3	2	2'-FANA	0.47	56
978783	3	4	2'-FANA	0.43	39

*Value represents the ALT at 1.8mg/kg

For the *in vivo* toxicity study in the table below, male BALB/C mice per modified oligonucleotide were administered 5, 50, or 150 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT were

measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity. The caspase assay was performed *in vitro* as described in Example 8.

Table 28 Effect of MOP backbone modifications combined with 2'-OMe modified sugar moieties

Compound ID	MOP position in central region	2'-OMe position in central region	CXCL12 IC ₅₀ (μM)	<i>in vivo</i> CXCL12 ED ₅₀ (mg/kg)	ALT @ 50 mg/kg (IU/L)	ALT @ 150 mg/kg (IU/L)
558807	n/a	n/a	0.18	2.88	8329	death
936053	n/a	2	0.17	1.75	75	40
1061302	1	1	0.09	0.39	101	2253
1061303	2	2	0.13	11	49	34
1061304	3	3	0.09	4.6	31	52
1061305	4	4	0.09	15.4	22	31

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Table 28b *in vitro* Caspase Activation

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Relative Caspase Activation (% Control)						
558807	98	106	112	139	288	587	1977
936053	106	111	113	91	98	107	153
1061302	98	90	106	111	149	456	1555
1061303	104	99	104	84	102	86	125
1061304	91	97	82	96	85	105	269
1061305	90	96	72	91	84	103	348

Table 28c *In Vivo* Dose-response of Gadd45a mRNA upon treatment with modified oligonucleotides complementary to CXCL12

Compound ID	5.0 mg/kg	50 mg/kg	150 mg/kg
	Expression level of Gadd45a mRNA (% Control)		
558807	120	473	n.d.
936053	76	169	219
1061302	188	178	357
1061303	55	66	66
1061304	58	66	97
1061305	67	18	20

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Table 28d *In Vivo* Dose-response of Tnfrsf10b mRNA upon treatment with modified oligonucleotides complementary to CXCL12

Compound ID	5.0 mg/kg	50 mg/kg	150 mg/kg
	Expression level of Tnfrsf10b mRNA (% Control)		
558807	137	8022	n.d.

936053	91	104	180
1061302	104	137	1217
1061303	90	92	110
1061304	70	75	149
1061305	79	60	50

Table 28e *In Vivo* Dose-response of P21 mRNA upon treatment with modified oligonucleotides complementary to CXCL12

Compound ID	5.0 mg/kg	50 mg/kg	150 mg/kg
	Expression level of P21 mRNA (% Control)		
558807	84	58138	n.d.
936053	239	81	299
1061302	87	315	14680
1061303	293	495	480
1061304	182	400	353
1061305	353	321	223

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Example 13 Effect of position-specific 2'-OMe on *in vitro* activity and toxicity of modified oligonucleotides with a variety of sequences

Modified oligonucleotides were synthesized as indicated in the table below. The compounds have the sugar motif kkk-d(10)-kkk or kkk-d-m-d(8)-kkk, where “k” represents a cEt, “d” represents an unmodified, 2'-β-D-deoxyribosyl sugar moiety, and “m” represents a 2'-OMe-β-D-ribofuranosyl sugar moiety. For sequences with a T at position 5 (from the 5' end) in the parent kkk-d(10)-kkk oligonucleotide, the kkk-d-m-d(8)-kkk contains a 2'-OMe modified U at this position. For sequences with a ¹⁴C at position 5 (from the 5' end) in the parent kkk-d(10)-kkk oligonucleotide, the kkk-d-m-d(8)-kkk contains a 2'-OMe modified C at this position, with no 5-Me group.

For the *in vivo* toxicity study in the table below, two male BALB/C mice per modified oligonucleotide were administered 150 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT was measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

For a subset of compounds, on-target activity was measured in the liver. RNA was isolated from the liver and measured by RT-qPCR using the primer probe sets described in Table 30 below. Results were normalized with Ribogreen® and are reported normalized to PBS-treated animals.

Levels of mRNA for Gadd45a, P21, and Tnfrsf10b were analyzed as in Example 1 for mice administered 150 mg/kg modified oligonucleotide. Results are normalized with Ribogreen® and presented relative to PBS-treated control animals.

The caspase assay was performed *in vitro* as described in Example 8.

Table 29 Targets and Sequences

Parent Compound ID	Corresponding compound with 2'-OMe at position 2 of the central region	Complementary mRNA	Sequence	SEQ ID NO
546006	1133071	HDAC2	GAGGATGGCAAGCACA	41
549334		AR	CACCTGCGGGAAGCTC	42
	1200896	AR	CACCUGCGGGAAGCTC	126
562920	1201379	VWF	TGTGCCCCAGCCCATT	43
572912	1200898	PABPN1	CTTCCACAGTATATCT	44
576095	1200899	EGLN2	TACTGGTAGTGTGCT	45
597605	1200900	HEGFL	TTGACACAAAGGGAGT	46
601840	1201381	MTDH	GAATCTCCTTTTCCAG	47
640599	1201862	EZH2	TTTACACGCTTCCGCC	48
694804		DNM2	AGACTCTCGGTTCCGA	49
	1202810		AGACUCTCGGTTCCGA	127
738431	1200905	Nestin	CTTTTCTATCAGTCTC	51
739428		WWTR1/TNS	CTTCTTGATGTCTTTC	52
	1201694		CTTCUTGATGTCTTTC	129
747137	1200907	FOXO1A	AAGTGTCATAAAACC	53
747149		FOXO1A	GGACTGAAATAGCAGA	54
	1203759		GGACUGAAATAGCAGA	130
747190		FOXO1A	AGGCTGGCCCCCACTG	55
	1203759		AGGCUGGCCCCCACTG	131
758252		CHOP/DDIT3	GGTTTTTGATTCTTCC	56
	1203759		GGTTUTTGAATTCTTCC	132
797793	1201073	DLL4	GCATGCCGCCCCGTCC	57
808013	1203761	CYBB	TCTTCATACAATAGCA	58
813942	1203762	CDK9	CGTTCAAATTCGTCT	59
832311	1201199	PEMT	TCCGGCTGCGGCTCAG	60

Table 30 Primer Probe Sets

Transcript	PP Set Name	Primer	Sequence	SEQ ID NO:
HDAC2	RTS3500	Forward	TGATGGTGTGAGGAAGCTTTTT	15
		Reverse	TCCCTCAAGTCTCCTGTTCCA	16
		Probe	ACAACAGATCGCGTGATGACCGTCTC	17
DNM2	RTS36436	Forward	AGAGGAGACCGAGCGAAT	61
		Reverse	CATGGTTTGTGTTGATGTACGAC	62
		Probe	CCTACATCAGGGAGCGAGAAGGGA	63
FOXO1A	RTS4973	Forward	GTCAAGACTACAACACACAGC	64
		Reverse	AAAACATAAAGGAGGGGTGAAGG	65

		Probe	CTGAAGGACTTTTAAATGTAGCCTGCTCACTA A	66
PABPN1	n/a	Forward	CCGGAGCTAGAAGCGATCAA	70
		Reverse	CCTTTAGCTTCTCAGCCTCTTCCT	71
		Probe	CTCGAGTCAGGGAGATG	72

Table 31 Toxicity and Activity

Compound ID	Position of 2'-altered nucleotide in central region	sugar modification of altered nucleotide	Gadd45a mRNA (% Control)	Tnfrsf10b mRNA (% Control)	P21 mRNA (% Control)	ALT @ 150 mg/kg	Relative Caspase Activation (% Control) @ 20 μ M	Complementary mRNA* (% Control)
PBS	n/a	n/a	100	100	111	28 @ 0	n.d.	100
546006	n/a	n/a	1885	4660	6556	131	291	38
1133071	2	2'-OMe	1357	5569	6541	245	279	37
549334	n/a	n/a	187	225	182	30	n.d.	n.d.
1200896	2	2'-OMe	165	126	130	28	n.d.	n.d.
562920	n/a	n/a	498	568	1336	109	473	n.d.
1201379	2	2'-OMe	171	200	402	32	473	n.d.
572912	n/a	n/a	357	7503	5043	3883	205	n.d.
1200898	2	2'-OMe	155	170	301	41	84	n.d.
576095	n/a	n/a	147	121	154	39	n.d.	n.d.
1200899	2	2'-OMe	401	154	169	32	n.d.	n.d.
597605	n/a	n/a	353	1965	2263	488	328	n.d.
1200900	2	2'-OMe	121	227	228	32	126	n.d.
601840	n/a	n/a	221	365	840	98	287	n.d.
1201381	2	2'-OMe	103	123	72	24	274	n.d.
640599	n/a	n/a	111	286	376	26	184	n.d.
1201862	2	2'-OMe	96	262	276	22	99	n.d.
694804	n/a	n/a	336	916	1297	1090	257	6
1202810	2	2'-OMe	106	238	257	36	166	16
715415	n/a	n/a	186	1211	1249	420	137	n.d.
1203758	2	2'-OMe	78	150	115	41	141	n.d.
738431	n/a	n/a	229	507	448	608	220	n.d.
1200905	2	2'-OMe	141	193	197	69	181	n.d.
739428	n/a	n/a	234	1975	2107	533	269	n.d.
1201694	2	2'-OMe	154	593	388	42	114	n.d.
747137	n/a	n/a	155	1379	1851	50	512	19
1200907	2	2'-OMe	99	716	824	39	168	27
747149	n/a	n/a	454	5765	4892	606	166	9
1203759	2	2'-OMe	105	119	211	33	109	22
747190	n/a	n/a	162	2856	4677	1315	393	2

1200961	2	2'-OMe	129	237	345	71	305	7
758252	n/a	n/a	158	989	861	725	355	n.d.
1233760	2	2'-OMe	94	106	182	47	187	n.d.
797793	n/a	n/a	190	1175	1181	1318	229	n.d.
1201073	2	2'-OMe	184	230	201	78	125	n.d.
808013	n/a	n/a	126	2153	4617	169	437	n.d.
1203761	2	2'-OMe	154	163	147	25	113	n.d.
813942	n/a	n/a	351	3758	4638	127	340	n.d.
1203762	2	2'-OMe	103	89	257	28	88	n.d.
832311	n/a	n/a	305	1059	878	739	288	n.d.
1201199	2	2'-OMe	294	720	597	208	256	n.d.

*Value represents the reduction of the mRNA that is complementary to the modified oligonucleotide as indicated in Table 29 above.

Example 14 Dose-response of position-specific 2'-OMe on *in vitro* and *in vivo* activity and toxicity of modified oligonucleotides with a variety of sequences.

On target *in vivo* activity and toxicity was measured for a subset of compounds described in Example 13 above. Two male BALB/c mice per group were administered 1.85, 5.55, 16.67, 50, or 150 mg/kg modified oligonucleotide once via subcutaneous injection, as indicated in the tables below. Mice were sacrificed after 1 week and mRNA was isolated from the liver and measured by RT-qPCR using the primer probe sets described in Table 30 above. Levels of mRNA for Gadd45a, P21, and Tnfrsf10b were analyzed as in Example 1. Results were normalized with Ribogreen and are reported normalized to PBS-treated animals. Plasma levels of ALT was measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity. The therapeutic index is calculated as a ratio of the maximum non-toxic dose divided by the *in vivo* ED50. The maximum non-toxic dose is the highest dose at which the ALT value remains less than 5x increased compared to PBS-treated mice, typically 150 IU/L.

Table 33 *in vivo* dose response activity

Compound Number	Target Expression (% Control)					ED50 (μg/g)
	1.9 mg/kg	5.6 mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg	
546006	86.8	75.6	78.1	56.2	41.4	87.9
1133071	81.6	74.5	61.4	52.9	37.6	53.9
572912	80.7	58.2	34.6	26.2	21.7	10.0
1200898	84.8	80.2	67.4	42.4	16.3	31.5
694804	62.8	38.2	15.3	7.8	7.6	3.2
1202810	71.0	46.7	33.2	21.0	10.1	5.8
747137	45.3	42.5	28.7	21.4	14.0	1.5
1200907	42.1	35.3	40.2	30.6	18.8	0.53

747149	72.8	42.2	23.6	14.6	7.3	6.0
1203759	52.9	40.6	24.4	21.5	18.3	2.1
715415	61.5	56.9	41.9	19.9	12.0	6.5
1203758	71.6	68.8	61.1	34.8	20.9	20.0

Table 34 *in vivo* dose response toxicity (ALT)

Compound Number	ALT (IU/L)				
	1.9 mg/kg	5.6 mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg
546006	29	29	22	26	173
1133071	24	25	25	44	356
572912	23	27	112	730	4674
1200898	23	24	25	28	32
694804	29	24	24	143	2160
1202810	22	24	24	23	61
747137	24	22	24	25	86
1200907	23	21	21	31	32
747149	26	26	38	157	1867
1203759	25	21	23	27	27
715415	23	21	25	77	1384
1203758	25	23	23	23	54

Table 34b *In Vivo* Dose-response of Gadd45a mRNA upon treatment with modified oligonucleotides complementary to HDAC2

	1.9 mg/kg	5.6 mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg
	Expression level of Gadd45a mRNA (% Control)				
546006	122	112	77	302	1070
1133071	94	134	154	396	873
572912	94	95	187	196	227
1200898	103	80	112	109	99
694804	126	106	161	163	459
1202810	115	93	91	188	169
747137	94	67	80	96	153
1200907	79	86	142	88	140
747149	123	172	146	283	575
1203759	100	147	102	172	154
715415	91	118	201	159	393
1203758	143	114	206	162	197

Table 34c *In Vivo* Dose-response of Tnfrsf10b mRNA upon treatment with modified oligonucleotides

Compound ID	1.9 mg/kg	5.6 mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg
	Expression level of Tnfrsf10b mRNA (% Control)				
546006	87	78	161	248	4235

1133071	95	96	157	622	5166
572912	210	190	551	4070	5847
1200898	135	116	105	170	179
694804	81	98	116	284	1775
1202810	88	110	88	128	241
747137	56	74	115	273	1013
1200907	99	86	15	239	453
747149	73	70	116	636	6027
1203759	87	55	57	97	105
715415	62	57	111	259	999
1203758	67	72	64	79	126

Table 34d *In Vivo* Dose-response of P21 mRNA upon treatment with modified oligonucleotides

Compound ID	1.9 mg/kg	5.6mg/kg	16.7 mg/kg	50 mg/kg	150 mg/kg
	Expression level of P21 mRNA (% Control)				
546006	103	90	172	342	5193
1133071	97	68	197	773	6571
572912	224	228	762	2787	3182
1200898	98	106	70	164	172
694804	108	76	72	172	2212
1202810	91	125	245	51	162
747137	43	59	122	294	1220
1200907	108	97	110	383	708
747149	95	44	207	985	3869
1203759	61	30	47	71	95
715415	46	24	45	213	757
1203758	36	34	18	26	35

Table 34e Therapeutic Index

Compound ID	2'-altered nucleotide position in central region	sugar modification of altered nucleotide	MNTD (mg/kg)	TI (MNTD/ED ₅₀)	Fold-TI improvement
546006	n/a	n/a	50	0.6	1.5
1133071	2	2'-OMe	50	0.9	
572912	n/a	n/a	16.7	2	>2.4
1200898	2	2'-OMe	>150	>4.8	
694804	n/a	n/a	50	16	>1.6
1202810	2	2'-OMe	>150	>26	
747137	n/a	n/a	>150	>99	~2.9
1200907	2	2'-OMe	>150	>284	
747149	n/a	n/a	50	11	>6.5
1203759	2	2'-OMe	>150	>72	
715415	n/a	n/a	50	8	n/a
1203758	2	2'-OMe	>150	>7.5	

Example 15 Effect of modified oligonucleotides on nucleolar localization of p54nrb

Selected modified nucleotides described in above were tested for their effect on HeLa cells by microscopy. HeLa cells were transfected by lipofectamine 2000 with 200nM of modified oligonucleotide for 2 hrs and then cellular protein p54nrb was stained by mP54 antibody (Santa Cruz Biotech, sc-376865) and DAPI was used to stain for the nucleus of cells. The number of cells with nucleolar p54nrb and the total number of cells in the images were counted. ALT data presented were previously described in Example 13 above.

Table 35 Nucleolar mislocalization of p54nrb and correlation with hepatotoxicity

Compound ID	2'-altered nucleotide position in central region	sugar modification of altered nucleotide	% cells with mislocalization of p54nrb	ALT @ 150 mg/kg
546006	n/a	n/a	56	131
1133071	2	2'-OMe	67	245
572912	n/a	n/a	75	3883
1200898	2	2'-OMe	3	41
758252	n/a	n/a	71	725
1233760	2	2'-OMe	4	47

Example 16 Effect of position-specific 2'-OMe on *in vitro* activity and toxicity of modified oligonucleotides with various sequences

Modified oligonucleotides with the sugar motifs lll-d(10)-lll and lll-d-m-d(8)-lll were synthesized, where "l" indicates a β -D-locked nucleic acid (β -D-LNA), "d" represents a 2'- β -D-deoxyribose sugar moiety and "m" represents a 2'-OMe- β -D-ribofuranosyl sugar moiety. Each internucleoside linkage is a phosphorothioate internucleoside linkage. For sequences with a T at position 5 (from the 5' end) in the parent lll-d(10)-lll oligonucleotide, the lll-d-m-d(8)-lll contains a 2'-OMe modified U at this position. For sequences with a ^mC at position 5 (from the 5' end) in the parent lll-d(10)-lll oligonucleotide, the lll-d-m-d(8)-lll contains a 2'-OMe modified C at this position lacking a 5-Me group.

Table 36 Modified Oligonucleotides

lll-d(10)-lll compound ID	lll-d-m-d(8)-lll compound ID	Complementary mRNA	Sequence (5'-3')	SEQ ID NO
1247569	1247570	HDAC2	GAGGATGGCAAGCACA	41
1247571	1247572	PABPN1	CTTCCACAGTATATCT	44
1247573		DNM2	AGACTCTCGGTTCCGA	49
	1247574		AGACUCTCGGTTCCGA	127
1247575	1247576	FOXO1A	AAGTGTCACATAAAACC	53
1247577	1247578	FOXO1A	GGACTGAAATAGCAGA	54

	1247578		GGACUGAAATAGCAGA	130

In vivo toxicity and on target *in vivo* activity was measured for the compounds described above. Two male balb/c mice per group were administered 16.67 or 150 mg/kg modified oligonucleotide once via subcutaneous injection, as indicated in the tables below. Mice were sacrificed after 72 hours and mRNA was isolated from the liver and measured by RT-qPCR using the primer probe sets described in Table 30 above. Levels of mRNA for P21, and Tnfrsf10b were analyzed as in Example 1. Results were normalized with Ribogreen and are reported normalized to PBS-treated animals.

Table 37 *in vivo* activity and toxicity

Compound Number	Complementary mRNA Expression (% Control)		ALT (IU/L)		P21 mRNA (% Control)		Tnfrsf10b mRNA (% Control)	
	16.7 mg/kg	150 mg/kg	16.7 mg/kg	150 mg/kg	16.7 mg/kg	150 mg/kg	16.7 mg/kg	150 mg/kg
1247569	70	35	37	2368	163	12778	158	7046
1247570	72	46	34	867	444	11860	320	6772
1247571	40	26	460	10838	3061	7588	2216	8133
1247572	54	16	26	330	90	928	124	679
1247573	7	19	59	20665	153	10379	157	4858
1247574	19	6	25	284	139	839	123	575
1247575	51	30	50	2404	390	11275	334	6365
1247576	57	27	25	85	142	1850	218	2033
1247577	52	25	34	2460	256	11736	193	14610
1247578	60	21	25	39	124	133	178	143
1247579	48	14	23	1696	95	3704	176	108
1247580	77	21	28	232	78	265	2850	307

Example 17 Effect of position-specific 2'-modifications on *in vitro* activity and *in vivo* liver toxicity of modified oligonucleotides complementary to CPT1A

Modified oligonucleotides were synthesized as indicated in the table below. These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking an altered nucleotide in the central region, a 5-10-5 MOE modified oligonucleotide, containing five nucleosides each comprising a 2'-MOE- β -D-ribofuranosyl sugar moiety in each of the 5' and 3' regions and 10 unmodified DNA nucleosides in the central region. Each internucleoside linkage is a phosphorothioate internucleoside linkage. The compounds in the table below are 100% complementary to mouse CPT1A, GENBANK NC_000085.6 truncated from 3319001 to 3389000 (SEQ ID NO: 6), at position 49870 to 49889. In certain

instances, a modified oligonucleotide comprising a T at position 5 is compared to a modified oligonucleotide comprising a 2'-OMe U at position 5.

Table 38 Modified oligonucleotides complementary to CPT1A

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	Chemistry Notation	SEQ ID NO
147420	n/a	n/a	$A_{es}A_{es}T_{es}G_{es}T_{es}G_{ds}^mC_{ds}^mC_{ds}T_{ds}G_{ds}^mC_{ds}T_{ds}G_{ds}T_{ds}^mC_{ds}^mC_{es}T_{es}T_{es}G_{es}A_e$	73
994947	n/a	OMe	$A_{es}A_{es}T_{es}G_{ms}T_{es}G_{ds}^mC_{ds}^mC_{ds}T_{ds}G_{ds}^mC_{ds}T_{ds}G_{ds}T_{ds}^mC_{ds}^mC_{es}T_{es}T_{es}G_{es}A_e$	73
994948	n/a	OMe	$A_{es}A_{es}T_{es}G_{es}U_{ms}G_{ds}^mC_{ds}^mC_{ds}T_{ds}G_{ds}^mC_{ds}T_{ds}G_{ds}T_{ds}^mC_{ds}^mC_{es}T_{es}T_{es}G_{es}A_e$	74
994949	1	OMe	$A_{es}A_{es}T_{es}G_{es}T_{es}G_{ms}^mC_{ds}^mC_{ds}T_{ds}G_{ds}^mC_{ds}T_{ds}G_{ds}T_{ds}^mC_{ds}^mC_{es}T_{es}T_{es}G_{es}A_e$	73
994950	2	OMe	$A_{es}A_{es}T_{es}G_{es}T_{es}G_{ds}C_{ms}^mC_{ds}T_{ds}G_{ds}^mC_{ds}T_{ds}G_d^sT_{ds}^mC_{ds}^mC_{es}T_{es}T_{es}G_{es}A_e$	73
994951	3	OMe	$A_{es}A_{es}T_{es}G_{es}T_{es}G_{ds}^mC_{ds}C_{ms}T_{ds}G_{ds}^mC_{ds}T_{ds}G_d^sT_{ds}^mC_{ds}^mC_{es}T_{es}T_{es}G_{es}A_e$	73

A subscript “d” indicates an unmodified, 2'-β-D-deoxyribose sugar moiety. A subscript “e” indicates a 2'-MOE-β-D-ribofuranosyl sugar moiety. A subscript “m” indicates a 2'-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine. A subscript “x” indicates a MOP internucleoside linkage. A subscript “(FANA)” indicates a nucleoside comprising an ara 2'-F modified sugar moiety.

For the *in vivo* toxicity and activity study in the table below, BALB/C mice per modified oligonucleotide were administered 200 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity. Liver mRNA was harvested and analyzed by RT-qPCR. Cpt1a mRNA was detected using primer probe setRTS40014 (forward sequence: AGATCAATCGGACCCTAGACA, SEQ ID NO: 75; reverse sequence: CAGCACCTTCAGCGAGTA; SEQ ID NO: 76; probe sequence: AAGAGGACGCCACTCACGATGTTC, SEQ ID NO: 77) and P21 and Tnfrsf10b mRNA were detected as described in Example 1.

Table 39 Activity and toxicity of modified oligonucleotides complementary CPT1A

Compound ID	position of altered nucleotide in central region	sugar modification of altered nucleotide	Cpt1a (% control)	P21 (% control)	Tnfrsf10b (% control)	ALT @ 200 mg/kg (IU/L)
147420	n/a	n/a	6.42	6616	8796	15308
994947	n/a	2'-OMe	6.49	6984	11499	18395
994948	n/a	2'-OMe	8.99	7085	10520	10535
994949	1	2'-OMe	5.90	6370	9595	12370
994950	2	2'-OMe	12.19	2219	2146	52
994951	3	2'-OMe	6.72	6275	10555	2991

For the *in vivo* activity study in the table below, three BALB/C mice per modified oligonucleotide were administered 2.5, 7.4, 22.2, 66.7, 200 mg/kg 147420 or 994950 by subcutaneous injection and sacrificed after 72 hours. Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity. Cpt1a mRNA was detected using RT-qPCR as described above.

Table 40 *In Vivo* Toxicity of modified oligonucleotides complementary CPT1A

Compound Number	ALT (IU/L)				
	2.5 mg/kg	7.4 mg/kg	22.2 mg/kg	66.7 mg/kg	200 mg/kg
147420	51	23	23	106	7794
994950	25	25	21	23	53

Table 41 *In Vivo* Activity of modified oligonucleotides complementary CPT1A

Compound Number	CPT1 mRNA (% Control)				
	2.5 mg/kg	7.4 mg/kg	22.2 mg/kg	66.7 mg/kg	200 mg/kg
147420	115.9	93.1	78.2	33.7	4.6
994950	116.0	117.2	105.6	55.9	21.9

Table 42 *In Vivo* Dose-response of Tnfrsf10b mRNA upon treatment with modified oligonucleotides

Compound Number	Tnfrsf10b mRNA (% Control)				
	2.5 mg/kg	7.4 mg/kg	22.2 mg/kg	66.7 mg/kg	200 mg/kg
147420	132	141	162	2341	8622
994950	119	133	125	153	1026

Table 43 *In Vivo* Dose-response of P21 mRNA upon treatment with modified oligonucleotides

Compound Number	P21 mRNA (% Control)				
	2.5 mg/kg	7.4 mg/kg	22.2 mg/kg	66.7 mg/kg	200 mg/kg
147420	141	94	240	4305	15334
994950	105	89	103	208	2413

Example 18 Effect of 2'-OMe modification in modified oligonucleotides complementary to Factor XI

Modified oligonucleotides were synthesized as indicated in the table below. The compounds have the sugar motif kkk-d(10)-kkk ("parent") or kkk-d-m-d(8)-kkk, where "k" represents a cEt, "d" represents an unmodified, 2'-β-D-deoxyribose sugar moiety, and "m" represents a 2'-OMe-ribofuranosyl sugar moiety.

For sequences with a T at position 5 (from the 5' end) in the parent kkk-d(10)-kkk oligonucleotide, the kkk-d-m-d(8)-kkk contains a 2'-OMe modified U at this position. For sequences with a ^mC at position 5 (from the 5' end) in the kkk-d(10)-kkk oligonucleotide, the kkk-d-m-d(8)-kkk contains a 2'-OMe modified C at this position, lacking the 5-Me group. Each internucleoside linkage is a phosphorothioate internucleoside linkage.

For the *in vitro* activity study in the table below, primary mouse hepatocytes were isolated from male balb/c mice and transfected with 0.9, 2.7, 8.2, 24.7, 74.0, 222, 667, or 2,000 nM modified oligonucleotide. After 24 hrs, mRNA was harvested and analyzed for FXI and RAPTOR as described above.

For the *in vivo* toxicity study in the table below, two male BALB/C mice per modified oligonucleotide were administered 150 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT was measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

For a subset of compounds, on-target activity was measured in the liver. RNA was isolated from the liver and measured by RT-qPCR using the primer probe set RTS2898, described in Example 4 above. Results were normalized with Ribogreen® and are reported normalized to PBS-treated animals.

Table 44 Sequences

kkk-d(10)- kkk compound ID	kkk-d-m-d(8)- kkk compound ID	Sequence (5'-3')	SEQ ID NO
464917	982034	GTCTGTGCATCTCTCC	22
464924		GTTATTGTGGTTGGCG	81
	1133247	GTTAUTGTGGTTGGCG	133
465156		ATTCTGTGTGCACTGC	82
	1133310	ATTCUGTGTGCACTGC	134
465162	1133316	TCTTGTCTGACATTCT	83
465163	1133317	TTTTGTGTCTTCTGTA	84
465172		CTGTTTGAGTTTTCTC	85
	1133326	CTGTUTGAGTTTTCTC	135
465174	1133328	CAAAGTGATACCAGTT	86
465175		AATCTTCCAGGGCCAC	87
	1133329	AATCUTCCAGGGCCAC	136
465176		TCATTTCTATGGAATA	88
	1133330	TCATUTCTATGGAATA	137
465178	1133332	GTCAGTATCCCAGTGT	89

465179	1133333	GGTTACAGTGGAAGAG	90
465181	1133335	TCTGGGTGTTCTTACG	91
465186	1133340	TTTCCTTGAGTAGTAG	92
465187	1133341	TCTCCTTGCTGTATTT	93

Table 45 Activity and Toxicity of Modified oligonucleotides complementary to Factor XI

Compound ID	altered nucleotide position in central region	sugar modification of altered nucleotide	<i>in vitro</i> FXI IC ₅₀ (nM)	<i>in vitro</i> RAPTOR IC ₅₀ (nM)	Relative Caspase Activation (% Control) @20 μ M	p21 @150 mg/kg	FXI @ 10 mg/kg	ALT @ 150mg/kg (IU/L)
464917	n/a	n/a	101	44	700	death	25.4	death
982034	2	2'-OMe	221	119	122	31922	40.8	13172
464924	n/a	n/a	115	>2000	332	19340	8.6	5365
1133247	2	2'-OMe	189	>2000	190	753	12.1	33
465156	n/a	n/a	98	129	934	82279	14.4	24858
1133310	2	2'-OMe	354	465	603	127	14.7	7034
465162	n/a	n/a	99	>2000	758	death	15.1	death
1133316	2	2'-OMe	144	>2000	189	4660	34.2	60
465163	n/a	n/a	163	>2000	115	34117	41.5	2347
1133317	2	2'-OMe	272	>2000	67	11844	79.4	478
465172	n/a	n/a	106	>2000	429	512	57.6	23
1133326	2	2'-OMe	176	>2000	157	237	64.8	20
465174	n/a	n/a	69	>2000	130	276	21.7	21
1133328	2	2'-OMe	393	>2000	113	167	33.8	23
465175	n/a	n/a	50	125	523	6957	37.8	1564
1133329	2	2'-OMe	99	170	501	1564	59.8	60
465176	n/a	n/a	111	>2000	219	344	98.6	27
1133330	2	2'-OMe	89	>2000	135	190	95.1	22
465178	n/a	n/a	11	115	364	900086	8.1	13168
1133332	2	2'-OMe	24	1653	247	5982	27.0	75
465179	n/a	n/a	74	>2000	188	4046	23.0	344
1133333	2	2'-OMe	82	>2000	102	122	62.4	23
465181	n/a	n/a	75	1571	487	17469	25.4	7087
1133335	2	2'-OMe	56	>2000	214	929	61.7	26
465186	n/a	n/a	75	>2000	200	42551	17.3	3709
1133340	2	2'-OMe	208	>2000	125	513	42.8	34
465187	n/a	n/a	35	475	393	778834*	10.4	11752*
1133341	2	2'-OMe	28	>2000	167	1984	38.6	36

*1/2 animals were found dead

5 Example 19 Effect of 2'-OMe incorporation on toxicity of modified oligonucleotides complementary to HDAC2

Modified oligonucleotides were synthesized as indicated in the table below. The compounds have the sugar motif kkk-d(10)-kkk ("parent") or kkk-d-m-d(8)-kkk, where "k" represents a cEt, "d" represents an

unmodified, 2'- β -D-deoxyribosyl sugar moiety, and "m" represents a 2'-OMe- β -D-ribofuranosylsugar moiety. For sequences with a T at position 5 (from the 5' end) in the parent kkk-d(10)-kkk oligonucleotide, the kkk-d-m-d(8)-kkk contains a 2'-OMe modified U at this position. For sequences with a mC at position 5 (from the 5' end) in the kkk-d(10)-kkk oligonucleotide, the kkk-d-m-d(8)-kkk contains a 2'-OMe modified C at this position, lacking the 5-Me group. Each internucleoside linkage is a phosphorothioate internucleoside linkage.

For the in vitro activity study in the table below, primary mouse hepatocytes were isolated from male balb/c mice and transfected with 0.9, 2.7, 8.2, 24.7, 74.0, 222, 667, or 2,000 nM modified oligonucleotide. After 24 hrs, mRNA was harvested and analyzed for HDAC2 and RAPTOR as described above. For the in vivo toxicity study in the table below, two male BALB/C mice per modified oligonucleotide were administered 10 or 150 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. One animal was administered an injection of saline as a control. Plasma levels of ALT was measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

For a subset of compounds, on-target activity was measured in the liver. RNA was isolated from the liver and measured by RT-qPCR using the primer probe set RTS3500 described above in Example 13. Results were normalized with Ribogreen® and are reported normalized to PBS-treated animals.

Table 46 Sequences

kkk-d(10)- kkk compound ID	kkk-d-m-d(8)- kkk compound ID	Sequence (5'-3')	SEQ ID NO
545984	1133060	TTGCCAATATCACCAT	94
545996		CAACUGAACCACCCGT	95
	1133066	CAACTGAACCACCCGT	138
546004	1133070	GCACAATATCATTAAC	96
546009	1132933	GACTCTCTGATGATAC	97
546023	1132940	CTATACCATCTCTCAT	98
546024	1133080	CATCATCTATACCATC	99
546034	1133085	ACACATTTAGCATGAC	100
546045		ATTATATGGCAACTCA	101
	1132951	ATTAUATGGCAACTCA	139
546049	1132953	GACTAATATGCAGTTT	102
546075	1132966	GTCAAATTCAAGGGTT	103
546095	1132976	CATAAAGCATGGTGGA	104
546108	1133122	TAGTCTCTGTCAGTTA	105
546109	1132983	GTACCTATAGTCTCTG	106
546110	1133123	TCATGTACCTATAGTC	107
546112	1133124	TCTTAATTTTCATGTAC	108
546118	1133127	ACCCTCAAGTCTCCTG	109

Table 47 *In vitro* Activity and Toxicity of Modified oligonucleotides complementary to HDAC2

Compound ID	altered nucleotide position in central region	sugar modification of altered nucleotide	<i>in vitro</i> HDAC 2 IC ₅₀ (nM)	<i>in vitro</i> RAPTOR IC ₅₀ (nM)	Relative Caspase Activation (% Control) @20 μM
546009	n/a	n/a	44	773	632
1132933	2	2'-OMe	89	>2000	193
546023	n/a	n/a	79	1643	825
1132940	2	2'-OMe	156	>2000	980
546045	n/a	n/a	72	460	469
1132951	2	2'-OMe	98	>2000	326
546049	n/a	n/a	82	>2000	127
1132953	2	2'-OMe	144	>2000	132
546075	n/a	n/a	81	>2000	149
1132966	2	2'-OMe	135	>2000	143
546095	n/a	n/a	78	>2000	126
1132976	2	2'-OMe	128	>2000	98
546109	n/a	n/a	30	>2000	396
1132983	2	2'-OMe	44	>2000	117
545984	n/a	n/a	89	452	1235
1133060	2	2'-OMe	126	>2000	270
545996	n/a	n/a	297	>2000	776
1133066	2	2'-OMe	111	>2000	327
546004	n/a	n/a	181	>2000	124
1133070	2	2'-OMe	164	>2000	90
546024	n/a	n/a	85	>2000	124
1133080	2	2'-OMe	45	>2000	123
546034	n/a	n/a	125	>2000	107
1133085	2	2'-OMe	125	>2000	104
546108	n/a	n/a	21	144	1265
1133122	2	2'-OMe	34	>2000	176
546110	n/a	n/a	17	>2000	82
1133123	2	2'-OMe	30	>2000	95
546112	n/a	n/a	178	>2000	106
1133124	2	2'-OMe	106	>2000	98
546118	n/a	n/a	6	181	425
1133127	2	2'-OMe	11	>2000	158

Table 48 *In vivo* Activity and Toxicity of Modified oligonucleotides complementary to HDAC2

Compound ID	HDAC 2 @ 10 mg/kg	HDAC2 @ 150mg/kg	P21 mRNA @ 150 mg/kg	Tnfrsf10b @ 150mg/kg	ALT @ 150mg/kg (IU/L)
546009	22	7.5	5739	7162	14907
1132933	40	7.5	98	176	31
546023	57	9.9	1586	754	820

1132940	61	12.7	1348	565	224
546045	68	17.2	5601	2362	1031
1132951	60	15.3	1726	970	183
546049	50	8.9	294	133	29
1132953	71	15.2	282	150	27
546075	71	16.2	282	232	21
1132966	61	27.7	741	621	86
546095	39	12.7	3303	2314	1063
1132976	50	15.3	685	512	94
546109	29	4.3	684	706	182
1132983	37	5.2	217	190	34
545984	31	4.9	14070	10327	37277
1133060	42	9.0	183	138	39
545996	56	14.7	613	458	433
1133066	60	24.2	215	156	28
546004	64	13.4	499	203	35
1133070	69	17.6	286	192	30
546024	34	6.2	381	169	25
1133080	41	8.1	452	201	26
546034	52	7.5	181	140	32
1133085	68	10.6	127	143	27
546108	3	n.d.	n.d.	n.d.	death
1133122	7	1.9	1524	1353	131
546110	15	6.2	23642	6298	5132
1133123	35	3.3	221	155	29
546112	52	14.3	817	350	34
1133124	59	13.9	822	571	29
546118	13	5.7	3853	3854	3894
1133127	15	4.8	470	473	139

For the FOB scores reported in the table below, mice per group were administered 100 µg modified oligonucleotide by intracerebroventricular (ICV) injection. At 3 hours and 2 weeks post-injection, mice were evaluated according to 7 different criteria. The criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse showed any movement without stimuli; (4) the mouse demonstrated forward movement after it was lifted; (5) the mouse demonstrated any movement after it was lifted; (6) the mouse responded to tail pinching; (7) regular breathing. For each of the 7 criteria, a mouse was given a subscore of 0 if it met the criteria and 1 if it did not. After all 7 criteria were evaluated, the FOB scores were summed for each mouse and averaged within each treatment group. The results are presented in the table below.

Two weeks after injection of modified oligonucleotide, mice were sacrificed and levels of HDAC, p21 and Aif1 were measured in the cortex and the spinal cord by RT-PCR as described above. Aif1 is a marker for inflammation. Results are presented below relative to control animals.

Table 48b *In vivo* Activity and Toxicity of Modified oligonucleotides complementary to HDAC2

Compound ID	3 hr FOB	2 week FOB	HDAC mRNA Cortex	HDAC mRNA Spinal Cord	p21 mRNA Cortex	p21 mRNA Spinal Cord	Aif1 mRNA Cortex	Aif1 mRNA Spinal cord
546009	5.5	5.5	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
1132933	3.5	0	45.3	45.3	148	227	96	129
546023	0	0	36.3	31.3	120	144	117	156
1132940	0	0	59.2	39.3	135	166	94	174
546045	4.5	0	43.4	39.2	136	284	113	161
1132951	3	0	61.4	42.6	128	200	86	121
546049	1	0	95.3	68.8	111	116	90	110
1132953	3	0	67.1	47.8	126	138	82	103
546075	7	7	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
1132966	2.5	0	39.9	40.9	129	174	116	130
546095	5.5	0	66.7	44.2	124	321	90	189
1132976	6	0	55	36	132	427	87	248
546109	7	7	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
1132983	7	7	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
545984	2.5	6.5	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
1133060	1	0	71.0	39.8	107	130	92	112
545996	3	0	59.1	48.9	122	220	104	171
1133066	7	7	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
546004	0	0	55.3	47.6	136	261	116	176
1133070	0	0	58.7	50.0	127	173	81	99
546024	6.5	0	20.2	20.5	134	211	115	140
1133080	1	0	34.6	18.4	109	139	88	112
546034	3	0	58.9	46.6	96	149	98	146
1133085	3	0	79.0	42.0	114	126	101	137
546108	2	6.5	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
1133122	3.5	1	25.4	17.7	97	166	120	178
546110	2.5	3	55.0	23.5	88	294	93	342
1133123	0	0	57.4	49.8	112	149	85	105
546112	3	0	68.5	46.6	108	119	97	420
1133124	1.5	0	70.8	52.8	122	107	157	873
546118	7	7	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
1133127	7	7	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

Example 20 Incorporation of 2'-OMe at various positions

5 Modified oligonucleotides were synthesized with kkk-m-d(9)-kkk, kkk-d-m-d(8)-kkk, kkk-dd-m-d(7)-kkk or kkk-d(3)-m-d(6)-kkk sugar motifs, respectively, where “m” represents a 2'-OMe-β-D-ribofuranosylsugar moiety, “k” represents a cEt, and “d” represents an unmodified, 2'-β-D-deoxyribosyl sugar moiety. In certain instances, 2'-OMeU replaces 2'-deoxyT. These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking an altered nucleotide in the central region, a 3-10-3 cEt modified oligonucleotide, containing three cEt nucleosides in each of the 5' and 3' regions and 10

unmodified DNA nucleosides in the central region. Each internucleoside linkage is a phosphorothioate internucleoside linkage. The compounds in the table below are 100% complementary to mouse CXCL12, GENBANK NT_039353.7 truncated from 69430515 to 69445350 (SEQ ID NO: 1), at position 6877 to 6892.

5

Table 49 Modified Oligonucleotides

Compound ID	altered nucleotide position in central region	sugar moiety of altered nucleotide	Chemistry Notation	SEQ ID NO
558807	n/a	n/a	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m$ $C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1061877	1	2'-OMe	$G_{ks}^m C_{ks} A_{ks} U_{ms} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m$ $C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	19
936053	2	2'-OMe	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ms} T_{ds} T_{ds}^m C_{ds} T_{ds}^m$ $C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1061879	3	2'-OMe	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} U_{ms} T_{ds}^m C_{ds} T_{ds}^m$ $C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	20
1061981	4	2'-OMe	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} U_{ms}^m C_{ds} T_{ds}^m$ $C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	21
1244110	5	2'-OMe	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ms} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1244111	6	2'-OMe	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} U_{ms}^m$ $C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	39
1244112	7	2'-OMe	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds} C_{ms} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1244113	8	2'-OMe	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m$ $C_{ds} A_{ms}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1244114	9	2'-OMe	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m$ $C_{ds} A_{ds} C_{ms} A_{ds} T_{ks} T_{ks} A_k$	18
1244115	10	2'-OMe	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m$ $C_{ds} A_{ds}^m C_{ds} A_{ms} T_{ks} T_{ks} A_k$	18

A subscript “d” indicates an unmodified, 2'-β-D-deoxyribose sugar moiety. A subscript “m” indicates a 2'-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine.

For the results in the tables below, *in vitro* activity and toxicity experiments were performed essentially as described in Example 1. For *in vitro* activity and toxicity studies, 3T3-L1 cells were transfected with 27 nM, 80 nM, 250 nM, 740 nM, 2,222 nM, 6,667 nM, or 20,000 nM of modified oligonucleotide by electroporation and levels of p21 were measured by RT-qPCR as described in Example 1 above. The caspase assay was performed as described in Example 8 above in 3T3-L1 cells. Localization of p54nrb in HeLa cells was quantitated as described in Example 15.

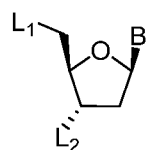
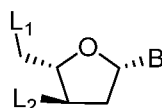
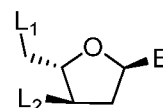
Table 50 *In vitro* activity and toxicity of modified oligonucleotides complementary to CXCL12

Compound ID	<i>in vitro</i> CXCL12 IC ₅₀ (nM)	<i>in vitro</i> Caspase (% control) @ 20 μ M	<i>in vitro</i> p21 (% control) @ 20 μ M	% nucleolar p54nrb
558807	47	641	307	92
1061877	13	519	266	43
936053	67	173	143	8
1061879	59	416	192	59
1061981	112	325	129	46
1244110	21	386	390	60
1244111	53	380	430	69
1244112	42	345	344	92
1244113	114	361	373	54
1244114	17	399	440	78
1244115	70	372	400	67

Example 21 Stereochemical Isomers of Nucleosides

Modified oligonucleotides containing modified nucleotides with various stereochemical configurations at positions 1', 3', and 5' of the 2'-deoxyfuranosyl sugar were synthesized. Amidites for the synthesis of β -L-DNA-containing nucleotides are commercially available (ChemGenes) and the synthesis of both α -L and β -L dT phosphoramidites has been reported (Morvan, *Biochem and Biophys Research Comm*, 172(2): 537-543, 1990). The altered nucleotides were contained within the central region of the oligonucleotide.

These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking an altered nucleotide in the central region, 558807, described in Table 1, Example 1 above. The compounds in Table 51 each comprise a 5' wing and a 3' wing each consisting of three linked cEt nucleosides and a central region comprising nucleosides each comprising 2'- β -D-deoxyribose sugar moieties aside from the altered nucleotide, as indicated. Each internucleoside linkage is a phosphodiester internucleoside linkage. The compounds in the table below are 100% complementary to mouse CXCL12, GENBANK NT_039353.7 truncated from 69430515 to 69445350 (SEQ ID NO: 1), at position 6877 to 6892.

 β -D-2'-DNA β -L-2'-DNA α -L-2'-DNA

B is any nucleobase and L₁ and L₂ are internucleoside linkages

Table 51 modified oligonucleotides with stereochemical modifications

Compound ID	position of altered nucleotide in central region	stereochemical configuration of altered nucleotide	Chemistry Notation (5' to 3')	SEQ ID NO
1215458	2	β -L-DNA	$G_{ks}^m C_{ks}^s A_{ks} T_{ds} [\beta\text{-L} G_{ds}] T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1215459	3	β -L-DNA	$G_{ks}^m C_{ks}^s A_{ks} T_{ds} G_{ds} [\beta\text{-L} T_{ds}] T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1215460	4	β -L-DNA	$G_{ks}^m C_{ks}^s A_{ks} T_{ds} G_{ds} T_{ds} [\beta\text{-L} T_{ds}]^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1215461	3	α -L-DNA	$G_{ks}^m C_{ks}^s A_{ks} T_{ds} G_{ds} [\alpha\text{-L} T_{ds}] T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1215462	4	α -L-DNA	$G_{ks}^m C_{ks}^s A_{ks} T_{ds} G_{ds} T_{ds} [\alpha\text{-L} T_{ds}]^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18

A subscript “d” indicates an unmodified, 2'- β -D-deoxyribose sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. [$\beta\text{-L} B_{ds}$] indicates a modified β -L-DNA nucleotide with a 2'-deoxyribose moiety, a phosphorothioate linkage, and base B. [$\alpha\text{-L} B_{ds}$] indicates a modified, α -L DNA nucleotide with a 2'-deoxyribose sugar moiety, a phosphorothioate linkage, and base B.

For the results in the tables below, *in vitro* activity and toxicity experiments were performed essentially as described in Example 1. For *in vitro* activity and toxicity studies, 3T3-L1 cells were transfected with 27 nM, 80 nM, 250 nM, 740 nM, 2,222 nM, 6,667 nM, or 20,000 nM of modified oligonucleotide by electroporation and levels of P21 and Gadd45a and Tnfrsf10b were measured by RT-qPCR as described in Example 1 above. The caspase assay was performed as described in Example 8 above in 3T3-L1 cells.

For the *in vivo* activity study in the tables below, 2 BALB/C mice per group were administered 1.8 mg/kg, 5.5 mg/kg, 16.7 mg/kg, 50 mg/kg, or 150 mg/kg doses of modified oligonucleotide, as indicated in the table below, by subcutaneous injection and sacrificed 72 hours later. For 558807, only 1.8 mg/kg, 5.5 mg/kg, and 16.7 mg/kg doses were tested for dose response, due to acute toxicity of higher doses. Liver mRNA was isolated and analyzed by RT-PCR as described in Example 1 above. Expression levels were normalized with Ribogreen® and are expressed relative to PBS-treated control mice.

Table 52 Activity and toxicity of modified oligonucleotides complementary CXCL12

Compound ID	<i>in vitro</i> CXCL12 IC ₅₀ (μ M)	<i>in vitro</i> RAPTOR IC ₅₀ (μ M)	<i>in vivo</i> CXCL12 ED ₅₀ (mg/kg)	ALT @ 50mg/kg (IU/L)	ALT @ 150mg/kg (IU/L)
PBS	n/a	n/a	n/a	25 @ 0 mg/kg	
558807	0.10	1	2.9	n.d.**	
1215458	0.41	>20	11	32	42

1215459	0.44	>20	13	31	37
1215460	0.41	>20	13	29	43
1215461	0.14	3	2.8	1725	6301
1215462	0.13	3	3.6	45	3652

**558807 treatment at 16.7 mg/kg leads to an ALT of 586 IU/L; mice that are treated with 558807 at 150mg/kg typically experience death before 72 hours post-treatment.

Table 53 *in vitro* Caspase Activation

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Relative Caspase Activation (% Control)						
558807	106	113	117	169	250	396	343
1215458	81	88	98	95	74	78	95
1215459	96	88	111	98	98	81	102
1215460	89	98	96	111	91	113	130
1215461	90	94	89	117	142	201	250
1215462	96	93	95	119	150	192	240

5

Table 53b *in vitro* P21 Expression

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of P21 mRNA (% Control)						
558807	98	116	122	115	115	135	184
1215458	104	127	135	153	139	140	130
1215459	99	116	134	154	158	141	147
1215460	85	109	118	120	118	122	109
1215461	105	107	128	136	139	147	153
1215462	110	127	143	150	139	124	143

Table 53c *in vitro* Tnfrsf10b Expression

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of Tnfrsf10b mRNA (% Control)						
558807	107	108	105	99	113	102	68
1215458	90	88	92	87	81	78	80
1215459	97	108	108	100	103	94	83
1215460	92	100	99	102	95	95	84
1215461	86	91	99	98	97	97	114
1215462	101	97	98	56	82	101	108

10

Table 53d *in vitro* Gadd45a Expression

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of Gadd45a mRNA (% Control)						
558807	123	134	135	136	164	180	223
1215458	132	142	141	135	125	104	87

1215459	163	167	183	190	179	150	110
1215460	127	142	140	141	143	120	95
1215461	117	141	150	165	168	167	128
1215462	110	139	143	138	133	150	137

Example 22 Stereochemical Isomers of Nucleosides

Modified oligonucleotides containing β -L-DNA nucleotides (described in Example 21 above) at various positions were synthesized. These modified oligonucleotides were compared to compound 558807, described in Table 1, Example 1 above. Compound 558807 contains 5-methyl cytosine for all cytosine nucleosides, as do compounds 1215458-1215460 described in the table below. The compounds in Table 54 each comprise a 5' wing and a 3' wing each consisting of three linked cEt nucleosides and a central region comprising nucleosides each comprising 2'- β -D-deoxyribose sugar moieties aside from the altered nucleotide, as indicated. Each internucleoside linkage is a phosphodiester internucleoside linkage.

Compounds 1244441-1244447 in the table below contain unmethylated cytosine in the central region of the compounds. The compounds in the table below are 100% complementary to mouse CXCL12, GENBANK NT_039353.7 truncated from 69430515 to 69445350 (SEQ ID NO: 1), at position 6877 to 6892.

Table 54 modified oligonucleotides with stereochemical modifications

Compound ID	position of altered nucleotide in central region	stereochemical configuration of altered nucleotide	Chemistry Notation	SEQ ID NO
1244441	1	β -L-DNA	$G_{ks}^m C_{ks} A_{ks} [\beta\text{-L} T_{ds}] G_{ds} T_{ds} T_{ds} C_{ds} T_{ds} C_{ds} A_{ds} C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1215458	2	β -L-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} [\beta\text{-L} G_{ds}] T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1215459	3	β -L-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} [\beta\text{-L} T_{ds}] T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1215460	4	β -L-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} [\beta\text{-L} T_{ds}]^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244442	5	β -L-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds} [\beta\text{-L} C_{ds}] T_{ds} C_{ds} A_{ds} C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244443	6	β -L-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds} C_{ds} [\beta\text{-L} T_{ds}] C_{ds} A_{ds} C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244444	7	β -L-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds} C_{ds} T_{ds} [\beta\text{-L} C_{ds}] A_{ds} C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244445	8	β -L-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds} C_{ds} T_{ds} C_{ds} [\beta\text{-L} A_{ds}] C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244446	9	β -L-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds} C_{ds} T_{ds} C_{ds} A_{ds} [\beta\text{-L} C_{ds}] A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244447	10	β -L-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds} C_{ds} T_{ds} C_{ds} A_{ds} C_{ds} [\beta\text{-L} A_{ds}] T_{ks} T_{ks} A_{ks}$	18

A subscript "d" indicates a nucleoside comprising an n unmodified, 2'- β -D-deoxyribose sugar moiety. A subscript "k" indicates a cEt. A subscript "s" indicates a phosphorothioate internucleoside linkage. $[\beta\text{-L} B_{ds}]$ indicates a modified β -L-DNA nucleotide with a 2'-deoxyribose sugar moiety, a phosphorothioate linkage, and base B.

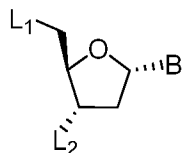
For the results in the tables below, *in vitro* activity and toxicity experiments were performed essentially as described in Example 1. For *in vitro* activity and toxicity studies, 3T3-L1 cells were transfected with 27 nM, 80 nM, 250 nM, 740 nM, 2, 222 nM, 6,667 nM, or 20,000 nM of modified oligonucleotide by electroporation and levels of P21 and Gadd45a and Tnfrsf10b were measured by RT-qPCR as described in Example 1 above. The caspase assay was performed as described in Example 8 above in 3T3-L1 cells. Localization of p54nrb in HeLa cells was quantitated as described in Example 15.

Table 55 *In vitro* activity and toxicity of modified oligonucleotides complementary to CXCL12

Compound ID	<i>in vitro</i> CXCL12 IC ₅₀ (nM)	<i>in vitro</i> Caspase (% control) @ 20 μ M
558807	0.029	321
1244441	0.471	108
1215458	0.200	104
1215459	0.191	111
1215460	0.130	133
1244442	0.134	185
1244443	0.083	279
1244444	0.109	213
1244445	0.198	249
1244446	0.127	243
1244447	0.080	333

Example 23 Stereochemical Isomers of Nucleosides

Modified oligonucleotides containing α -D-DNA nucleotides (see below) at various positions were synthesized. These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking an altered nucleotide in the central region. The compounds in Table 54 each comprise a 5' wing and a 3' wing each consisting of three linked cEt nucleosides and a central region comprising nucleosides each comprising 2'- β -D-deoxyribsyl sugar moieties aside from the altered nucleotide, as indicated. Each internucleoside linkage is a phosphodiester internucleoside linkage. The compounds in the table below are 100% complementary to mouse CXCL12, GENBANK NT_039353.7 truncated from 69430515 to 69445350 (SEQ ID NO: 1), at position 6877 to 6892.



α -D-2'-DNA

Table 56 modified oligonucleotides with stereochemical modifications

Compound ID	position of altered nucleotide in central region	stereochemical configuration of altered nucleotide	Chemistry Notation	SEQ ID NO
1244458	none	none	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds} C_{ds} T_{ds} C_{ds} A_{ds} C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244448	1	α -D-DNA	$G_{ks}^m C_{ks} A_{ks} [\alpha\text{-D } T_{ds}] G_{ds} T_{ds} T_{ds} C_{ds} T_{ds} C_{ds} A_{ds} C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244449	2	α -D-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} [\alpha\text{-D } G_{ds}] T_{ds} T_{ds} C_{ds} T_{ds} C_{ds} A_{ds} C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244450	3	α -D-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} [\alpha\text{-D } T_{ds}] T_{ds} C_{ds} T_{ds} C_{ds} A_{ds} C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244451	4	α -D-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} [\alpha\text{-D } T_{ds}] C_{ds} T_{ds} C_{ds} A_{ds} C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244452	5	α -D-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds} [\alpha\text{-D } C_{ds}] T_{ds} C_{ds} A_{ds} C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244453	6	α -D-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds} C_{ds} [\alpha\text{-D } T_{ds}] C_{ds} A_{ds} C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244454	7	α -D-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds} C_{ds} T_{ds} [\alpha\text{-D } C_{ds}] A_{ds} C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244455	8	α -D-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds} C_{ds} T_{ds} C_{ds} [\alpha\text{-D } A_{ds}] C_{ds} A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244456	9	α -D-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds} C_{ds} T_{ds} C_{ds} A_{ds} [\alpha\text{-D } C_{ds}] A_{ds} T_{ks} T_{ks} A_{ks}$	18
1244457	10	α -D-DNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds} C_{ds} T_{ds} C_{ds} A_{ds} C_{ds} [\alpha\text{-D } A_{ds}] T_{ks} T_{ks} A_{ks}$	18

A subscript “d” indicates a nucleoside comprising an n unmodified, 2’-β-D-deoxyribosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. [α -D-B_{ds}] indicates a modified, α -D-DNA nucleotide with a 2’-deoxyribosyl sugar moiety, a phosphorothioate linkage, and base B.

For the results in the tables below, *in vitro* activity and toxicity experiments were performed essentially as described in Example 1. For *in vitro* activity and toxicity studies, 3T3-L1 cells were transfected with 27 nM, 80 nM, 250 nM, 740 nM, 2, 222 nM, 6,667 nM, or 20,000 nM of modified oligonucleotide by electroporation and levels of p21 were measured by RT-qPCR as described in Example 1 above. The caspase assay was performed as described in Example 8 above in 3T3-L1 cells. Localization of p54nrb in HeLa cells was quantitated as described in Example 15.

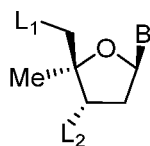
Table 57 *In vitro* activity and toxicity of modified oligonucleotides complementary CXCL12

Compound ID	<i>in vitro</i> CXCL12 IC ₅₀ (nM)	<i>in vitro</i> Caspase (% control) @ 20 μ M	<i>in vitro</i> p21 (% control) @ 20 μ M	% nucleolar p54nrb
1244458	19	785	327	86
1244448	35	269	135	66
1244449	169	111	101	8
1244450	103	96	169	11
1244451	45	261	206	78
1244452	393	295	146	83
1244453	80	417	255	92

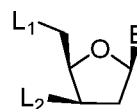
1244454	512	287	240	65
1244455	125	409	310	83
1244456	247	233	269	96
1244457	31	854	400	100

Example 24 4'-methyl and Xylo DNA

Modified oligonucleotides containing an altered nucleotide with a 4'-methyl modified sugar moiety or a 2'-deoxy-β-D-xylofuranosyl (2'-deoxy-β-D-XNA) sugar moiety at various positions were synthesized (see Table 58 below). Synthesis of oligonucleotides comprising 2'-deoxy-β-D-XNA nucleosides has been described previously (Wang, et. al., *Biochemistry*, 56(29): 3725-3732, 2017). Synthesis of oligonucleotides comprising 4'-methyl modified nucleosides has been described previously (e.g., Detmer et. al., *European J. Org. Chem*, 1837-1846, 2003). . The compounds in Table 58 each comprise a 5' wing and a 3' wing each consisting of three linked cEt nucleosides and a central region comprising nucleosides each comprising 2'-β-D-deoxyribose sugar moieties aside from the altered nucleotide, as indicated. Each internucleoside linkage is a phosphodiester internucleoside linkage. These compounds were compared to a compound comprising a 2'-OMe modified sugar moiety at position 2 of the central region, 936053, described in Example 1 above. The compounds in the table below are 100% complementary to mouse CXCL12, GENBANK NT_039353.7 truncated from 69430515 to 69445350 (SEQ ID NO: 1), at position 6877 to 6892.



4'-methyl-β-D-2'-DNA



2'-deoxy-β-D-XNA

Table 58 modified oligonucleotides with stereochemical modifications

Compound ID	position of altered nucleotide in central region	modification of altered nucleotide	Chemistry Notation	SEQ ID NO
936053	2	2'-OMe	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ms} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1244461	3	4'-Me	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{[4m]s} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1244462	4	4'-Me	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{[4m]s}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1263776	3	β-D-XNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} [\beta-D T_{xs}] T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1263777	4	β-D-XNA	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} [\beta-D T_{xs}]^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18

A subscript "d" indicates an unmodified, 2'-β-D-deoxyribose sugar moiety. A subscript "k" indicates a cEt. A subscript "s" indicates a phosphorothioate internucleoside linkage. A superscript "m" indicates 5-methyl Cytosine. A subscript "[4m]" indicates a 4'-methyl-2'-β-D-deoxyribose sugar moiety. [β-D-B_{xs}]

indicates a modified, β -D-XNA (xylo) nucleotide with a 2'-deoxyxylosyl sugar moiety, a phosphorothioate linkage, and base B.

For *in vivo* activity and toxicity studies, 3 BALB/c mice per group were administered 10 or 150 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed after 72 hours. Four animals were administered saline to serve as a control. RT-PCR was performed as described in Example 1 to determine mRNA levels of CXCL12, P21, Tnfrsf10b, and Gadd45a. Plasma levels of ALT was measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

Table 59 *In vivo* activity and toxicity of modified oligonucleotides complementary to CXCL12

Compound ID	<i>in vivo</i> CXCL12 @ 10 mg/kg (% control)	<i>in vivo</i> CXCL12 @ 150 mg/kg (% control)	<i>in vivo</i> P21 @ 150 mg/kg (% control)	<i>in vivo</i> Tnfrsf10b @ 150 mg/kg (% control)	<i>in vivo</i> Gadd45a @ 150 mg/kg (% control)	<i>in vivo</i> ALT @ 10 mg/kg (IU/L)	<i>in vivo</i> ALT @ 150 mg/kg (IU/L)
PBS	100	100	100	100	100	26 (@ 0 mg/kg)	
936053	37	13	175	448	216	23	83
1244461	22	5	2994	4663	1124	31	5080
1244462	30	7*	1038	717*	407*	28	1789*
1263776	19	11	4846	10686	1032	27	9234
1263777	13	n.d.	n.d.	n.d.	n.d.	58	death

*Value represents the average of 2 samples.

Example 25 Microscopy

Selected modified nucleotides described in the Examples above were tested for their effect on HeLa cells by microscopy. HeLa cells were transfected by lipofectamine 2000 with 200nM of modified oligonucleotide for 2 hrs and then cellular protein p54nrb was stained by mP54 antibody (Santa Cruz Biotech, sc-376865) and DAPI was used to stain for the nucleus of cells.

For experiments reported in the tables below, the number of cells with nucleolar p54nrb and the total number of cells in the images were counted and a percentage of cells with mislocalization of p54nrb was calculated. Where the same compound appears in multiple tables, these represent the results from independent experiments.

Table 60 Nucleolar mislocalization of p54nrb

Compound ID	Cells with nucleolar p54nrb	Total cells	% cells with mislocalization
Mock	0	74	0
558807	45	51	88

Table 61 Nucleolar mislocalization of p54nrb

Compound ID	Sugar Motif	% cells with mislocalization	ALT @ 150mg/kg (IU/L)
464917	kkk-d(10)-kkk	75	death
982034	kkk-d-m-(8)-kkk	<7	13,172
465175	kkk-d(10)-kkk	57	1,564
1133329	kkk-d-m-(8)-kkk	48	60
465181	kkk-d(10)-kkk	58	7,087
1133335	kkk-d-m-(8)-kkk	<1	26
545984	kkk-d(10)-kkk	98	37,277
1133060	kkk-d-m-(8)-kkk	0	39

For experiments reported in the tables below, selected images were qualitatively analyzed and assigned a score of (-), indicating that no p54nrb mislocalization to the nucleolus was observed, or a score of (+) indicating that mislocalization of p54nrb to the nucleolus was observed in some cells, or (++) indicating that p54nrb mislocalization to the nucleolus was observed in most or all cells.

Table 62 Nucleolar mislocalization of p54nrb and correlation with toxicity

Compound ID	Complementary mRNA	Mislocalization of p54nrb	ALT @ max dose*
558807	CXCL12	++	death
936049	CXCL12	++	8,622
936053	CXCL12	-	46
892826	CXCL12	-	10,463
766677	CXCL12	-	23
828911	CXCL12	-	27
936051	CXCL12	+	death
936052	CXCL12	-	1,110
1070041	CXCL12	+	96
1061314	CXCL12	-	26
1061302	CXCL12	+	2,253
1061303	CXCL12	-	34
1061304	CXCL12	-	52
1061305	CXCL12	-	31
1076587	CXCL12	-	n.d.
1076588	CXCL12	+	n.d.
1069852	CXCL12	-	n.d.
1061328	CXCL12	+	n.d.
1061955	CXCL12	-	86
1061964	CXCL12	-	n.d.
1244441	CXCL12	-	n.d.
1215458	CXCL12	-	n.d.
1215459	CXCL12	-	n.d.
1215460	CXCL12	-	n.d.
1244442	CXCL12	-	n.d.

1244443	CXCL12	+	n.d.
1244444	CXCL12	++	n.d.
1244445	CXCL12	++	n.d.
1244446	CXCL12	++	n.d.
1244447	CXCL12	++	n.d.
464917	FXI	+	18,316
465977	FXI	+	death
483706	FXI	+	1,424
443919	FXI	-	68
820685**	FXI	-	59
508031	SOD1	++	16,317
895154	SOD1	+	206
895155	SOD1	-	41
895156	SOD1	+	1,242
508034	SOD1	+	22,396
508037	SOD1	-	20
529933	SOD1	-	11

*Data presented in previous examples; maximum administered dose is 150 mg/kg for modified oligonucleotides complementary to CXCL12, 100 mg/kg for modified oligonucleotides complementary to SOD1, and 33 mg/kg for compounds complementary to FXI, except that the ALT for 820685 is at 100 mg/kg.

**820685 has the same sequence as 464917 and a sugar motif of kkk-m(10)-kkk.

5

Example 26 Nucleolar mislocalization of p54nrb with fluorescently-labeled modified oligonucleotides

Modified oligonucleotides described in the tables above were conjugated to Cy3 or FAM on the 3'-end via a phosphorothioate linker or on the 5'-end via a phosphorothioate linker to generate a compound comprising a conjugate group that comprises a fluorophore, resulting in a fluorescently labeled modified oligonucleotide.

10 Fluorescently labeled modified oligonucleotides were incubated with HeLa cells at 200nM for 2 hours and cells were imaged by fluorescent microscopy. Cellular protein p54nrb was stained by mP54 antibody (Santa Cruz Biotech, sc-376865) and DAPI was used to stain for the nucleus of cells. For experiments reported in the tables below, images were qualitatively analyzed and assigned a score of (-), indicating that no p54nrb mislocalization to the nucleolus was observed, or a score of (+) indicating that mislocalization of p54nrb to the

15 nucleolus was observed in some cells, or (++) indicating that p54nrb mislocalization to the nucleolus was observed in most or all cells.

Table 63 Fluorescently Labeled Modified Oligonucleotides

Unlabelled compound ID	Fluorescently-labelled compound ID	Chemistry notation for Fluorescently-labelled compound	SEQ ID NO:
558807	925819	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{ks} - Cy3$	18
766676	925820	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{ks} - Cy3$	18
766677	925821	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{dx} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{ks} - Cy3$	18
766678	925822	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{ks} - Cy3$	18
766679	925826	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{dx}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{ks} - Cy3$	18
766684	925824	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{dx} A_{ds} T_{ks} T_{ks} A_{ks} - Cy3$	18

936049	958339	Cy3-G _{ks} ^m C _{ks} A _{ks} U _{ms} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	19
936053	958340	Cy3-G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ms} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
892826	958341	Cy3-G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} U _{ms} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	20
558807	1189295	FAM-G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _{ks}	18
1061955	1189310	FAM-G _{ks} ^m C _{ks} A _{ks} T _{ds} I _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _{ks}	30
766677	1215929	FAM-G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{dx} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _{ks}	18
936053	1189369	FAM-G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ms} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
942944	1215928	FAM-G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} ^{(R)-m} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
464917	813223	Cy3-G _{ks} T _{ks} ^m C _{ks} T _{ds} G _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} T _{ks} ^m C _{ks} ^m C _k	22
508031	828939	Cy3-T _{ks} G _{ks} A _{ks} G _{ds} G _{ds} T _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ks} G _{ks} G _k	26
482050	841864	Cy3-A _{ks} T _{ks} ^m C _{ks} A _{ds} T _{ds} G _{ds} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ks} T _{ks} T _k	24
449093	489982	FAM-T _{ks} T _{ks} ^m C _{ks} A _{ds} G _{ds} T _{ds} ^m C _{ds} A _{ds} T _{ds} G _{ds} A _{ds} ^m C _{ds} T _{ds} T _{ks} ^m C _{ks} ^m C _k	28
465178	869208	Cy3-G _{ks} T _{ks} ^m C _{ks} A _{ds} G _{ds} T _{ds} A _{ds} T _{ds} ^m C _{ds} ^m C _{ds} ^m C _{ds} A _{ds} G _{ds} T _{ks} G _{ks} T _k	89
575013	869198	Cy3- ^m C _{ks} A _{ks} G _{ks} A _{ds} T _{ds} A _{ds} T _{ds} A _{ds} G _{ds} G _{ds} A _{ds} ^m C _{ds} T _{ds} G _{ks} G _{ks} A _k	110
549139	869199	Cy3-G _{ks} A _{ks} ^m C _{ks} G _{ds} ^m C _{ds} G _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} A _{ds} A _{ds} G _{ds} G _{ks} T _{ks} T _k	111
508032	869200	Cy3-G _{ks} G _{ks} A _{ks} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ds} T _{ds} G _{ds} G _{ds} ^m C _{ds} ^m C _{ds} A _{ks} ^m C _{ks} A _k	112
464932	869201	Cy3-G _{ks} G _{ks} ^m C _{ks} ^m C _{ds} A _{ds} ^m C _{ds} ^m C _{ds} A _{ds} ^m C _{ds} G _{ds} ^m C _{ds} T _{ds} G _{ds} T _{ks} ^m C _{ks} A _k	113
465131	869202	Cy3-T _{ks} G _{ks} ^m C _{ks} ^m C _{ds} A _{ds} ^m C _{ds} ^m C _{ds} G _{ds} T _{ds} A _{ds} G _{ds} A _{ds} ^m C _{ds} A _{ks} ^m C _{ks} G _k	114
147420	841863	Cy3- A _{es} A _{es} T _{es} G _{es} T _{es} G _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} T _{ds} G _{ds} T _{ds} ^m C _{ds} ^m C _{es} T _{es} T _{es} G _{es} A _e	73

A subscript “d” indicates an unmodified, 2’-β-D-deoxyribosyl sugar moiety. A subscript “e” indicates a 2’-MOE-β-D-ribofuranosyl sugar moiety. A subscript “m” indicates a 2’-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine.. A subscript “x” indicates a MOP internucleoside linkage.

Table 64 Nucleolar mislocalization of p54nrb

Unlabelled compound ID	Fluorescently-labelled Compound ID	Complementary mRNA	Mislocalization of p54nrb	ALT @ 150mg/kg of unlabelled modified oligonucleotide
558807	925819	CXCL12	++	death
766676	925820	CXCL12	++	5,475
766677	925821	CXCL12	-	23
766678	925822	CXCL12	-	67
766679	925823	CXCL12	+	3,347
766684	925824	CXCL12	++	death
936049	958339	CXCL12	++	8,622
936053	958340	CXCL12	-	46
892826	958341	CXCL12	+	10,463
558807	1189295	CXCL12	++	death
1061955	1189310	CXCL12	-	86
766677	1215929	CXCL12	-	23
936053	1189369	CXCL12	-	46
942944	1215928	CXCL12	+	233

Table 65 Nucleolar mislocalization of p54nrb

Unlabelled compound ID	Fluorescently-labelled Compound ID	Complementary mRNA	Mislocalization of p54nrb	ALT @ 200 mg/kg of unlabelled modified oligonucleotide
147420	841863	CPT1A	++	7,794

For *in vivo* maximum tolerated doses reported in the table below, 2-4 BALB/C mice per group were administered modified oligonucleotide at 3.7, 11, 33, 100, or 300 mg/kg by subcutaneous injection and sacrificed after 72 hours. Maximum tolerated dose is the highest dose at which ALT is below 5x that in PBS-treated control mice, or ~150 IU/L.

Table 67 Nucleolar mislocalization of p54nrb

Unlabelled compound ID	Fluorescently-labelled compound ID	Complementary mRNA	Mislocalization of p54nrb, labelled modified oligonucleotide	Maximum tolerated dose unlabelled modified oligonucleotide (mg/kg, mouse)
464917	813223	FXI	+	11
508031	828939	SOD1	++	33
482050	841864	PTEN	++	33
449093	489982	SRB1	++	33
465178	869208	FXI	+	100
575013	869198	FXII	-	>300
549139	869199	none	-	>300
508032	869200	SOD1	-	>300
464932	869201	FXI	-	>300
465131	869202	FXI	-	>300

Table 68 Nucleolar mislocalization of p54nrb

Unlabelled compound ID	Fluorescently-labelled compound ID	Cells with nucleolar p54nrb	Total cells	% cells with p54nrb mislocalization
558807	925819	57	74	77
936049	958339	51	72	71
936053	958340	6	65	9
892826	958341	30	53	57

Example 27 *In Vivo* and *In vitro* toxicity of LNA-containing modified oligonucleotides

Modified oligonucleotides in the table below have a 3-10-3 sugar motif with LNA nucleosides on the 5' and 3' ends and DNA nucleosides in the central region.

Table 69 Modified Oligonucleotides

Compound ID	Chemistry notation	SEQ ID NO:
569713	G _{ls} A _{ls} ^m C _{ls} G _{ds} ^m C _{ds} G _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} A _{ds} A _{ds} G _{ds} G _{ls} T _{ls} T _l	111
569717	A _{ls} T _{ls} ^m C _{ls} A _{ds} T _{ds} G _{ds} G _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} ^m C _{ls} T _{ls} T _l	24
569719	G _{ls} T _{ls} ^m C _{ls} T _{ds} G _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} T _{ls} ^m C _{ls} ^m C _l	22
569721	T _{ls} G _{ls} A _{ls} G _{ds} G _{ds} T _{ds} ^m C _{ds} ^m C _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} ^m C _{ds} T _{ls} G _{ls} G _l	26
814336	G _{ls} ^m C _{ls} A _{ls} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ls} T _{ls} A _l	18

A subscript “d” indicates an unmodified, 2’-β-D-deoxyribose sugar moiety. A subscript “l” indicates a β-D-LNA sugar moiety. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine.

- 5 Modified nucleotides with 3-10-3 lll-d(10)-lll sugar motifs were tested for their effect on 3T3 cells by microscopy. 3T3 cells were transfected by lipofectamine 2000 with 200nM of modified oligonucleotide for 2 hrs and then cellular protein p54nrb was stained by mP54 antibody (Santa Cruz Biotech, sc-376865) and DAPI was used to stain for the nucleus of cells. For experiments reported in the tables below, images were qualitatively analyzed and assigned a score of (-), indicating that no p54nrb mislocalization to the nucleolus was observed, or a scale of (+) indicating that mislocalization of p54nrb to the nucleolus was observed in some cells, or (++) indicating that p54nrb mislocalization to the nucleolus was observed in most or all cells.
- 10 Modified nucleotides with 3-10-3 lll-d(10)-lll or kkk-d(10)-kkk sugar motifs were tested *in vivo*. For *in vivo* toxicity data, 2-4 BALB/C mice were administered modified oligonucleotide by subcutaneous injection at the doses indicated in the table below. Mice were sacrificed after 72 hours and mRNA was isolated and analyzed as described in Example 1 above. ALT values in plasma were obtained using a clinical chemistry analyzer.
- 15

Table 70 Modified oligonucleotide dosages administered to mice

Compound ID	Dose 1 (mg/kg)	Dose 2 (mg/kg) (Maximum dose)
549139	300	n/a
569713	300	n/a
482050	33	100
569717	33	100
464917	11	33
569719	11	33
508031	33	100
569721	33	100
558807	17	51
814336	17	51

Table 71 *In vitro* p54nrb localization and *in vitro* toxicity

Compound ID	Complementary mRNA	Mislocalization of p54nrb	ALT @ maximum dose	P21 mRNA at maximum dose (% control)	Tnfrsf10b mRNA at maximum dose (% control)
549139	none	-	35	306	252
569713	none	-	44	449	241
482050	PTEN	n.d.	6555	10,430	4,232
569717	PTEN	n.d.	270	17,295	9,568
464917	FXI	++	13,920	9,590	7,731
569719	FXI	+	14,449	13,020	6,569
508031	SOD1	++	18,550	8,909	6,678
569721	SOD1	+	33,246	12,193	9,169
558807	CXCL12	++	9,510	11,904	6,831
814336	CXCL12	++	death*	n.d.	n.d.

*At 17 mg/kg, ALT was 4725, P21 mRNA was 11,567, and Tnfrsf10b mRNA was 8,636.

For the *in vitro* study reported in the tables below, 3T3-L1 cells were electroporated with 27 nM, 80 nM, 250 nM, 740 nM, 2,222 nM, 6,667 nM, or 20,000 nM of modified oligonucleotide and levels of P21 and Gadd45a were measured by RT-qPCR as described in Example 1 above. Caspase-3 and caspase-7 activation was measured using the Caspase-Glo® 3/7 Assay System (G8090, Promega). Levels of caspase activation correlate with apoptotic cell death.

Table 72 *in vitro* Caspase Activation

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Caspase Activation						
549139	2693	2272	2536	2170	2664	2128	2406
569713	2219	1988	1996	1892	2099	2178	3202
464917	1988	2116	1907	2365	6580	13268	24228
569719	2080	2183	2610	4225	10773	14199	20524
508031	7082	6602	7123	8876	14962	20060	29955
569721	7905	7741	8508	10364	20715	24370	49476
558807	7272	7887	8672	12555	19397	25124	28133
814336	7308	7975	9150	12927	21327	26992	26794

Table 73 *in vitro* P21 Expression

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
	Expression level of P21 mRNA (% Control)						
549139	108	104	93	97	97	88	99
569713	116	105	94	127	129	139	166
464917	129	132	145	149	275	595	1044
569719	120	118	144	160	332	731	922
508031	100	90	99	102	100	124	247
569721	116	104	123	119	148	123	470
558807	95	126	123	123	104	119	193
814336	86	100	96	85	119	170	254

Table 74 *in vitro* Gadd45a Expression

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
Expression level of Gadd45a mRNA (% Control)							
549139	113	125	105	83	72	61	35
569713	168	139	116	154	135	162	147
464917	153	170	187	210	376	906	933
569719	165	168	217	220	514	1223	1086
508031	106	115	111	112	114	211	345
569721	165	168	158	136	212	326	451
558807	200	198	222	216	200	235	263
814336	117	113	139	148	169	198	278

Table 75 *in vitro* Tnfrsf10b Expression

Compound ID	27 nM	80 nM	250 nM	740 nM	2,222 nM	6,667 nM	20,000 nM
Expression level of Tnfrsf10b mRNA (% Control)							
549139	93	96	87	87	89	98	96
569713	116	111	79	119	115	128	114
464917	122	127	129	93	116	186	125
569719	105	107	117	88	119	151	36

5

Example 28 Total Protein Binding of modified oligonucleotides complementary to SOD1

Modified oligonucleotides described in the examples above were evaluated for their total protein binding in HeLa nuclear lysate. Cellular proteins were captured with the biotin-conjugated modified oligonucleotide 791136, which has a 5'-biotin-TEG, the sugar motif kkk-d(10)-kkk and the same sequence as 464917, GTCTGTGCATCTCTCC (SEQ ID NO: 22) and eluted with increasing concentrations of 508031, 895154, 895155, and 895156, described in Example 6 above. Eluted proteins were run on an SDS-PAGE gel. See Figure 1. Increased total protein binding is observed for compound 508031 and 895154 compared to compound 895155 and 895156.

15 Example 29 Total protein binding of modified oligonucleotides complementary to FXI

Modified oligonucleotides described in the examples above were evaluated for their total protein binding in HeLa nuclear lysate. Cellular proteins were captured with the biotin-conjugated modified oligonucleotide 791136, which has a 5'-biotin-TEG, the sugar motif kkk-d(10)-kkk and the same sequence as 464917, GTCTGTGCATCTCTCC (SEQ ID NO: 22) and eluted with increasing concentrations of 464917, 465977, 483706, and 820685, described in Examples 4 and 25 above. Eluted proteins were run on an SDS-PAGE gel. See Figure 2A. Increased total protein binding is observed for compound 464917 and 465977 compared to compounds 483706 and 820685. A series of western blots was done to detect SSBP1, NCL1, PCNA, p54nrb, RNase H1, and PSF. Results are shown in Figure 2B.

In an independent experiment, cellular proteins were captured with 791136 and eluted with increasing concentrations of 464917, 465178, 464392, and 465131. See Figure 3. Increased total protein binding is observed for compound 464917 compared to 465178, 464932, and 465131.

5 Example 30 Total protein binding, activity and toxicity with MOP linkages

Modified oligonucleotides were evaluated for their total protein binding in cells. Cellular proteins were captured with the biotin-conjugated modified oligonucleotide 592590, which has a 5'-biotin-TEG, the sugar motif kkk-d(10)-kkk and the sequence GCTAGCCTCTGGATTT (SEQ ID NO:115) and eluted with the modified oligonucleotides described in the table below. Eluted proteins were run on an SDS-PAGE gel and visualized. Decreased protein binding is observed for compounds with decreased toxicity compared to 558807, in particular for compounds 766654, 766655, and 766666. See Figure 4.

Table 76 Modified oligonucleotides containing Two MOP linkages

Compound ID	Linkage Mod position in central region	Target	Chemistry Notation	SEQ ID NO
766653	1, 2	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{dx} G _{dx} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766654	2, 3	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{dx} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766655	3, 4	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{dx} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766656	4, 5	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{dx} ^m C _{dx} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766657	5, 6	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{dx} T _{dx} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766658	6, 7	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{dx} ^m C _{dx} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766659	7, 8	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{dx} A _{dx} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
766665	8, 9	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{dx} ^m C _{dx} A _{ds} T _{ks} T _{ks} A _k	18
766664	9, 10	CXCL12	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{dx} A _{dx} T _{ks} T _{ks} A _k	18

15 A subscript “d” indicates an unmodified, 2'-β-D-deoxyribose sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine. A subscript “x” indicates a MOP internucleoside linkage.

In vitro activity and *in vivo* activity and toxicity experiments were performed essentially as described in Example 1. For *in vivo* toxicity studies, a single BALB/C mouse per dose of modified oligonucleotide was administered 16.7 mg/kg, 50 mg/kg, or 150 mg/kg modified oligonucleotide by subcutaneous injection and sacrificed 72 hours later. ALT levels were measured using an automated clinical chemistry analyzer. For the *in vivo* activity study in the table below, 1 BALB/C mouse per group was administered 1.8 mg/kg, 5.5 mg/kg, 16.7 mg/kg, 50 mg/kg or 150 mg/kg modified oligonucleotide subcutaneously and sacrificed after 24 hours.

Table 77 *in vivo* Activity and Toxicity

Compound ID	MOP linkage positions	<i>in vivo</i> CXCL12 ED50 (mg/kg)	ALT @ 50 mg/kg (IU/L)	ALT @ 150 mg/kg (IU/L)
PBS	n/a	n/a	26 (@0mg/kg)	
558807	n/a	2.9	19,806	death
766653	1, 2	23.6	32	33
766654	2, 3	31.6	28	30
766655	3, 4	32.7	28	27
766656	4, 5	26.7	25	29
766657	5, 6	7.0	213	5,503
766658	6, 7	6.2	64	1,380
766659	7, 8	10.6	51	3,423
766665	8, 9	5.5	3,437	11,954
766664	9, 10	6.2	4,045	death

5 Example 31 Self-Structure of modified oligonucleotides complementary to CXCL12

T_m was determined for self-structures of modified oligonucleotides described in the examples above. Compounds in the table below are complementary to CXCL12 and have sequences corresponding to SEQ ID NO: 18-21. T_m was also determined for duplexes of the modified oligonucleotides described in the examples above in complex with a RNA 20-mer with the sequence GAUAAUGUGAGAACAUGCCU (SEQ ID NO: 116).

Table 78 T_m of Modified Oligonucleotides complementary to CXCL12, Self-Structure and Duplex

Compound ID	linkage-altered nucleotide (position in central region)	Sugar-modification of altered nucleotide (position in central region)	T _m (°C) Self structure	T _m (°C) duplex
558807	none	none	48.6	65.1
1061955	none	inosine (2)	32.9	57.5
766676	MOP(1)	none	44.6	63.3
766677	MOP(2)	none	45.3	63.5
766678	MOP(3)	none	47.9	63.1
766679	MOP(4)	none	47.1	62.6
766680	MOP(5)	none	n.d.	63
766681	MOP(6)	none	n.d.	62.9
766682	MOP(7)	none	n.d.	63.8
766683	MOP(8)	none	n.d.	63.3
766684	MOP(9)	none	n.d.	64.1
766685	MOP(10)	none	n.d.	63.9
936053	none	2'-OMe (2)	49.0	67.0
828911	none	2'-MOE (2)	48.2	66.8
1070041	none	cEt (2)	52.7	69.5
936051	none	2'-FANA (2)	46.1	64.8

936052	none	2'-ribo-F (2)	47.2	66.0
1123320	none	5'-(<i>R</i>)-Me (2)	49.4	65.5
1123322	none	5'-(<i>S</i>)-Me (2)	43.0	62.0
942943	none	5'-(<i>R</i>)-Me (3)	47.3	62.3
957908	none	5'-(<i>S</i>)-Me (3)	45.1	65.1
942944	none	5'-(<i>R</i>)-Me (4)	49.5	62.3
957909	none	5'-(<i>S</i>)-Me (4)	46.2	66.3
957910	none	5'-(<i>R</i>)-allyl (3)	44.4	62.1
957911	none	5'-(<i>R</i>)-allyl (4)	47.3	62.4
957912	none	5'-(<i>S</i>)-allyl (3)	41.7	64.0
957913	none	5'-(<i>S</i>)-allyl (4)	47.1	64.6
1069852	none	pseudoU (2)	24.4	54.4
1061328	none	pseudoU (3)	44.6	55.3
1215458	none	β -L-DNA (2)	n.d.	58
1215459	none	β -L-DNA (3)	43	59
1215460	none	β -L-DNA (4)	45	62
1215461	none	α -L-DNA (3)	41	63
1215462	none	α -L-DNA (4)	49	65

Table 79 Tm of Modified Oligonucleotide Self-Structure

Compound ID	Target	Tm (°C)
449093	SRB1	< 40
464917	FXI	< 40
482050	PTEN	33.4
508031	SOD-1	58.9

Example 32 2'-modifications in 5' and 3'-regions of modified oligonucleotides

- 5 Modified oligonucleotides containing various sugar modification motifs were synthesized as indicated in the table below. The compounds in the table below are 100% complementary to mouse CXCL12, GENBANK NT_039353.7 truncated from 69430515 to 69445350 (SEQ ID NO: 1) at positions 6877 to 6892 (16-mers) or 6875 to 6894 (20-mers).

10 Table 80 modified oligonucleotides with 2'-sugar modifications

Compound ID	2'-modified sugars on 5'-end	2'-modified sugars on 3'-end	Chemistry Notation	SEQ ID NO
558807	kkk	kkk	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
1035522	kkk	eee	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{es} T _{es} A _e	18
1035523	eee	kkk	G _{es} ^m C _{es} A _{es} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
985648	eee	eee	G _{es} ^m C _{es} A _{es} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{es} T _{es} A _e	18
1069842	kkeee	eeekk	A _{ks} G _{ks} G _{es} ^m C _{es} A _{es} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{es} T _{es} A _{es} T _{ks} ^m C _k	117
1069843	kkeee	kkkkk	A _{ks} G _{ks} G _{es} ^m C _{es} A _{es} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _{ks} T _{ks} ^m C _k	117
1069844	kkkkk	eeekk	A _{ks} G _{ks} G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{es} T _{es} A _{es} T _{ks} ^m C _k	117
386864	eeeeee	eeeeee	A _{es} G _{es} G _{es} ^m C _{es} A _{es} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{es} T _{es} A _{es} T _{es} ^m C _e	117
1069845	kkkkk	kkkkk	A _{ks} G _{ks} G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _{ks} T _{ks} ^m C _k	117

1069846	eekkkk	kkkkk	A _{es} G _{es} G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _{ks} T _{ks} ^m C _k	117
1069847	kkkkk	kkkee	A _{ks} G _{ks} G _{ks} ^m C _{ks} A _{ss} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _{ks} T _{es} ^m C _e	117

A subscript “d” indicates an unmodified, 2’-β-D-deoxyribose sugar moiety. A subscript “k” indicates a cEt.

A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine. A subscript “e” indicates a 2’-MOE-β-D-ribofuranosyl sugar moiety. A subscript “m” indicates a 2’-O-methyl-β-D-ribofuranosyl sugar moiety.

- 5 For the *in vitro* study reported in the tables below, 3T3-L1 cells were electroporated with 27 nM, 80 nM, 250 nM, 740 nM, 2, 222 nM, 6,667 nM, or 20,000 nM of modified oligonucleotide and levels of CXCL12 were measured by RT-qPCR as described in Example 1 above. Caspase activation was measured as described in Example 4 above. Results are presented relative to the caspase activation in control cells not treated with modified oligonucleotide. Mislocalization of p54nrb was analyzed as described in Example 15 above. For experiments reported in the tables below, selected images were qualitatively analyzed and assigned a score of (-), indicating that no p54nrb mislocalization to the nucleolus was observed, or a score of (+) indicating that mislocalization of p54nrb to the nucleolus was observed in some cells, or (++) indicating that p54nrb mislocalization to the nucleolus was observed in most or all cells. Treatment of HeLa cells with certain modified oligonucleotides caused a filamentous appearance of p54nrb in cells. This is indicated by a “f” in the table below.

Table 81 *in vitro* Activity and Toxicity

Compound ID	Caspase (% control)	CXCL12 IC ₅₀ (nM)	p54nrb mislocalization
558807	1135	30	++
1035522	1261	35	+, f
1035523	244	100	+, f
985648	207	200	-, f
1069842	353	350	+, f
1069843	670	100	++
1069844	748	350	+
386864	1104	200	-,f
1069845	213	350	++
1069846	963	100	+
1069847	923	250	+

Example 33 Effect of treatment of b.END cells with modified oligonucleotides

- 20 For the *in vitro* study reported in the tables below, b.END.3 cells were electroporated with 3.125, 6.25, 12.5, 25, or 50 nM of modified oligonucleotide 464917 (hepatotoxic) or 549148 (nontoxic). 549148 is a 3-10-3 cEt modified oligonucleotide with the sequence GGCTACTACGCCGTCA (SEQ ID NO: 118),

which is not complementary to any known mouse gene. Expression levels of p21 and Gadd45a mRNA were measured after 0, 1, 2, 4, and 6 hours by RT-qPCR as described in Example 1.

Table 82 Relative mp21 mRNA dose response/time course in b.END cells

Compound	Dose (nM)	% Control mp21 mRNA			
		1 hrs	2 hrs	4 hrs	6 hrs
464917	0	100	100	100	100
464917	3.125	102	134	147	174
464917	6.25	113	149	169	242
464917	12.50	107	141	199	250
464917	25.0	122	183	330	394
464917	50.0	113	210	399	427
549148	0	100	100	100	100
549148	3.125	111	42	140	107
549148	6.25	88	90	128	126
549148	12.50	120	86	119	109
549148	25.0	114	111	147	107
549148	50.0	111	94	126	119

5

Table 82a Relative mGadd45a mRNA dose response/time course in b.END cells

Compound	Dose (nM)	% Control mGadd45a mRNA			
		1 hrs	2 hrs	4 hrs	6 hrs
464917	0	100	100	100	100
464917	3.125	87	88	203	396
464917	6.25	81	154	259	565
464917	12.50	85	173	331	905
464917	25.0	102	247	715	1586
464917	50.0	132	420	1376	3339
549148	0	100	100	100	100
549148	3.125	85	31	106	109
549148	6.25	72	95	103	125
549148	12.50	85	87	106	127
549148	25.0	85	103	144	123
549148	50.0	97	107	131	198

Example 34 Nucleolar delocalization of p54nrb in various cell lines

Cells were plated at 20,000 cells/well and transfected with Lipofectamine 2,000 and 60nM of modified oligonucleotide 791143, compound 464917 labeled on the 3'-end with Cy3. Cells were visualized 6 hours after transfection.

10

Table 83 p54nrb nucleolar mislocalization

Compound ID	Cell line	p54nrb nucleolar mislocalization
791143	U2OS	+
791143	NIH3T3	++

Cells were plated at 20,000 cells/well and transfected by free uptake with modified oligonucleotide 791143 as indicated in the table below. Cells were visualized 5 hours after transfection.

Table 84 p54nrb nucleolar mislocalization

Compound ID	Cell line	p54nrb nucleolar mislocalization
791143	MHT	+
791143	HeLa	++

- 5 Cells were plated at 20,000 cells/well and transfected by NEON electroporation at 1400V, 20ms, 2 pulses with 60 nM modified oligonucleotide 813223, compound 464917 labeled on the 5'-end with Cy3. Cells were visualized 5 hours after transfection.

Table 85 p54nrb nucleolar mislocalization

Compound ID	Cell line	p54nrb nucleolar mislocalization
813223	HeLa	++

- 10 Cells were transfected with 60nM modified oligonucleotide 813223 or compound 813225. Compound 813225 is the control oligonucleotide 549148 described above labeled on the 5'-end with Cy3. Cells were visualized 4 hours after transfection.

Table 85b p54nrb nucleolar mislocalization

Compound ID	Cell line	p54nrb nucleolar mislocalization
813223	b.END3	++
813225	b.END3	-
813223	NIH3T3	+
813223	primary neuron	+
813223	primary hepatocyte	++

15 **Example 35 Effect of depletion of RNaseH1 on toxicity of modified oligonucleotides**

HeLa cells were plated at 150,000 cells/well and transfected with control siRNA targeting luciferase or siRNA targeted to RNaseH1 (s48357 or s48358 from ThermoFisher) at a final concentration of 3 nM using Lipofectamine RNAiMAX for 48 hours. Modified oligonucleotides 464917 and 549148 were added to the cells by free uptake. 549148 is a 3-10-3 cEt modified oligonucleotide with the sequence

- 20 GGCTACTACGCCGTCA (SEQ ID NO: 118), which is not complementary to any known mouse gene. Confocal microscopy was used to visualize p54nrb localization as described in Example 15 above.

Table 86 *in vitro* p54nrb mislocalization

Compound ID	siRNA	p54nrb nucleolar mislocalization
464917	mock	++
464917	RNaseH1a	-
464917	RNaseH1b	-

Table 87 *in vitro* P21 Expression in HeLa cells

Compound ID	siRNA	0 nM	3.125 nM	6.25 nM	12.5 nM	25 nM	50 nM
Expression level of P21 mRNA (% Control)							
464917	Luci	90	134	141	143	171	201
464917	H1	78	79	82	83	84	95
549148	Luci	100	119	105	84	94	82
549148	H1	99	86	92	81	79	85

5

Table 88 *in vitro* Gadd45a Expression in HeLa cells

Compound ID	siRNA	0 nM	3.125 nM	6.25 nM	12.5 nM	25 nM	50 nM
Expression level of P21 mRNA (% Control)							
464917	Luci	73	119	126	179	270	463
464917	H1	65	82	110	117	154	260
549148	Luci	100	89	107	102	97	83
549148	H1	72	83	103	103	105	96

Example 36 Protein Binding of modified oligonucleotides

Modified oligonucleotides described in the examples above were evaluated for their protein binding in cells.

Cellular proteins were captured with the biotin-conjugated modified oligonucleotide 791136, which has a 5'-

10 biotin-TEG, the sugar motif kkk-d(10)-kkk, a full phosphorothioate backbone, and the same sequence as 464917, GTCTGTGCATCTCTCC (SEQ ID NO: 22). Proteins were eluted with increasing concentrations of 464917 or 549148. Eluted proteins were run on an SDS-PAGE gel and analyzed by western blot for p54nrb, FUS, RNaseH1, SSBP1, Ku70, PSPC1, SND1, FUBP, NCL1, and Ku80. Band intensities are represented in the table below: -, no band; +, faint band; ++, medium band; +++, intense band. See Figure 5A.

15

Table 89 Protein binding of modified oligonucleotides

Protein	Relative band intensity 464917		Relative band intensity 549148	
	0.625 μ M	5 μ M	0.625 μ M	5 μ M
p54nrb	-	+++	-	+
FUS	-	++	-	-
RNaseH1	-	++	-	+
SSBP1	++	++	+	+
Ku70	+	++	+	+
PSPC1	-	+	-	+
SND1	++	+++	+	++
FUBP	+	++	+	+

NCL1	+	++	+	+
Ku80	+	++	++	++

Total protein binding to 464917 and 549418 was tested using biotin-464917 or biotin-549148 to capture cellular proteins, which were then eluted with increasing concentrations of 464917 or 549148. The hepatotoxic compound 464917 shows increased global protein binding compared to 549148; see Figure 5B.

5

Example 37 *In vitro* Activity and Toxicity of modified oligonucleotides comprising modified internucleoside linkages

Modified oligonucleotides were designed based on the control oligonucleotide 558807, described in Example 1 herein and synthesized using standard procedures. Modified internucleoside linkages (1 or 2) were positioned at various positions within the central region of the oligonucleotides as illustrated below. The resulting modified oligonucleotides were tested for their ability to inhibit CXCL12 (Chemokine ligand 12) and Raptor expression levels. The potency of the modified oligonucleotides was evaluated and compared to the control oligonucleotide.

The modified oligonucleotides were tested *in vitro* in mouse b.END cells by electroporation. Cells at a density of 20,000 cells per well are transfected using electroporation with 0.027, 0.082, 0.25, 0.74, 2.22, 6.67 and 20 μ M concentrations of each of the oligonucleotides listed below. After a treatment period of approximately 24 hours, RNA is isolated from the cells and mRNA levels are measured by quantitative real-time PCR and the CXCL12 mRNA and Raptor mRNA levels are adjusted according to total RNA content, as measured by RIBOGREEN®.

20

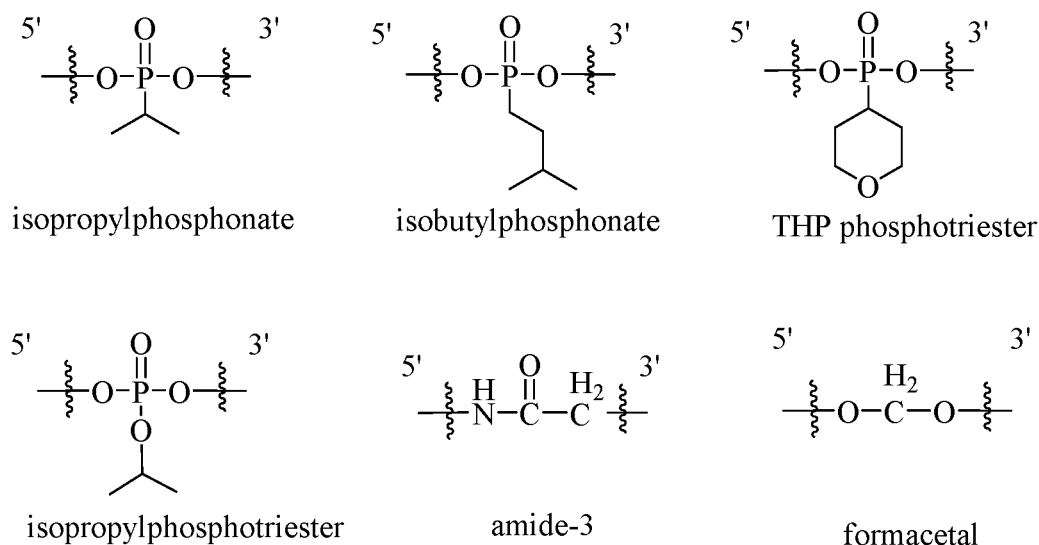
Table 90 Modified Oligonucleotides

Compound ID	Linkage-altered nucleotide position in central region	Linkage mod "x"	Chemistry Notation	SEQ ID NO
558807	n/a	n/a	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
857528	3	THP phosphotriester	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _x T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
857529	3	isopropylphosphotriester	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
857530	3	isobutylphosphonate	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
857505	3	isopropylphosphonate	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
883401	3	amide-3	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
883521	3	formacetal	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
857532	4	THP phosphotriester	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{dx} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
857533	4	isopropylphosphotriester	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{dx} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
857531	4	isopropylphosphonate	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{dx} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
857534	4	isobutylphosphonate	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{dx} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18

857537	3,4	isopropylphosphonate	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{dx}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
857540	3,4	isobutylphosphonate	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{dx}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
857538	3,4	THP phosphotriester	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{dx}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18

A subscript “d” indicates a an unmodified, 2’-β-D-deoxyribosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine. A subscript “x” indicates a modified internucleoside linkage as indicated in the “linkage mod x” column. These linkages are illustrated below.

5



10

The half maximal inhibitory concentration (IC₅₀) of each oligonucleotide listed above was calculated by plotting the concentration of oligonucleotide versus the percent inhibition of CXCL12 mRNA or Raptor mRNA expression achieved at each concentration, and noting the concentration of oligonucleotide at which 50% inhibition of CXCL12 mRNA expression is achieved compared to the control. The results are presented in the table below.

Table 91 *In vitro* Activity and Toxicity

Compound ID	IC ₅₀ (μM) CXCL12	Raptor % Control (4 μM)	Raptor IC50* (μM)
558807	0.17	47	3.7
857505	0.15	82	>4
857530	0.32	87	>4
857528	0.23	110	>4
857529	1.09	74	>4
883401	30	65	>4
883521	0.40	94	>4
857531	0.27	99	>4
857534	0.12	57	>4
857532	0.16	69	>4

857533	0.10	61	>4
857537	1.4	82	>4
857540	0.48	65	>4
857538	0.33	110	>4
857539	0.13	74	>4

*IC₅₀ values can only be calculated when less than the highest dose in the experiment, in this case, 4 μM

Example 38

Modified oligonucleotides were designed based on 558807. Each modified oligonucleotide has a modified internucleoside linkage positioned between nucleosides 3 and 4 counting from the 5'-gap junction (not including the 3 cEt modified nucleosides in the 5'-wing) as illustrated below. Each of the modified oligonucleotides is conjugated with a HPPO-GalNAc conjugate group at the 3'-end as illustrated below. The oligonucleotides were evaluated for reduction in CXCL12 (Chemokine ligand 12) mRNA expression levels *in vivo*. The transaminase levels (ALT and AST) for each dose were also measured.

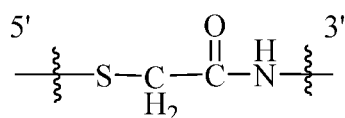
Six week old BALB/C mice (purchased from Charles River) were injected subcutaneously once at dosage 0.2, 0.6, 1.8 or 50 mg/kg with the modified oligonucleotides shown below or with saline control. For compound 855156, mice were injected with 0.21, 0.62, 1.85, or 5.56 mg/kg modified oligonucleotide. Each treatment group consisted of 3 animals. The mice were sacrificed 72 hours following administration, and organs and plasma were harvested for further analysis.

Table 92 Modified Oligonucleotides

Compound ID	Linkage-altered nucleotide position in central region	Linkage mod "x"	Chemistry Notation	SEQ ID NO
895566	3	isopropylphosphonate	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k -HPPO -GalNAc	18
895567	3	THP phosphotriester	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k -HPPO -GalNAc	18
895568	3	isopropylphosphotriester	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k -HPPO -GalNAc	18
895569	3	isobutylphosphonate	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k -HPPO -GalNAc	18
895570	3	formacetal	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k -HPPO -GalNAc	18
913196	3	amide-3	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k -HPPO -GalNAc	18
920046	3	TANA	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k -HPPO -GalNAc	18
951972	3	(R)-MOP	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k -HPPO -GalNAc	18
951973	3	(S)-MOP	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dx} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k -HPPO -GalNAc	18

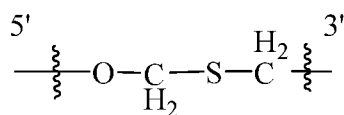
974343	3	alt-thioformacetal	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{k}-$ HPPO -GalNAc	18
974344	3	glycine amide	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{k}-$ HPPO -GalNAc	18
1011295	3	thioformacetal	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{k}-$ HPPO -GalNAc	18
1011296	3	MMI	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{k}-$ HPPO -GalNAc	18

A subscript “d” indicates an unmodified, 2’-β-D-deoxyribose sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine. A subscript “x” indicates a modified internucleoside linkage as indicated in the “linkage mod x” column. These linkages are illustrated above and below.

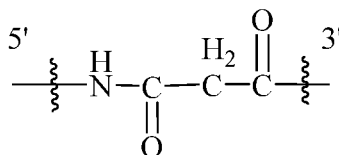


5

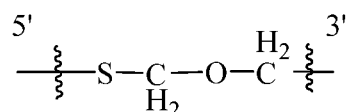
TANA



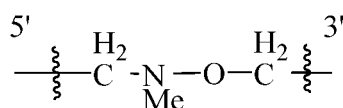
alt-thioformacetal



glycine amide

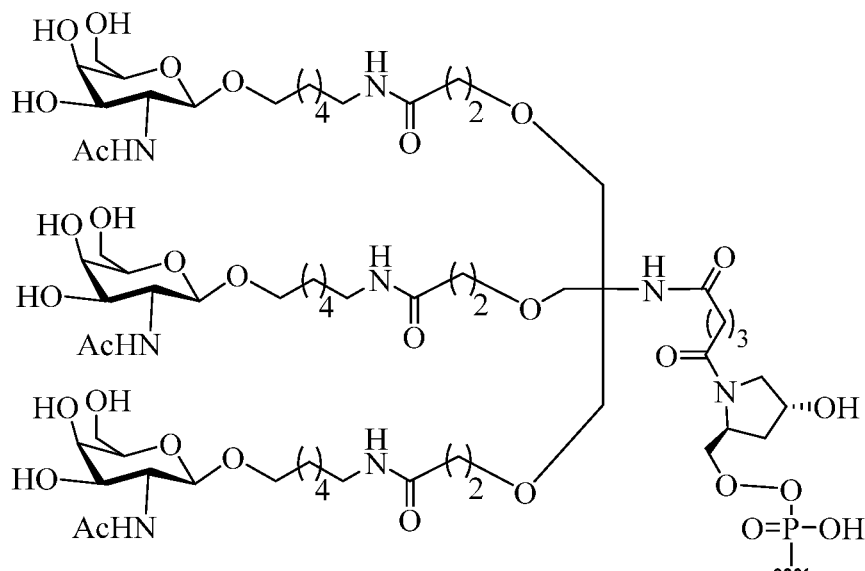


thioformacetal



MMI

Each modified oligonucleotide in the study includes a 3’- HPPO -GalNAc conjugate group which is attached to the 3’-oxygen of the oligomeric compound. The 3’- HPPO -GalNAc conjugate group is illustrated below wherein the phosphate group is attached to the 3’-oxygen atom:



Liver tissues were homogenized and mRNA levels were quantitated using real-time PCR and normalized to RIBOGREEN as described herein. Plasma chemistry markers such as liver transaminase levels, alanine aminotransferase (ALT) in serum were measured relative to saline injected mice.

- 5 The ED₅₀ values were calculated by plotting the concentrations of oligonucleotides used versus the percent inhibition of CXCL12 mRNA expression achieved at each concentration, and noting the concentration of oligonucleotide at which 50% inhibition of CXCL12 mRNA expression was achieved compared to the control.

Table 93 *In vivo* Toxicity

Compound ID	Linkage-altered nucleotide position in Central region	Linkage Mod	ALT (at 50 mg/kg)
855156*	n/a	n/a	4298**
855161	3	MOP	31
895566	3	isopropylphosphonate	24
895567	3	THP phosphotriester	25
895568	3	isopropylphosphotriester	38
895569	3	isobutylphosphonate	28
895570	3	formacetal	31
913196	3	amide-3	29
920046	3	TANA	24
951972	3	(<i>R</i>)-MOP	47
951973	3	(<i>S</i>)-MOP	45
974343	3	alt-thioacetal	39
974344	3	glycine amide	30
1011295	3	thioacetal	38
1011296	3	MMI	56

10 *Described in Table 25 above

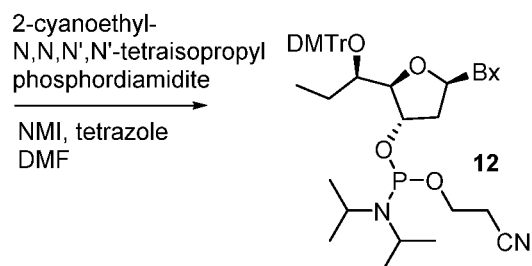
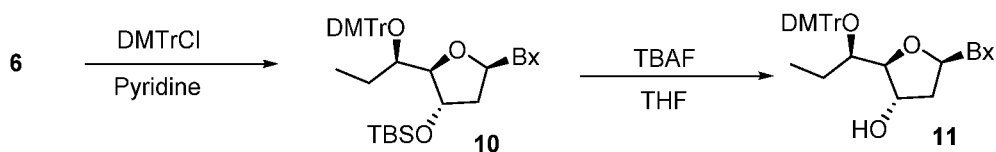
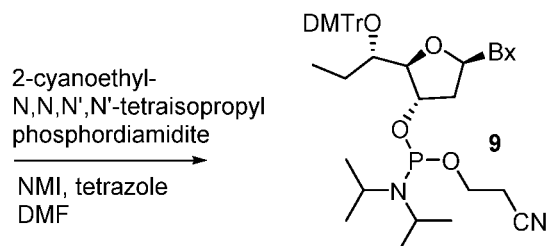
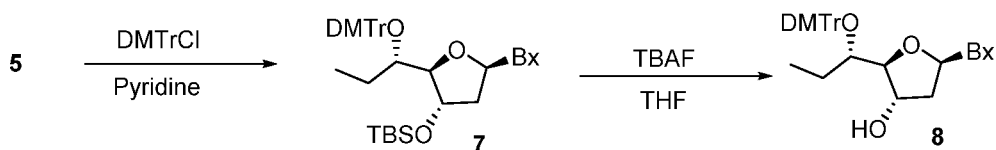
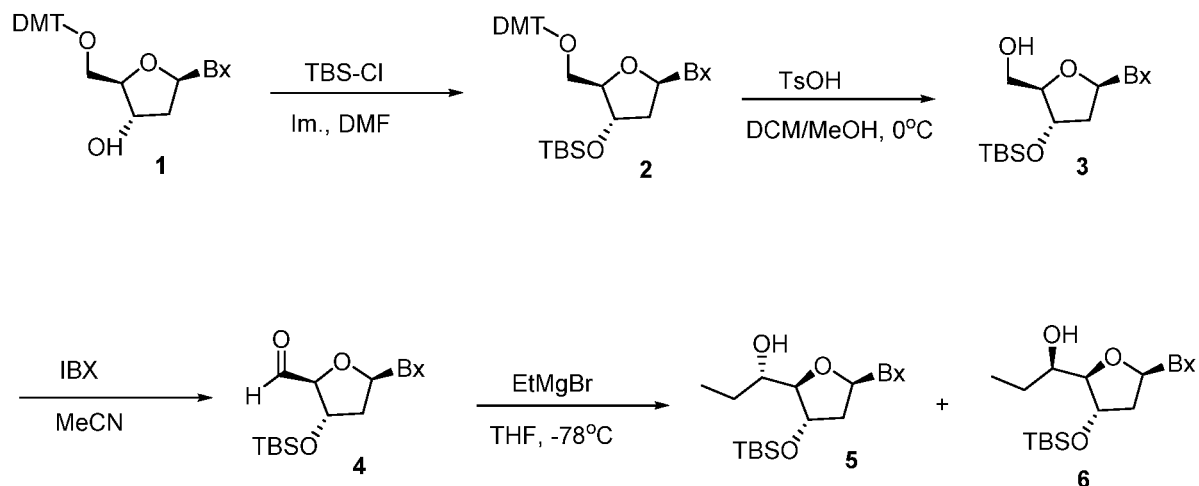
**Values determined in an independent experiment and shown for comparison; ALT value is at 5.56 mg/kg modified oligonucleotide

Table 93b *In Vivo* CXCL12 mRNA levels

Compound ID	0.21 mg/kg	0.62 mg/kg	1.85 mg/kg	5.56 mg/kg	50 mg/kg
	Expression level of CXCL12 mRNA (% Control)				
855156*	81	63	45	31	n.d.
895566	68	55	42	n.d.	22
895567	59	50	36	n.d.	18
895568	69	49	37	n.d.	17
895569	72	51	41	n.d.	18
895570	68	50	38	n.d.	17
913196	62	48	44	n.d.	19
920046	80	58	58	n.d.	25
855161	67	51	38	32	21
951972	77	61	39	29	20
951973	81	59	37	32	19
974343	86	56	37	27	16
974344	79	69	44	34	23
1011295	78	62	44	31	30
1011296	77	63	49	51	29

5

Example 39 Synthesis of 5'-(*R*)-Ethyl and 5'-(*S*)-Ethyl Phosphoramidites



1 was synthesized by The National Institutes of Pharmaceutical R&D

Bx = N(Bz)-A, N(iBu)-G, N(Bz)MeC, T

5'-(*R*)-ethyl and 5'-(*S*)-ethyl phosphordiamidites were prepared as per the scheme illustrated above.

Example 40 Time course of modified oligonucleotides in HeLa cells

HeLa cells were transfected with a modified oligonucleotide listed in the tables below. At 0, 0.5, 1, 2, 4, and 6 hours after transfection, cells were lysed and mRNA was isolated and analyzed by RT-qPCR. Primer probe set HTS3934 (forward sequence: TGGAGACTCTCAGGGTCGAAA, SEQ ID NO: 122; reverse sequence: GGCGTTTGGAGTGGTAGAAATC, SEQ ID NO: 123; probe sequence: CGGCGGCAGACCAGCATGAC, SEQ ID NO: 124) was used to detect human p21 mRNA, and primer probe set HS00169255_m1 (ThermoFisher)) was used to detect human Gadd45a mRNA. Results are normalized to untreated cells.

Table 94 Relative hp21 mRNA timecourse in HeLa cells

Compound	% Control human p21 mRNA					
	0 hrs	0.5 hrs	1 hrs	2 hrs	4hrs	6 hrs
464917	100	123	133	241	259	557
558807	97.8	113	135	187	253	528
549148	120	120	129	187	138	147
549139	102	125	124	143	133	213

Table 95 Relative hGadd45a mRNA timecourse in HeLa cells

Compound	% Control human Gadd45a mRNA					
	0 hrs	0.5 hrs	1 hrs	2 hrs	4hrs	6 hrs
464917	100	157	281	375	632	746
558807	105	188	227	297	261	412
549148	106	156	200	231	156	180
549139	94	157	213	229	167	237

HeLa cells were transfected with various concentrations of modified oligonucleotide as indicated in the table below. At 0, 1, 2, 4, 6, and 8 hours after transfection, cells were lysed and mRNA was isolated and analyzed by RT-qPCR as described above.

Table 96 Relative hp21 mRNA dose response/time course in HeLa cells

Compound	Dose (nM)	% Control human p21 mRNA					
		0 hrs	1 hrs	2 hrs	4 hrs	6 hrs	8 hrs
464917	0	100	114	87	105	107	97
464917	3.125	100	109	76	111	179	126
464917	6.25	100	110	86	113	219	159
464917	12.50	100	112	86	126	287	239
464917	25.0	100	110	98	153	313	399
464917	50.0	100	96	94	165	392	490
464917	100.0	100	108	106	191	450	600
464917	200.0	100	99	100	230	510	660
549148	0	100	89	106	113	106	79
549148	3.125	100	105	100	117	126	96
549148	6.25	100	88	99	128	115	84
549148	12.50	100	95	108	107	115	107
549148	25.0	100	95	123	130	140	111
549148	50.0	100	101	111	122	131	114

549148	100.0	100	98	89	131	104	100
549148	200.0	100	93	95	163	102	99

Table 97 Relative hGadd45a mRNA dose response/time course in HeLa cells

Compound	Dose (nM)	% Control human p21 mRNA					
		0 hrs	1 hrs	2 hrs	4 hrs	6 hrs	8 hrs
464917	0	100	97	80	109	110	88
464917	3.125	100	117	95	156	208	170
464917	6.25	100	121	111	176	176	205
464917	12.50	100	139	126	165	271	261
464917	25.0	100	147	136	176	279	420
464917	50.0	100	130	171	203	368	700
464917	100.0	100	143	194	261	835	1234
464917	200.0	100	113	198	213	890	1111
549148	0	100	98	104	104	111	99
549148	3.125	100	124	133	120	132	133
549148	6.25	100	151	140	155	160	142
549148	12.50	100	159	159	131	120	144
549148	25.0	100	173	172	148	156	180
549148	50.0	100	155	170	164	104	164
549148	100.0	100	140	129	141	160	190
549148	200.0	100	121	115	128	107	185

Example 41 Time course of toxicity of modified oligonucleotide 464917 *in vivo*

- 5 The modified oligonucleotide 464917 was administered subcutaneously at 11, 33, or 100 mg/kg to 9 BALB/C mice per dosing group. Three mice from each group were sacrificed at 24 hours, three at 48 hours, and the last three at 72 hours after dosing. mRNA was isolated and analyzed as described in Example 1. ALT values in plasma were obtained using a clinical chemistry analyzer.

Table 98 Time Course of Activity and Toxicity in mice

Compound	Dose (mg/kg)	24 hrs	48 hrs	72 hrs	24 hrs	48 hrs	72 hrs
		ALT			mFXI mRNA		
464917	0	44	58	29	100	100	100
464917	11	40	132	311*	20	17	11*
464917	33	98	2015	8072	2.7	2.6	5.7
464917	100	168	12261	26659*	1.7	0.5	0.07**

10 *Data represents a single mouse

**Data represents the average of two mice

Table 99 Time Course of Toxicity in mice

Compound	Dose (mg/kg)	24 hrs	48 hrs	72 hrs	24 hrs	48 hrs	72 hrs
		mP21 mRNA			mTnfrsf10b mRNA		
464917	0	100	100	100	100	100	100
464917	11	518	607	2060*	272	845	3401*
464917	33	6451	1846	5221	2071	5333	7013
464917	100	163667	4067	4910**	5451	12293	7402**

15 *Data represents a single mouse

**Data represents the average of two mice

Example 42 Nucleolar Delocalization of p54nrb *in vivo*

Compound 959265 is compound 464917 conjugated to a Cy3 on the 5'-end and HPPO-GalNAc on the 3'-end. Balb/c mice were administered 15 mg/kg of 959265 by subcutaneous injection. Hepatocytes were isolated and purified 40 hours after administration of modified oligonucleotide and plated on a confocal dish for 6-7 hours. After 6-7 hours, cells were fixed with formaldehyde and stained for p54nrb with immunofluorescent staining for p54nrb. Levels of FXI and p21 were detected by RT-qPCR as described above.

A single dose of 959265 at 15 mg/kg reduced FXI to 10.6% of control values. Levels of p21 mRNA were upregulated 1,046%. Isolated hepatocytes were observed to contain p54nrb that had been localized to the nucleolus or no detectable p54nrb.

Example 43 Nucleolar Delocalization of p54nrb *in vivo*

Balb/c mice were administered 100 mg/kg of 464917 or 549148 by subcutaneous injection. Hepatocytes were isolated and purified 16 hours after administration of modified oligonucleotide and plated on a confocal dish for 1-2 hours. After 1-2 hours, cells were fixed with formaldehyde and stained for p54nrb with immunofluorescent staining for p54nrb.

Localization of p54nrb to the nucleolus of hepatocytes was observed for compound 464917 but not for compound 549148.

Example 44 *In vivo* activity and toxicity of compounds containing a MOP neutral linkage

Six week old BALB/C mice (purchased from Charles River) were injected subcutaneously once at dosage 0.2, 0.6, 1.8 5.4, or 50 mg/kg with the modified oligonucleotides shown below or with saline control. For compound 855156, mice were injected with 0.2, 0.6, 1.8, 5.4, or 15 mg/kg modified oligonucleotide. Each treatment group consisted of 3 animals. The mice were sacrificed 72 hours following administration, and organs and plasma were harvested for further analysis.

Liver tissues were homogenized and mRNA levels were quantitated using real-time PCR and normalized to RIBOGREEN as described herein. Plasma chemistry markers such as liver transaminase levels, alanine aminotransferase (ALT) in serum were measured relative to saline injected mice.

The ED₅₀ values were calculated by plotting the concentrations of oligonucleotides used versus the percent inhibition of CXCL12 mRNA expression achieved at each concentration, and noting the concentration of oligonucleotide at which 50% inhibition of CXCL12 mRNA expression was achieved compared to the control.

Table 100 Modified Oligonucleotides

Compound ID	position of linkage-altered nucleotide in central region	Linkage mod	Chemistry Notation	SEQ ID NO
869742	n/a	n/a	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{ks} T_k$ -HPPO -GalNAc	125
898384	3	MOP	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{dx} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{ks} T_k$ -HPPO -GalNAc	125
898385	2, 3	MOP	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{dx} T_{dx} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{ks} T_k$ -HPPO -GalNAc	125

A subscript “d” indicates an unmodified, 2’-β-D-deoxyribosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine. A subscript “x” indicates a MOP internucleoside linkage.

5

Table 101 *In vivo* Toxicity

Compound ID	Linkage Mod position in Central region	Linkage Mod	ALT at 15 mg/kg	ALT at 50 mg/kg
855156	n/a	n/a	9,639	n/a
869742	n/a	n/a	2,001	n/a
898384	3	MOP	30	32
898385	2, 3	MOP	32	30

Table 102 *In Vivo* CXCL12 mRNA levels

Compound ID	0.2 mg/kg	0.6 mg/kg	1.8 mg/kg	5.4 mg/kg	15 mg/kg	50 mg/kg
	Expression level of CXCL12 mRNA (% Control)					
855156	64	42	23	19	16	n/a
869742	87	58	32	23	18	n/a
898384	87	91	49	40	36	31
898385	91	90	64	64	55	41

10 Example 45

Modified oligonucleotides were tested for toxicity *in vivo* in Balb/c mice.

Table 103 Modified Oligonucleotides

Compound ID	Chemistry notation	SEQ ID NO:
575013	$m C_{ks} A_{ks} G_{ks} A_{ds} T_{ds} A_{ds} T_{ds} A_{ds} G_{ds} G_{ds} A_{ds}^m C_{ds} T_{ds} G_{ks} G_{ks} A_k$	110
465131	$T_{ks} G_{ks}^m C_{ks}^m C_{ds} A_{ds}^m C_{ds}^m C_{ds} G_{ds} T_{ds} A_{ds} G_{ds} A_{ds}^m C_{ds} A_{ks}^m C_{ks} G_k$	114
549139	$G_{ks} A_{ks}^m C_{ks} G_{ds}^m C_{ds} G_{ds}^m C_{ds}^m C_{ds} T_{ds} G_{ds} A_{ds} A_{ds} G_{ds} G_{ks} T_{ks} T_k$	111
464932	$G_{ks} G_{ks} A_{ks}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ds} T_{ds} G_{ds} G_{ds}^m C_{ds}^m C_{ds} A_{ks}^m C_{ks} A_k$	112

A subscript “d” indicates an unmodified, 2’-β-D-deoxyribosyl sugar moiety. A subscript “k” indicates a cEt modified sugar moiety. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine.

For *in vivo* toxicity studies, 3 BALB/c mice per group were administered the indicated dose of modified oligonucleotide by subcutaneous injection and sacrificed after 72 hours. Four animals were administered saline to serve as a control. RT-PCR was performed as described in Example 1 to determine mRNA levels of CXCL12, P21, Tnfrsf10b, and Gadd45a. Plasma levels of ALT were measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

For the *in vitro* toxicity study in the table below, the caspase assay was performed essentially as described in Example 8 in 3T3-L1 cells. The caspase assay was performed in HeLa cells by free uptake at 2μM modified oligonucleotide and in b.END3 cells by free uptake at 50 μM modified oligonucleotide.

Table 104 *In vivo* and *in vitro* toxicity of modified oligonucleotides

Compound ID	<i>in vivo</i> Dose (mg/kg)	ALT (IU/L)	<i>in vivo</i> P21 (% control)	<i>in vivo</i> Tnfrsf10b (% control)	<i>in vitro</i> caspase @20 μM, 3T3-L1(% control)	<i>in vitro</i> caspase @2 μM, HeLa (% control)	<i>in vitro</i> caspase @50 μM, b.END (% control)
575013	100	12	54	105	237	100	140
465131	100	21	111	164	114	119	n.d.
549139	100	24	118	135	125	111	113
549148	100	24	72	83	184	121	159
464932	100	5	150	180	280	113	187
449093	33	2324	42802	3835	2703	306	783
	100	9983	150994	3744			
482050	33	1470	7890	4725	1502	203	439
	100	6555	10430	4232			
508031	33	648	2980	2239	1082	255	357
	100	18550	8909	6678			
558807	17	1877	2763	1168	910	408	413
	51	9510	11904	6831			
464917	11	601	6098	3516	1724	219	552
	33	13920	9590	7731			

Example 46 Time course of toxicity and activity of modified oligonucleotide 464932 or 464917 *in vivo*

The modified oligonucleotide 464932, described in Example 45 above, or 464917, described in Example 4 above, was administered subcutaneously at 33 mg/kg to BALB/C mice. Three mice from each dosing group were sacrificed at each indicated time point and mRNA was isolated and analyzed as described in Example 1. ALT values in plasma were obtained using a clinical chemistry analyzer and were normalized to saline-treated animals.

Table 105 Time Course of Activity and Toxicity in mice

Treatment	Measurement	8 hrs	12 hrs	16 hrs	24 hrs	48 hrs	72 hrs
PBS	ALT	20	41	40	40	44	41
464932	ALT	49	64	58	47	39	108
	mFXI	174	104	40	53	19	12
	mP21	94	115	71	182	47	185
	mTnfrsf10b	133	101	112	108	117	140
464917	ALT	39	49	53	41	1903	13917
	mFXI	100	56	12	19	4	5
	mP21	138	391	829	3751	1854	12716
	mTnfrsf10b	118	221	714	1250	6369	8781

Example 47 Time course of toxicity and activity of modified oligonucleotide 558807 or 558765 *in vivo*

Modified oligonucleotide 558765 is a 3-10-3 cEt gapmer with a full phosphorothioate backbone and the sequence A^mCAT^mCTT^mCAGAT^mCATT (SEQ ID NO: 144). The modified oligonucleotide 558807 or 558765 was administered subcutaneously at 51 mg/kg to BALB/C mice. Three mice from each dosing group were sacrificed at each indicated time point and mRNA was isolated and analyzed as described in Example 1. ALT values in plasma were obtained using a clinical chemistry analyzer and were normalized to saline-treated animals.

Table 106 Time Course of Activity and Toxicity in mice

Treatment	Measurement	8 hrs	12 hrs	16 hrs	24 hrs	48 hrs	72 hrs
PBS	ALT	21	42	40	40	44	41
558765	ALT	34	53	46	92	33	36
	mCXCL12	109	94	20	54	29	26
	mP21	143	116	92	209	48	404
	mTnfrsf10b	106	70	118	98	154	215
558807	ALT	36	50	53	36	1888	7272
	mCXCL12	43	18	5	10	3	3
	mP21	136	142	86	580	1573	1642
	mTnfrsf10b	101	148	236	292	3375	7454

Example 48 Toxicity improvement *in vivo* with incorporation 2'-OMe modified-nucleoside in the central region

BALB/c mice were administered 1.8, 5.5, 16.7, or 50 mg/kg of 558807 or 1.8, 5.5, 16.7, 50, 100, 200, or 300 mg/kg of 936053 and sacrificed after 72 hours. Plasma levels of ALT were measured with a clinical chemistry analyzer and mRNA was isolated and analyzed as described in Example 1. Therapeutic

index (TI) was calculated as the maximum non-toxic dose divided by the ED50. Compound 936053 differs from compound 558807 only in the presence of a 2'-OMe group at position 5 from the 5' end of the compound, or position 2 of the central region.

Table 107 *in vivo* dose response

Compound ID	Dose (mg/kg)	ALT (IU/L)	<i>in vivo</i> P21 (% control)	<i>in vivo</i> Tnfrsf10b (% control)	<i>in vivo</i> Gadd45a (% control)	CXCL12 mRNA (% control)	ED50 (mg/kg)	MTND (mg/kg)	Therapeutic Index
558807	1.8	24	118	120	147	67.5	2.75	5.5	2
	5.5	27	63	103	176	20.3			
	16.7	586	625	788	879	9.7			
	50	death	n.d.	n.d.	n.d.	n.d.			
936053	1.8	34	104	78	61	65.3	4.86	200	41
	5.5	26	94	137	99	47.4			
	16.7	23	104	110	91	32.7			
	50	23	89	122	90	14.4			
	100	42	n.d.	n.d.	n.d.	n.d.			
	200	109	n.d.	n.d.	n.d.	n.d.			
	300	231	n.d.	n.d.	n.d.	n.d.			

Example 49 Toxicity improvement of modified oligonucleotides targeted to FXI

BALB/c mice were administered 1.8, 5.5, 16.7, 50 or 150 mg/kg of modified oligonucleotide by subcutaneous injection. Each group contained 3 mice. A group of 4 mice was administered PBS as a control. Plasma levels of ALT were measured with a clinical chemistry analyzer and mRNA was isolated and analyzed as described in Example 1. Modified oligonucleotides are described in Example 18. Each pair of compounds, presented adjacent to each other in the table below, represents a compound with the motif kkk-d(10)-kkk (464xxx) and the same sequence with the motif kkk-d-m-d(8)-kkk (1133xxx). In instances where position 5 in the original sequence is a T, this nucleoside is a 2'-OMeU in the kkk-d-m-d(8)-kkk sequence.

Table 108 *in vivo* dose response

Compound ID	Dose (mg/kg)	ALT (IU/L)	<i>in vivo</i> P21 (% control)	FXI mRNA (% control)	ED50 (mg/kg)	MTND (mg/kg)	Therapeutic Index
464924	1.8	27	136	59.7	2.4	16.7	7.0
	5.5	27	144	20.4			
	16.7	31	167	2.5			
	50	646	551	0.4			
	150	4509	1160	0.4			
1133247	1.8	32	130	75.0	3.4	>150	>44
	5.5	30	67	29.3			
	16.7	30	94	5.4			
	50	37	123	1.9			
	150	53	304	1.4			

465172	1.8	26	131	73.5	6.7	>150	>22
	5.5	22	102	57.8			
	16.7	23	99	28.8			
	50	25	102	13.8			
	150	33	177	6.2			
1133326	1.8	25	51	81.1	16.3	>150	>9
	5.5	25	64	81.8			
	16.7	24	55	49.0			
	50	24	78	21.1			
	150	22	90	11.8			
465174	1.8	25	192	67.5	4.2	>150	>36
	5.5	29	172	46.8			
	16.7	22	31	18.0			
	50	20	49	7.5			
	150	29	83	5.7			
1133328	1.8	21	40	74.8	4.8	>150	>32
	5.5	23	38	44.3			
	16.7	28	42	18.6			
	50	26	25	13.0			
	150	31	38	10.7			
465178	1.8	26	43	47.2	1.7	16.7	10
	5.5	35	119	18.4			
	16.7	73	627	4.3			
	50	1067	3509	0.7			
	150	11596	4849	0.4			
1133332	1.8	23	101	47.8	1.8	150	83
	5.5	35	42	30.7			
	16.7	33	136	13.1			
	50	41	600	3.7			
	150	117	1414	1.3			

Example 50 Toxicity improvement of modified oligonucleotides targeted to HDAC2

BALB/c mice were administered 1.8, 5.5, 16.7, 50 or 150 mg/kg of modified oligonucleotide by subcutaneous injection. Each group contained 3 mice. A group of 4 mice was administered PBS as a control.

- 5 Plasma levels of ALT were measured with a clinical chemistry analyzer and mRNA was isolated and analyzed as described in Example 1. Modified oligonucleotides are described in Example 19. Each pair of compounds, presented adjacent to each other in the table below, represents a compound with the motif kkk-d(10)-kkk (546xxx) and the same sequence with the motif kkk-d-m-d(8)-kkk (1133xxx). In instances where position 5 in the original sequence is a T, this nucleoside is a 2'-OMeU in the kkk-d-m-d(8)-kkk sequence.

10

Table 109 *in vivo* dose response

Compound ID	Dose (mg/kg)	ALT (IU/L)	HDAC2 mRNA (% control)	ED50 (mg/kg)	MTND (mg/kg)	Therapeutic Index
546108	1.8	33	74	3.2	16.7	5.2
	5.5	47	26.2			
	16.7	168	3.8			

	50	1713	4.8			
	150	17844	4.5			
1133122	1.8	29	91.6	5.5	>150	>27
	5.5	25	48.3			
	16.7	2	11.0			
	50	43	1.1			
	150	78	1.1			
546110	1.8	25	72.9	6.4	16.7	2.6
	5.5	27	57.4			
	16.7	37	29.4			
	50	416	6.7			
	150	2817	6.0			
1133123	1.8	24	71.0	6.8	>150	>22
	5.5	80	49.6			
	16.7	25	47.8			
	50	25	8.0			
	150	28	3.0			
546118	1.8	30	69.9	23.8	16.7	0.7
	5.5	29	70.1			
	16.7	40	50.8			
	50	365	39.1			
	150	1681	36.0			
1133127	1.8	35	77.2	24.9	>150	>6
	5.5	25	60.6			
	16.7	26	57.1			
	50	25	39.9			
	150	33	34.4			

Example 51 Toxicity improvement of modified oligonucleotides

Modified oligonucleotides were tested for toxicity *in vivo* in Balb/c mice. Compound 865060 has the motif kkk-d(10)-kkkk and compound 865061 has the motif kkkk-d(10)-kkk. Compounds 1269430 and 1269431 are otherwise identical compounds to 865060 and 865061, respectively, containing a 2'-OMe modified sugar moiety at the second position in the central region.

Table 110 Modified Oligonucleotides

Compound ID	Chemistry notation	SEQ ID NO:
865060	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{ks} T_k$	125
865061	$G_{ks} G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	141
1269430	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ms} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_{ks} T_k$	125
1269431	$G_{ks} G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ms} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	141

A subscript “d” indicates an unmodified, 2’-β-D-deoxyribosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “m” indicates a 2’-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine.

For *in vivo* toxicity studies, 3 BALB/c mice per group were administered the indicated dose of modified oligonucleotide by subcutaneous injection and sacrificed after 72 hours. Four animals were administered saline to serve as a control. RT-PCR was performed as described in Example 1 to determine mRNA levels of CXCL12, P21, Tnfrsf10b, and Gadd45a. Plasma levels of ALT was measured using an automated clinical chemistry analyzer. Increased ALT is indicative of acute liver toxicity.

For the *in vitro* toxicity study in the table below, the caspase assay was performed essentially as described in Example 8 in 3T3-L1 cells, the percent nucleolar p54nrb was visualized as described in Example 11, and the p21 mRNA levels were determined as described in Example 11.

Table 111 *In vivo* and *in vitro* toxicity of modified oligonucleotides

Compound ID	<i>in vitro</i> CXCL12 IC ₅₀ (nM)	Relative Caspase Activation (% Control) @20 μM	<i>in vitro</i> p21 mRNA (% Control) @20 μM	<i>in vitro</i> % nucleolar p54nrb	<i>in vivo</i> p21 @150 mg/kg	<i>in vivo</i> Tnfrsf10b mRNA @150 mg/kg	ALT @150mg/kg (IU/L)
558807	183	432	285	82	7152*	5504*	9928*
936053	259	114	114	0	166	204	12
865060	310	355	224	64	7604*	9339*	11058*
1269430	308	110	127	0	209	350	10
865061	510	738	198	75	12531	6351	9014
1269431	849	116	134	0	376	661	52

*Value at 50 mg/kg dose; mice administered 150 mg/kg did not survive

Example 52 Long-term toxicity improvement of modified oligonucleotides

Modified oligonucleotides were tested for toxicity *in vivo* in Balb/c mice. Mice were administered 50 mg/kg modified oligonucleotide once a week for six weeks and ALT was measured using an automated clinical chemistry analyzer. Compounds in the table below are described in Example 13. Each pair of compounds represents an oligonucleotide with the sugar motif kkk-d(10)-kkk (upper) and an oligonucleotide with the same sequence having the sugar motif kkk-d-m-d(8)-kkk (lower).

Table 112 Long-term Toxicity

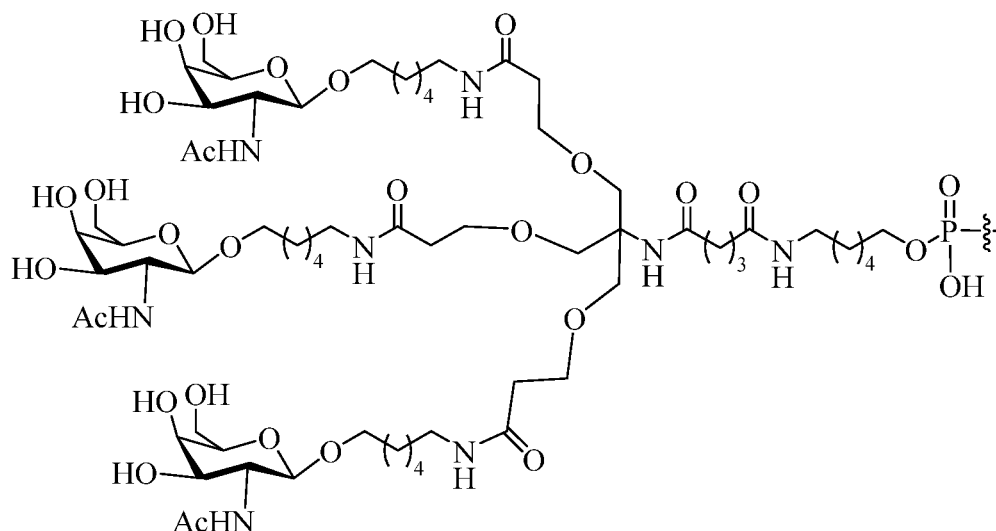
Compound ID	Week of Dosing					
	1	2	3	4	5	6
	ALT (IU/L)					
PBS	35	65	27	45	55	23
572912	398	1036	2667	2787	n.d.	n.d.

1200898	36	53	70	112	187	513
797793	1210	972	1674	2703	3831	3635
1201073	99	143	165	178	217	330
576095	46	83	1017	1763	2886	4118
1200899	50	57	129	550	1225	1392

n.d. indicates that the mice were sacrificed prior to the measurement date.

Example 53

Modified oligonucleotides were designed based on 546118. Each of the modified oligonucleotides is conjugated with a THA-GalNAc conjugate group at the 3'-end. THA-GalNAc refers to this structure:



wherein the phosphate group is attached to the 3'-oxygen atom of the 3' nucleoside.

The oligonucleotides were evaluated for reduction in HDAC2 mRNA expression levels in vivo. P21 and Tnfrsf10b mRNA levels were also measured. The transaminase levels (ALT and AST) for each dose were also measured.

Six week old BALB/C mice (purchased from Charles River) were injected subcutaneously once at dosage 0.023, 0.067, 0.2, 0.6, 1.8, 5.4, 15, or 50 mg/kg with the modified oligonucleotides shown below or with saline control. Each treatment group consisted of 3 animals. The mice were sacrificed 72 hours following administration, and organs and plasma were harvested for further analysis.

Table 113 Modified Oligonucleotides

Compound ID	position of altered nucleotide in central region	modification of altered nucleotide	Chemistry Notation	SEQ ID NO
1270732	N/A	N/A	$A_{ks}^m C_{ks}^m C_{ks}^m C_{ds} T_{ds}^m C_{ds} A_{ds} A_{ds} G_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds}^m C_{ks} T_{ks}$ G _k -THAGalNAc	109
1270733	2	2'-OMe	$A_{ks}^m C_{ks}^m C_{ks}^m C_{ds} U_{ms}^m C_{ds} A_{ds} A_{ds} G_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds}^m C_{ks} T_{ks}$ G _k -THAGalNAc	140
1270734	2	MOP	$A_{ks}^m C_{ks}^m C_{ks}^m C_{ds} T_{dx}^m C_{ds} A_{ds} A_{ds} G_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds}^m C_{ks} T_{ks}$ G _k -THAGalNAc	109

A subscript “d” indicates an unmodified, 2’-β-D-deoxyribosyl sugar moiety. A subscript “m” indicates a 2’-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine. A subscript “x” indicates a MOP internucleoside linkage.

Table 114 *In vivo* Activity and Toxicity of Modified Oligonucleotides

Compound ID	Dose (mg/kg)	ALT (IU/L)	P21 mRNA (% Control)	Tnfrsf10b mRNA (% Control)	HDAC2 ED50 (mg/kg)
1270732	0.023	34	106	n.d.	0.060
	0.067	7	74	n.d.	
	0.2	15	113	80	
	0.6	13	112	76	
	1.8	33	537	118	
	5.4	122	688	271	
	15	1467	2606	1418	
	50	3429	5197	3064	
1270733	0.023	22	71	n.d.	0.066
	0.067	43	91	n.d.	
	0.2	18	89	80	
	0.6	20	103	104	
	1.8	17	81	81	
	5.4	23	154	81	
	15	11	172	110	
	50	22	988	353	
1270734	0.023	13	64	n.d.	0.084
	0.067	22	65	n.d.	
	0.2	31	158	93	
	0.6	7	230	149	
	1.8	12	64	93	
	5.4	20	169	110	
	15	318	1513	608	
	50	1650	2894	1368	

n.d. means a value was not determined.

Example 54

Modified oligonucleotides were designed based on 546110, described in Example 19 above. Each of the modified oligonucleotides is conjugated with a THA-GalNAc conjugate group at the 3'-end as described in Example 53 above. The oligonucleotides were evaluated for reduction in HDAC2 mRNA expression levels in vivo. P21 and Tnfrsf10b mRNA levels were also measured. The transaminase levels (ALT and AST) for each dose were also measured.

Six week old BALB/C mice (purchased from Charles River) were injected subcutaneously once at dosage 0.016, 0.08, 0.40, 2.0, or 50 mg/kg with the modified oligonucleotides shown below or with saline control. Each treatment group consisted of 3 animals. The mice were sacrificed 72 hours following administration, and organs and plasma were harvested for further analysis.

Table 115 Modified Oligonucleotides

Compound ID	position of altered nucleotide in central region	modification of altered nucleotide	Chemistry Notation (5' to 3')	SEQ ID NO
1270729	n/a	n/a	T _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} A _{ds} ^m C _{ds} ^m C _{ds} T _{ds} A _{ds} T _{ds} A _{ds} G _{ks} T _{ks} ^m C _k -THA-GalNAc	107
1270733	2	2'-OMe	T _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ms} T _{ds} A _{ds} ^m C _{ds} ^m C _{ds} T _{ds} A _{ds} T _{ds} A _{ds} G _{ks} T _{ks} ^m C _k -THA-GalNAc	107
1270734	2	MOP	T _{ks} ^m C _{ks} A _{ks} T _{ds} G _{dx} T _{ds} A _{ds} ^m C _{ds} ^m C _{ds} T _{ds} A _{ds} T _{ds} A _{ds} G _{ks} T _{ks} ^m C _k -THA-GalNAc	107

A subscript "d" indicates an unmodified, 2'-β-D-deoxyribose sugar moiety. A subscript "k" indicates a cEt. A subscript "m" indicates a 2'-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript "s" indicates a phosphorothioate internucleoside linkage. A superscript "m" before a C indicates 5-methyl Cytosine. A subscript "x" indicates a MOP internucleoside linkage.

Table 116 *In vivo* Activity and Toxicity of Modified Oligonucleotides

Compound ID	Dose (mg/kg)	ALT (IU/L)	P21 mRNA (% Control)	Tnfrsf10b mRNA (% Control)	HDAC2 ED50 (mg/kg)
1270729	0.016	6	69	123	0.76
	0.08	14	61	136	
	0.40	13	71	142	
	2.0	17	174	154	
	50	3655	7927	5297	
1270730	0.016	31	107	124	1.05
	0.08	10	144	132	
	0.40	17	65	99	
	2.0	9	88	123	
	50	11	110	164	
1270731	0.016	22	88	135	1.28

	0.08	13	86	101	
	0.40	20	135	138	
	2.0	13	66	137	
	50	6	76	164	

n.d. means a value was not determined.

Example 55

Modified oligonucleotides were designed based on 747149, described in Example 13 above. Each of the modified oligonucleotides is conjugated with a THA-GalNAc conjugate group at the 3'-end as described in Example 53 above. The oligonucleotides were evaluated for reduction in FBO1A mRNA expression levels in vivo. P21 and Tnfrsf10b mRNA levels were also measured. The transaminase levels (ALT and AST) for each dose were also measured.

Six week old BALB/C mice (purchased from Charles River) were injected subcutaneously once at dosage 0.025, 0.10, 0.40, 1.6, 6.4, or 50 mg/kg with the modified oligonucleotides shown below or with saline control. Each treatment group consisted of 3 animals. The mice were sacrificed 72 hours following administration, and organs and plasma were harvested for further analysis.

Table 117 Modified Oligonucleotides

Compound ID	position of altered nucleotide in central region	modification of altered nucleotide	Chemistry Notation (5' to 3')	SEQ ID NO
1270738	N/A	N/A	G _{ks} G _{ks} A _{ks} ^m C _{ds} T _{ds} G _{ds} A _{ds} A _{ds} A _{ds} T _{ds} A _{ds} G _{ds} ^m C _{ds} A _{ks} G _{ks} A _k -THA-GalNAc	54
1270739	2	2'-OMe	G _{ks} G _{ks} A _{ks} ^m C _{ds} U _{ms} G _{ds} A _{ds} A _{ds} A _{ds} T _{ds} A _{ds} G _{ds} ^m C _{ds} A _{ks} G _{ks} A _k -THA-GalNAc	130
1270740	2	MOP	G _{ks} G _{ks} A _{ks} ^m C _{ds} T _{dx} G _{ds} A _{ds} A _{ds} A _{ds} T _{ds} A _{ds} G _{ds} ^m C _{ds} A _{ks} G _{ks} A _k -THA-GalNAc	54

A subscript "d" indicates an unmodified, 2'-β-D-deoxyribose sugar moiety. A subscript "k" indicates a cEt. A subscript "s" indicates a phosphorothioate internucleoside linkage. A superscript "m" before a C indicates 5-methyl Cytosine. A subscript "x" indicates a MOP internucleoside linkage. A subscript "m" indicates a 2'-O-methyl-β-D-ribofuranosyl sugar moiety.

Table 118 *In vivo* Activity and Toxicity of Modified Oligonucleotides

Compound ID	Dose (mg/kg)	ALT (IU/L)	P21 mRNA (% Control)	Tnfrsf10b mRNA (% Control)	FBO1A ED50 (mg/kg)
1270738	0.025	29	49	114	1.23
	0.10	18	46	119	

	0.40	30	156	133	
	1.6	62	273	258	
	6.4	177	1020	1426	
	50	1467	4296	10211	
1270739	0.025	10	66	115	5.16
	0.10	14	54	120	
	0.40	9	39	93	
	1.6	16	34	98	
	6.4	12	88	116	
	50	26	163	115	
1270740	0.025	25	59	94	3.33
	0.10	20	79	143	
	0.40	22	81	110	
	1.6	7	68	146	
	6.4	27	195	165	
	50	102	1378	439	

Example 56

Modified oligonucleotides were designed based on 464924, described in Example 18 above. Each of the modified oligonucleotides is conjugated with a THA-GalNAc conjugate group at the 3'-end as described in Example 53 above. The oligonucleotides were evaluated for reduction in FXI mRNA expression levels in vivo. P21 and Tnfrsf10b mRNA levels were also measured. The transaminase levels (ALT and AST) for each dose were also measured.

Six week old BALB/C mice (purchased from Charles River) were injected subcutaneously once at dosage 0.025, 0.10, 0.40, 1.6, 6.4, or 50 mg/kg with the modified oligonucleotides shown below or with saline control. Each treatment group consisted of 3 animals. The mice were sacrificed 72 hours following administration, and organs and plasma were harvested for further analysis.

Table 119 Modified Oligonucleotides

Compound ID	position of altered nucleotide in central region	modification of altered nucleotide	Chemistry Notation (5' to 3')	SEQ ID NO
1270735	N/A	N/A	G _{ks} T _{ks} T _{ks} A _{ds} T _{ds} T _{ds} G _{ds} T _{ds} G _{ds} G _{ds} T _{ds} T _{ds} G _{ds} G _{ks} ^m C _{ks} G _k -THA-GalNAc	81
1270736	2	2'-OMe	G _{ks} T _{ks} T _{ks} A _{ds} U _{ms} T _{ds} G _{ds} T _{ds} G _{ds} G _{ds} T _{ds} T _{ds} G _{ds} G _{ks} ^m C _{ks} G _k -THA-GalNAc	133
1270737	2	MOP	G _{ks} T _{ks} T _{ks} A _{ds} T _{dx} T _{ds} G _{ds} T _{ds} G _{ds} G _{ds} T _{ds} T _{ds} G _{ds} G _{ks} ^m C _{ks} G _k -THA-GalNAc	81

A subscript "d" indicates an unmodified, 2'-β-D-deoxyribose sugar moiety. A subscript "k" indicates a cEt. A subscript "m" indicates a 2'-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript "s" indicates a

phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine. A subscript “x” indicates a MOP internucleoside linkage.

Table 120 *In vivo* Activity and Toxicity of Modified Oligonucleotides

Compound ID	Dose (mg/kg)	ALT (IU/L)	P21 mRNA (% Control)	Tnfrsf10b mRNA (% Control)	FBO1A ED50 (mg/kg)
1270735	0.025	9	86	93	0.86
	0.10	8	26	66	
	0.40	10	94	81	
	1.6	22	69	95	
	6.4	3	114	137	
	50	30	266	308	
1270736	0.025	17	95	70	0.81
	0.10	26	53	65	
	0.40	29	77	58	
	1.6	11	53	93	
	6.4	12	64	90	
	50	28	92	125	
1270740	0.025	17	63	77	1.47
	0.10	14	83	101	
	0.40	9	62	72	
	1.6	21	98	105	
	6.4	12	33	104	
	50	11	168	214	

5 Example 57 Introduction of 5'-Alkyl Modifications *in vivo*

Modified oligonucleotides containing a 5'-alkyl modified nucleoside in the central region were synthesized.

The oligonucleotides were evaluated for reduction in target mRNA expression levels *in vivo*. The transaminase levels (ALT and AST) for each dose were measured.

10 For the *in vitro* toxicity study in the table below, the caspase assay was performed essentially as described in Example 8 in Hepa1-6 cells.

For the *in vivo* toxicity and activity study in the table below, six week old BALB/C mice (purchased from Charles River) were injected subcutaneously once at dosage 1.8, 5.5, 16.7, 50, or 150 mg/kg with the modified oligonucleotides shown below or with saline control. Each treatment group consisted of 3 animals.

15 The mice were sacrificed 72 hours following administration, and organs and plasma were harvested for further analysis.

Table 121 Modified Oligonucleotides

Compound ID	Chemistry notation	SEQ ID NO:
546108	T _{ks} A _{ks} G _{ks} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} T _{ds} G _{ds} T _{ds} ^m C _{ds} A _{ds} G _{ds} T _{ks} T _{ks} A _k	105
1133122	T _{ks} A _{ks} G _{ks} T _{ds} C _{ms} T _{ds} ^m C _{ds} T _{ds} G _{ds} T _{ds} ^m C _{ds} A _{ds} G _{ds} T _{ks} T _{ks} A _k	105

1280765	$T_{ks}A_{ks}G_{ks}T_{ds}{}^mC_{dx}T_{ds}{}^mC_{ds}T_{ds}G_{ds}T_{ds}{}^mC_{ds}A_{ds}G_{ds}T_{ks}T_{ks}A_k$	105
1280766	$T_{ks}A_{ks}G_{ks}T_{ds}{}^mC_{ds}T_{[(R)-\mu]s}{}^mC_{ds}T_{ds}G_{ds}T_{ds}{}^mC_{ds}A_{ds}G_{ds}T_{ks}T_{ks}A_k$	105
1280767	$T_{ks}A_{ks}G_{ks}T_{ds}{}^mC_{ds}T_{ds}{}^mC_{[(R)-\mu]s}T_{ds}G_{ds}T_{ds}{}^mC_{ds}A_{ds}G_{ds}T_{ks}T_{ks}A_k$	105
1280768	$T_{ks}A_{ks}G_{ks}T_{ds}{}^mC_{ds}T_{[(R)-\epsilon]s}{}^mC_{ds}T_{ds}G_{ds}T_{ds}{}^mC_{ds}A_{ds}G_{ds}T_{ks}T_{ks}A_k$	105
1280769	$T_{ks}A_{ks}G_{ks}T_{ds}{}^mC_{ds}T_{ds}{}^mC_{[(R)-\epsilon]s}T_{ds}G_{ds}T_{ds}{}^mC_{ds}A_{ds}G_{ds}T_{ks}T_{ks}A_k$	105
694804	$A_{ks}G_{ks}A_{ks}{}^mC_{ds}T_{ds}{}^mC_{ds}T_{ds}{}^mC_{ds}G_{ds}G_{ds}T_{ds}{}^mC_{ds}{}^mC_{ks}G_{ks}A_k$	49
1202810	$A_{ks}G_{ks}A_{ks}{}^mC_{ds}U_{ms}{}^mC_{ds}T_{ds}{}^mC_{ds}G_{ds}G_{ds}T_{ds}T_{ds}{}^mC_{ds}{}^mC_{ks}G_{ks}A_k$	127
1280776	$A_{ks}G_{ks}A_{ks}{}^mC_{ds}T_{dx}{}^mC_{ds}T_{ds}{}^mC_{ds}G_{ds}G_{ds}T_{ds}T_{ds}{}^mC_{ds}{}^mC_{ks}G_{ks}A_k$	49
1280785	$A_{ks}G_{ks}A_{ks}{}^mC_{ds}T_{ds}{}^mC_{[(R)-\mu]s}T_{ds}{}^mC_{ds}G_{ds}G_{ds}T_{ds}T_{ds}{}^mC_{ds}{}^mC_{ks}G_{ks}A_k$	49
1280795	$A_{ks}G_{ks}A_{ks}{}^mC_{ds}T_{ds}{}^mC_{ds}T_{[(R)-\mu]s}{}^mC_{ds}G_{ds}G_{ds}T_{ds}T_{ds}{}^mC_{ds}{}^mC_{ks}G_{ks}A_k$	49
1280804	$A_{ks}G_{ks}A_{ks}{}^mC_{ds}T_{ds}{}^mC_{[(R)-\epsilon]s}T_{ds}{}^mC_{ds}G_{ds}G_{ds}T_{ds}T_{ds}{}^mC_{ds}{}^mC_{ks}G_{ks}A_k$	49
1280810	$A_{ks}G_{ks}A_{ks}{}^mC_{ds}T_{ds}{}^mC_{ds}T_{[(R)-\epsilon]s}{}^mC_{ds}G_{ds}G_{ds}T_{ds}T_{ds}{}^mC_{ds}{}^mC_{ks}G_{ks}A_k$	49
465178	$G_{ks}T_{ks}{}^mC_{ks}A_{ds}G_{ds}T_{ds}A_{ds}T_{ds}{}^mC_{ds}{}^mC_{ds}{}^mC_{ds}A_{ds}G_{ds}T_{ks}G_{ks}T_k$	89
1133332	$G_{ks}T_{ks}{}^mC_{ks}A_{ds}G_{ms}T_{ds}A_{ds}T_{ds}{}^mC_{ds}{}^mC_{ds}{}^mC_{ds}A_{ds}G_{ds}T_{ks}G_{ks}T_k$	89
1280775	$G_{ks}T_{ks}{}^mC_{ks}A_{ds}G_{dx}T_{ds}A_{ds}T_{ds}{}^mC_{ds}{}^mC_{ds}{}^mC_{ds}A_{ds}G_{ds}T_{ks}G_{ks}T_k$	89
1280784	$G_{ks}T_{ks}{}^mC_{ks}A_{ds}G_{ds}T_{[(R)-\mu]s}A_{ds}T_{ds}{}^mC_{ds}{}^mC_{ds}{}^mC_{ds}A_{ds}G_{ds}T_{ks}G_{ks}T_k$	89
1280794	$G_{ks}T_{ks}{}^mC_{ks}A_{ds}G_{ds}T_{ds}A_{[(R)-\mu]s}T_{ds}{}^mC_{ds}{}^mC_{ds}{}^mC_{ds}A_{ds}G_{ds}T_{ks}G_{ks}T_k$	89
1280803	$G_{ks}T_{ks}{}^mC_{ks}A_{ds}G_{ds}T_{[(R)-\epsilon]s}A_{ds}T_{ds}{}^mC_{ds}{}^mC_{ds}{}^mC_{ds}A_{ds}G_{ds}T_{ks}G_{ks}T_k$	89
1281809	$G_{ks}T_{ks}{}^mC_{ks}A_{ds}G_{ds}T_{ds}A_{[(R)-\epsilon]s}T_{ds}{}^mC_{ds}{}^mC_{ds}{}^mC_{ds}A_{ds}G_{ds}T_{ks}G_{ks}T_k$	89
546110	$T_{ks}{}^mC_{ks}A_{ks}T_{ds}G_{ds}T_{ds}A_{ds}{}^mC_{ds}{}^mC_{ds}T_{ds}A_{ds}T_{ds}A_{ds}G_{ks}T_{ks}{}^mC_k$	107
1133201	$T_{ks}{}^mC_{ks}A_{ks}T_{ds}G_{ms}T_{ds}A_{ds}{}^mC_{ds}{}^mC_{ds}T_{ds}A_{ds}T_{ds}A_{ds}G_{ks}T_{ks}{}^mC_k$	107
1280778	$T_{ks}{}^mC_{ks}A_{ks}T_{ds}G_{dx}T_{ds}A_{ds}{}^mC_{ds}{}^mC_{ds}T_{ds}A_{ds}T_{ds}A_{ds}G_{ks}T_{ks}{}^mC_k$	107
1280779	$T_{ks}{}^mC_{ks}A_{ks}T_{ds}G_{ds}T_{[(R)-\mu]s}A_{ds}{}^mC_{ds}{}^mC_{ds}T_{ds}A_{ds}T_{ds}A_{ds}G_{ks}T_{ks}{}^mC_k$	107
1280789	$T_{ks}{}^mC_{ks}A_{ks}T_{ds}G_{ds}T_{ds}A_{[(R)-\mu]s}{}^mC_{ds}{}^mC_{ds}T_{ds}A_{ds}T_{ds}A_{ds}G_{ks}T_{ks}{}^mC_k$	107
1280798	$T_{ks}{}^mC_{ks}A_{ks}T_{ds}G_{ds}T_{[(R)-\epsilon]s}A_{ds}{}^mC_{ds}{}^mC_{ds}T_{ds}A_{ds}T_{ds}A_{ds}G_{ks}T_{ks}{}^mC_k$	107
1281804	$T_{ks}{}^mC_{ks}A_{ks}T_{ds}G_{ds}T_{ds}A_{[(R)-\epsilon]s}{}^mC_{ds}{}^mC_{ds}T_{ds}A_{ds}T_{ds}A_{ds}G_{ks}T_{ks}{}^mC_k$	107
464924	$G_{ks}T_{ks}T_{ks}A_{ds}T_{ds}T_{ds}G_{ds}T_{ds}G_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ks}{}^mC_{ks}G_k$	81
1133247	$G_{ks}T_{ks}T_{ks}A_{ds}U_{ms}T_{ds}G_{ds}T_{ds}G_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ks}{}^mC_{ks}G_k$	133
1280774	$G_{ks}T_{ks}T_{ks}A_{ds}T_{dx}T_{ds}G_{ds}T_{ds}G_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ks}{}^mC_{ks}G_k$	81
1280783	$G_{ks}T_{ks}T_{ks}A_{ds}T_{ds}T_{[(R)-\mu]s}G_{ds}T_{ds}G_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ks}{}^mC_{ks}G_k$	81
1280793	$G_{ks}T_{ks}T_{ks}A_{ds}T_{ds}T_{ds}G_{[(R)-\mu]s}T_{ds}G_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ks}{}^mC_{ks}G_k$	81
747149	$G_{ks}G_{ks}A_{ks}{}^mC_{ds}T_{ds}G_{ds}A_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}{}^mC_{ds}A_{ks}G_{ks}A_k$	54
1203759	$G_{ks}G_{ks}A_{ks}{}^mC_{ds}U_{ms}G_{ds}A_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}{}^mC_{ds}A_{ks}G_{ks}A_k$	130
1280778	$G_{ks}G_{ks}A_{ks}{}^mC_{ds}T_{dx}G_{ds}A_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}{}^mC_{ds}A_{ks}G_{ks}A_k$	54
1280787	$G_{ks}G_{ks}A_{ks}{}^mC_{ds}T_{ds}G_{[(R)-\mu]s}A_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}{}^mC_{ds}A_{ks}G_{ks}A_k$	54
1280797	$G_{ks}G_{ks}A_{ks}{}^mC_{ds}T_{ds}G_{ds}A_{[(R)-\mu]s}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}{}^mC_{ds}A_{ks}G_{ks}A_k$	54

A subscript “d” indicates an unmodified, 2'-β-D-deoxyribose sugar moiety. A subscript “k” indicates a cEt.

A subscript “s” indicates a phosphorothioate internucleoside linkage. A subscript “[(R)-μ]” indicates a 5'-(R)-Me-β-D-2'-deoxyribose sugar moiety. A subscript “[(R)-ε]” indicates a 5'-(R)-ethyl-β-D-2'-deoxyribose sugar moiety.

5

Table 122 Activity and Toxicity *in vitro* and *in vivo*

Compound ID	Target	position of altered nucleoside in central region	modification of altered nucleoside	<i>in vivo</i> Target ED ₅₀ (mg/kg)	<i>in vivo</i> ALT @150 mg/kg	Relative Caspase Activation (% Control) @20 μM
546108	HDAC2	N/A	N/A	n.d.	n.d.	2436
1133122	HDAC2	2	2'-OMe	6.1	127	103
1280765	HDAC2	2	MOP	7.7	29	157

1280766	HDAC2	3	5'-(<i>R</i>)-Me	4.5	61	158
1280767	HDAC2	4	5'-(<i>R</i>)-Me	5.9	79	122
1280768	HDAC2	3	5'-(<i>R</i>)-Et	8.6	39	70
1280769	HDAC2	4	5'-(<i>R</i>)-Et	9.6	55	90
694804	DMN2	N/A	N/A	n.d.	n.d.	1443
1202810	DMN2	2	2'-OMe	14.7	50	70
1280776	DMN2	2	MOP	8.6	24	214
1280785	DMN2	3	5'-(<i>R</i>)-Me	6.2	92	285
1280795	DMN2	4	5'-(<i>R</i>)-Me	7.3	27	113
1280804	DMN2	3	5'-(<i>R</i>)-Et	14.9	36	135
1280810	DMN2	4	5'-(<i>R</i>)-Et	16.2	26	211
465178	FXI	N/A	N/A	n.d.	n.d.	506
1133332	FXI	2	2'-OMe	2.0	119	168
1280775	FXI	2	MOP	2.5	153	136
1280784	FXI	3	5'-(<i>R</i>)-Me	1.7	260	145
1280794	FXI	4	5'-(<i>R</i>)-Me	2.3	358	165
1280803	FXI	3	5'-(<i>R</i>)-Et	4.9	122	104
1281809	FXI	4	5'-(<i>R</i>)-Et	21.2	56	93
546110	FXI	N/A	N/A	n.d.	n.d.	404
1133201	FXI	2	2'-OMe	10.6	127	96
1280778	FXI	2	MOP	26.6	29	105
1280779	FXI	3	5'-(<i>R</i>)-Me	10.9	61	84
1280789	FXI	4	5'-(<i>R</i>)-Me	11.7	79	74
1280798	FXI	3	5'-(<i>R</i>)-Et	30.5	39	78
1281804	FXI	4	5'-(<i>R</i>)-Et	31.5	55	80
464924	FXI	N/A	N/A	n.d.	n.d.	n.d.
1133247	FXI	2	2'-OMe	4.6	51	n.d.
1280774	FXI	2	MOP	3.7	37	n.d.
1280783	FXI	3	5'-(<i>R</i>)-Me	3.6	48	n.d.
1280793	FXI	4	5'-(<i>R</i>)-Me	2.3	351	n.d.
747149	FOXO1A	N/A	N/A	n.d.	n.d.	n.d.
1203759	FOXO1A	2	2'-OMe	24.9	30	n.d.
1280778	FOXO1A	2	MOP	8.5	35	n.d.
1280787	FOXO1A	3	5'-(<i>R</i>)-Me	65.9	62	n.d.
1280797	FOXO1A	4	5'-(<i>R</i>)-Me	20.4	22	n.d.

Example 58 Nucleosides with chiral phosphorothioate linkages

Modified oligonucleotides containing chirally-controlled phosphorothioate linkages in the central region were synthesized. The compounds in the table below are 100% complementary to mouse CXCL12, GENBANK NT_039353.7 truncated from 69430515 to 69445350 (SEQ ID NO: 1), at position 6877 to 6892.

- 5 Each compound has the kkk-d(10)-kkk sugar motif, wherein each “k” represents a 2'-constrained ethyl modified sugar moiety and each “d” represents a 2'-deoxy sugar moiety. Internucleoside linkages 1, 2, 3, 14, and 15 are stereorandom phosphorothioate linkages. Internucleoside linkages 4-13 have the stereochemistry indicated in the table below, wherein a subscript “s” indicates a stereorandom phosphorothioate internucleoside linkage, a subscript “r” indicates a phosphorothioate internucleoside linkage having the (Rp) configuration and a subscript “q” indicates a phosphorothioate internucleoside linkage having the (Sp) configuration.
- 10

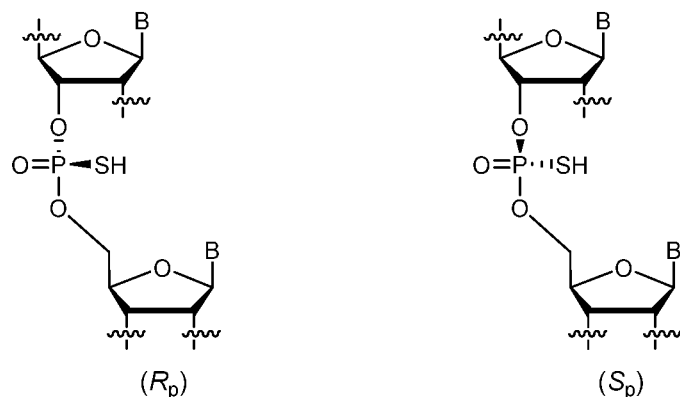


Table 123 modified oligonucleotides with stereochemically-controlled phosphorothioate linkages

Compound ID	Chemistry Notation	SEQ ID NO
558807	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
1220041	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dq} T _{dq} T _{dq} ^m C _{dq} T _{dq} ^m C _{dq} A _{dq} ^m C _{dq} A _{dq} T _{ks} T _{ks} A _k	18
1220042	G _{ks} ^m C _{ks} A _{ks} T _{dr} G _{dq} T _{dq} T _{dq} ^m C _{dq} T _{dq} ^m C _{dq} A _{dq} ^m C _{dq} A _{dq} T _{ks} T _{ks} A _k	18
1220043	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dr} T _{dq} T _{dq} ^m C _{dq} T _{dq} ^m C _{dq} A _{dq} ^m C _{dq} A _{dq} T _{ks} T _{ks} A _k	18
1220044	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dq} T _{dr} T _{dq} ^m C _{dq} T _{dq} ^m C _{dq} A _{dq} ^m C _{dq} A _{dq} T _{ks} T _{ks} A _k	18
1220045	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dq} T _{dq} T _{dr} ^m C _{dq} T _{dq} ^m C _{dq} A _{dq} ^m C _{dq} A _{dq} T _{ks} T _{ks} A _k	18
1220046	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dq} T _{dq} T _{dq} ^m C _{dr} T _{dq} ^m C _{dq} A _{dq} ^m C _{dq} A _{dq} T _{ks} T _{ks} A _k	18
1220051	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dq} T _{dq} T _{dq} ^m C _{dq} T _{dr} ^m C _{dq} A _{dq} ^m C _{dq} A _{dq} T _{ks} T _{ks} A _k	18
1220047	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dq} T _{dq} T _{dq} ^m C _{dq} T _{dq} ^m C _{dr} A _{dq} ^m C _{dq} A _{dq} T _{ks} T _{ks} A _k	18
1220048	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dq} T _{dq} T _{dq} ^m C _{dq} T _{dq} ^m C _{dq} A _{dr} ^m C _{dq} A _{dq} T _{ks} T _{ks} A _k	18
1220049	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dq} T _{dq} T _{dq} ^m C _{dq} T _{dq} ^m C _{dq} A _{dq} ^m C _{dr} A _{dq} T _{ks} T _{ks} A _k	18
1220050	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dq} T _{dq} T _{dq} ^m C _{dq} T _{dq} ^m C _{dq} A _{dq} ^m C _{dq} A _{dr} T _{ks} T _{ks} A _k	18
1237987	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dq} T _{dq} T _{dq} ^m C _{dq} T _{dq} ^m C _{dq} A _{dq} ^m C _{dr} A _{dr} T _{ks} T _{ks} A _k	18
1237988	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dq} T _{dq} T _{dq} ^m C _{dq} T _{dq} ^m C _{dr} A _{dr} ^m C _{dq} A _{dq} T _{ks} T _{ks} A _k	18
1237989	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dq} T _{dq} T _{dq} ^m C _{dr} T _{dr} ^m C _{dq} A _{dq} ^m C _{dq} A _{dq} T _{ks} T _{ks} A _k	18
1237990	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dq} T _{dr} T _{dr} ^m C _{dq} T _{dq} ^m C _{dq} A _{dq} ^m C _{dq} A _{dq} T _{ks} T _{ks} A _k	18
1237991	G _{ks} ^m C _{ks} A _{ks} T _{dr} G _{dr} T _{dq} T _{dq} ^m C _{dq} T _{dq} ^m C _{dq} A _{dq} ^m C _{dq} A _{dq} T _{ks} T _{ks} A _k	18
1220052	G _{ks} ^m C _{ks} A _{ks} T _{dr} G _{dr} T _{dr} T _{dr} ^m C _{dr} T _{dr} ^m C _{dr} A _{dr} ^m C _{dr} A _{dr} T _{ks} T _{ks} A _k	18
1220053	G _{ks} ^m C _{ks} A _{ks} T _{dq} G _{dr} T _{dr} T _{dr} ^m C _{dr} T _{dr} ^m C _{dr} A _{dr} ^m C _{dr} A _{dr} T _{ks} T _{ks} A _k	18
1220054	G _{ks} ^m C _{ks} A _{ks} T _{dr} G _{dq} T _{dr} T _{dr} ^m C _{dr} T _{dr} ^m C _{dr} A _{dr} ^m C _{dr} A _{dr} T _{ks} T _{ks} A _k	18
1220055	G _{ks} ^m C _{ks} A _{ks} T _{dr} G _{dr} T _{dq} T _{dq} ^m C _{dr} T _{dr} ^m C _{dr} A _{dr} ^m C _{dr} A _{dr} T _{ks} T _{ks} A _k	18
1220056	G _{ks} ^m C _{ks} A _{ks} T _{dr} G _{dr} T _{dr} T _{dq} ^m C _{dr} T _{dr} ^m C _{dr} A _{dr} ^m C _{dr} A _{dr} T _{ks} T _{ks} A _k	18
1220057	G _{ks} ^m C _{ks} A _{ks} T _{dr} G _{dr} T _{dr} T _{dr} ^m C _{dq} T _{dr} ^m C _{dr} A _{dr} ^m C _{dr} A _{dr} T _{ks} T _{ks} A _k	18
1220058	G _{ks} ^m C _{ks} A _{ks} T _{dr} G _{dr} T _{dr} T _{dr} ^m C _{dr} T _{dq} ^m C _{dr} A _{dr} ^m C _{dr} A _{dr} T _{ks} T _{ks} A _k	18
1220059	G _{ks} ^m C _{ks} A _{ks} T _{dr} G _{dr} T _{dr} T _{dr} ^m C _{dr} T _{dr} ^m C _{dq} A _{dr} ^m C _{dr} A _{dr} T _{ks} T _{ks} A _k	18
1220060	G _{ks} ^m C _{ks} A _{ks} T _{dr} G _{dr} T _{dr} T _{dr} ^m C _{dr} T _{dr} ^m C _{dr} A _{dq} ^m C _{dr} A _{dr} T _{ks} T _{ks} A _k	18

1220061	$G_{ks}^m C_{ks} A_{ks} T_{dr} G_{dr} T_{dr} T_{dr}^m C_{dr} T_{dr}^m C_{dr} A_{dr}^m C_{dq} A_{dr} T_{ks} T_{ks} A_k$	18
1220062	$G_{ks}^m C_{ks} A_{ks} T_{dr} G_{dr} T_{dr} T_{dr}^m C_{dr} T_{dr}^m C_{dr} A_{dr}^m C_{dr} A_{dq} T_{ks} T_{ks} A_k$	18
1220063	$G_{ks}^m C_{ks} A_{ks} T_{dq} G_{dq} T_{dr} T_{dq}^m C_{dq} T_{dr}^m C_{dq} A_{dq}^m C_{dr} A_{dr} T_{ks} T_{ks} A_k$	18
1220064	$G_{ks}^m C_{ks} A_{ks} T_{dr} G_{dr} T_{dq} T_{dr}^m C_{dr} T_{dq}^m C_{dr} A_{dr}^m C_{dq} A_{dq} T_{ks} T_{ks} A_k$	18

A subscript “d” an unmodified, 2’-β-D-deoxyribose sugar moiety. A subscript “k” indicates a cEt.. A superscript “m” before a C indicates 5-methyl Cytosine. A subscript “s” indicates a stereorandom phosphorothioate internucleoside linkage, a subscript “r” indicates a phosphorothioate internucleoside linkage having the (Rp) configuration, and a subscript “q” indicates a phosphorothioate internucleoside linkage having the (Sp) configuration.

For in vitro activity studies, 3T3-L1 cells were plated at 20,000 cells/well and transfected with 27 nM, 80 nM, 250 nM, 740 nM, 2,222 nM, 6,667 nM, or 20,000 nM modified oligonucleotide by electroporation. mRNA was harvested and analyzed by RT-qPCR. CXCL12 mRNA was detected with primer probe set RTS 2605 (forward sequence CCAGAGCCAACGTCAAGCAT, SEQ ID NO: 9; reverse sequence: CAGCCGTGCAACAATCTGAA, SEQ ID NO: 10; probe sequence: TGAAAATCCTCAACACTCCAACTGTGCC, SEQ ID NO: 11) and P21 mRNA was detected with primer probe set Mm04207341_m1 (ThermoFisher).

Caspase-3 and caspase-7 activation was measured using the Caspase-Glo® 3/7 Assay System (G8090, Promega). Levels of caspase activation correlate with apoptotic cell death. Results are presented relative to the caspase activation in control cells not treated with modified oligonucleotide. Localization of p54nrb in HeLa cells was visualized with confocal microscopy. HeLa cells were transfected by lipofectamine 2000 with 200nM of modified oligonucleotide for 2 hrs and then cellular protein p54nrb was stained by mP54 antibody (Santa Cruz Biotech, sc-376865) and DAPI was used to stain for the nucleus of cells. The number of cells with nucleolar p54nrb and the total number of cells in the images were counted. The self-structure T_m of each compound was determined.

Table 124 *In vitro* activity, toxicity, and T_m of modified oligonucleotides complementary to CXCL12

Compound ID	<i>in vitro</i> CXCL12 IC ₅₀ (nM)	<i>in vitro</i> Caspase (% control) @ 20 μM	P21 mRNA (% control) @ 20 μM	% nucleolar p54nrb	T _m (°C)
558807	39	1437	353	90	64.4
1220041	388	223	182	0	61.3
1220042	159	584	431	32	62.1
1220043	114	838	488	88	62
1220044	181	489	251	18	61.5
1220045	222	321	259	9.7	61.9
1220046	145	572	635	28	61.7

1220051	237	310	167	20	61.6
1220047	60	814	238	38	61.5
1220048	74	287	174	38	61.3
1220049	77	323	243	17	61.6
1220050	132	174	121	6.4	61.5
1237987	26	317	273	3.9	62.2
1237988	20	336	236	23	62.1
1237989	72	300	394	28	62.2
1237990	186	299	355	14	62.5
1237991	35	562	585	77	63

Table 125 *In vitro* activity, toxicity, and T_m of modified oligonucleotides complementary to CXCL12

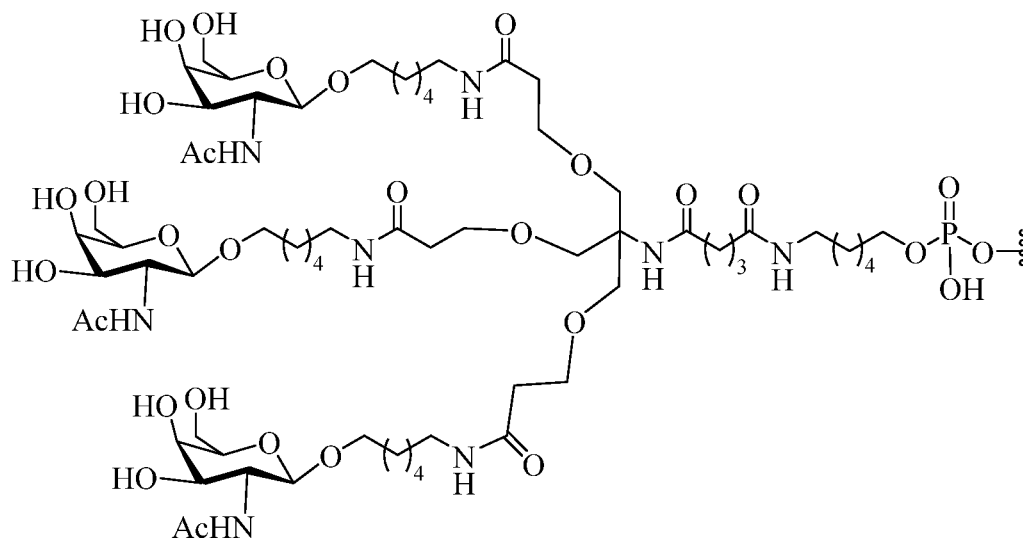
Compound ID	<i>in vitro</i> CXCL12 IC ₅₀ (nM)	<i>in vitro</i> Caspase (% control) @ 20 μ M	P21 mRNA (% control) @ 20 μ M	% nucleolar p54nrb	T _m
558807	95	647	235	93	64.4
1220052	63	484	272	98	67.4
1220053	99	621	261	95	66.2
1220054	197	495	192	96	66.8
1220055	51	606	370	100	66.9
1220056	103	569	369	97	67
1220057	104	593	330	92	67.1
1220058	125	578	273	100	67.3
1220059	109	525	351	62	66.7
1220060	61	553	328	100	67.3
1220061	84	409	329	100	67.1
1220062	123	550	394	100	67.1
1220063	111	138	128	12	63.1
1220064	53	160	218	100	65.3

Example 59 Nucleosides with chiral phosphorothioate linkages and 3'-GalNAc

- 5 Modified oligonucleotides containing chirally-controlled phosphorothioate linkages in the central region and a 3'-THA-GalNAc were synthesized. The compounds in the table below are 100% complementary to mouse CXCL12, GENBANK NT_039353.7 truncated from 69430515 to 69445350 (SEQ ID NO: 1), at position 6877 to 6892. Each compound has the kkk-d(10)-kkk sugar motif, wherein each "k" represents a 2'-constrained ethyl modified sugar moiety and each "d" represents a 2'-deoxy sugar moiety.
- 10 Internucleoside linkages 1, 2, 3, 14, and 15 are stereorandom phosphorothioate linkages. Internucleoside linkages 4-13 have the stereochemistry indicated in the table below, wherein a subscript "s" indicates a stereorandom phosphorothioate internucleoside linkage, a subscript "r" indicates a phosphorothioate

internucleoside linkage having the (Rp) configuration and a subscript “q” indicates a phosphorothioate internucleoside linkage having the (Sp) configuration.

THA-GalNAc refers to this structure at the 3' end of the molecule:



5

wherein the phosphate group is attached to the 3'-oxygen atom of the 3' nucleoside.

Table 126 Modified oligonucleotides

Compound ID	Chemistry Notation	SEQ ID NO
558807	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
855156	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$ -THA-GalNAc	18
1220050	$G_{ks}^m C_{ks} A_{ks} T_{dq} G_{dq} T_{dq} T_{dq}^m C_{dq} T_{dq}^m C_{dq} A_{dq}^m C_{dq} A_{dr} T_{ks} T_{ks} A_k$	18
1277251	$G_{ks}^m C_{ks} A_{ks} T_{dq} G_{dq} T_{dq} T_{dq}^m C_{dq} T_{dq}^m C_{dq} A_{dq}^m C_{dq} A_{dr} T_{ks} T_{ks} A_k$ -THA-GalNAc	18
1220059	$G_{ks}^m C_{ks} A_{ks} T_{dr} G_{dr} T_{dr} T_{dr}^m C_{dr} T_{dr}^m C_{dr} A_{dr}^m C_{dr} A_{dr} T_{ks} T_{ks} A_k$	18
1277252	$G_{ks}^m C_{ks} A_{ks} T_{dr} G_{dr} T_{dr} T_{dr}^m C_{dr} T_{dr}^m C_{dr} A_{dr}^m C_{dr} A_{dr} T_{ks} T_{ks} A_k$ -THA-GalNAc	18
1220063	$G_{ks}^m C_{ks} A_{ks} T_{dq} G_{dq} T_{dr} T_{dq}^m C_{dq} T_{dr}^m C_{dq} A_{dq}^m C_{dr} A_{dr} T_{ks} T_{ks} A_k$	18
1277253	$G_{ks}^m C_{ks} A_{ks} T_{dq} G_{dq} T_{dr} T_{dq}^m C_{dq} T_{dr}^m C_{dq} A_{dq}^m C_{dr} A_{dr} T_{ks} T_{ks} A_k$ -THA-GalNAc	18
1237988	$G_{ks}^m C_{ks} A_{ks} T_{dq} G_{dq} T_{dq} T_{dq}^m C_{dq} T_{dq}^m C_{dr} A_{dr}^m C_{dq} A_{dr} T_{ks} T_{ks} A_k$	18
1277254	$G_{ks}^m C_{ks} A_{ks} T_{dq} G_{dq} T_{dq} T_{dq}^m C_{dq} T_{dq}^m C_{dr} A_{dr}^m C_{dq} A_{dr} T_{ks} T_{ks} A_k$ -THA-GalNAc	18

A subscript “d” indicates an unmodified, 2'-β-D-deoxyribose sugar moiety.. A subscript “k” indicates a cEt.

10 A superscript “m” indicates 5-methyl Cytosine. A subscript “s” indicates a stereorandom phosphorothioate internucleoside linkage, a subscript “r” indicates a phosphorothioate internucleoside linkage having the (Rp) configuration, and a subscript “q” indicates a phosphorothioate internucleoside linkage having the (Sp) configuration.

Table 127 *In vitro* toxicity and activity of modified oligonucleotides

Compound ID	<i>in vitro</i> CXCL12 IC ₅₀ (nM)	<i>in vitro</i> Caspase (% control) @ 20 μ M	% nucleolar p54nrb
855156	40	1437	90
1277251	130	174	6.4
1277252	111	525	62
1277253	111	138	12
1277254	20	336	24

Example 60 Nucleosides with two chiral phosphate linkages in an otherwise stereorandom phosphorothioate nucleotide

5 Modified oligonucleotides containing chirally-controlled phosphorothioate linkages at two positions of the central region were synthesized. The compounds in the table below are 100% complementary to mouse CXCL12, GENBANK NT_039353.7 truncated from 69430515 to 69445350 (SEQ ID NO: 1), at position 6877 to 6892. Each compound with an ID in the range of 1273959-1273967 has a kkk-d(10)-kkk sugar motif, wherein each “k” represents a 2’-constrained ethyl modified sugar moiety and each “d” represents a 2’-deoxy sugar moiety. Each compound with an ID in the range of 1276491-1276497 has a kkk-d-m-d(8)-kkk sugar motif, wherein each “k” represents a cEt and each “d” represents a nucleoside comprising an unmodified, 2’- β -D-deoxyribosyl sugar moiety and each “m” represents nucleoside comprising a 2’-O-methyl modified sugar moiety. Internucleoside linkages are as indicated in the table below, wherein a subscript “s” indicates a stereorandom phosphorothioate internucleoside linkage, a subscript “r” indicates a phosphorothioate internucleoside linkage having the (Rp) configuration and a subscript “q” indicates a phosphorothioate internucleoside linkage having the (Sp) configuration. Each compound contains an “Rp/Sp” unit comprising an internucleoside linkage having the (Rp) configuration followed by an internucleoside linkage having the (Sp) configuration, from 5’-3’.

Compounds were tested in 3T3-L1 cells for caspase activation as described in Example 1 above.

Table 128 Modified oligonucleotides

Compound ID	Chemistry Notation	SEQ ID NO
1273959	G _{ks} ^m C _{ks} A _{ks} T _{dr} G _{dq} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
1273960	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{dr} T _{dq} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
1273961	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{dr} T _{dq} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
1273962	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{dr} ^m C _{dq} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18
1273963	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{dr} T _{dq} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	18

1273964	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{dr}^m C_{dq} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1273965	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{dr} A_{dq}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1273966	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{dr}^m C_{dq} A_{ds} T_{ks} T_{ks} A_k$	18
1273967	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{dr} A_{dq} T_{ks} T_{ks} A_k$	18
1276491	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ms} T_{dr} T_{dq}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1276492	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ms} T_{ds} T_{dr}^m C_{dq} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1276493	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ms} T_{ds} T_{ds}^m C_{dr} T_{dq}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1276494	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ms} T_{ds} T_{ds}^m C_{ds} T_{dr}^m C_{dq} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1276495	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ms} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{dr} A_{dq}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1276496	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ms} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{dr}^m C_{dq} A_{ds} T_{ks} T_{ks} A_k$	18
1276497	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ms} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{dr} A_{dq} T_{ks} T_{ks} A_k$	18

A subscript “d” indicates an unmodified, 2’-β-D-deoxyribose sugar moiety. A subscript “k” indicates a cEt.

A superscript “m” before a C indicates 5-methyl Cytosine. A subscript “s” indicates a stereorandom

phosphorothioate internucleoside linkage, a subscript “r” indicates a phosphorothioate internucleoside linkage having the (Rp) configuration, and a subscript “q” indicates a phosphorothioate internucleoside linkage

5 having the (Sp) configuration. A subscript “m” represents a 2’-O-methyl modified sugar moiety.

Table 129 Caspase activation in 3T3L1 cells

Compound ID	<i>in vitro</i> Caspase (% control) @ 20 μM
1273959	1138
1273960	654
1273961	1036
1273962	752
1273963	1349
1273964	907
1273965	984
1273966	750
1273967	785
1276491	116
1276492	450
1276493	234
1276494	85
1276495	214
1276496	165
1276497	148

Example 61

Modified oligonucleotides were designed based on compounds 546108, 546118, 465178, and 694804, described in Examples 18, 18, 19, and 13, respectively. For sequences with a T at position 5 (from

the 5' end) in the parent kkk-d(10)-kkk oligonucleotide, the kkk-d-m-d(8)-kkk contains a 2'-OMe modified U at this position. For sequences with a mC at position 5 (from the 5' end) in the parent kkk-d(10)-kkk oligonucleotide, the kkk-d-m-d(8)-kkk contains a 2'-OMe modified C at this position, lacking the 5-methyl group. Each of the modified oligonucleotides is conjugated with a THA-GalNAc conjugate group at the 3'-end. The oligonucleotides were evaluated for *in vivo* toxicity at a single dose after 72 hours.

Six week old BALB/C mice (purchased from Charles River) were injected subcutaneously once at 50 mg/kg with the modified oligonucleotides shown below or with saline control. Each treatment group consisted of 3 animals. The mice were sacrificed 72 hours following administration, and organs and plasma were harvested for further analysis.

Table 130 Modified Oligonucleotides

Compound ID	Target	position of altered nucleotide in central region	modification of altered nucleotide	Chemistry Notation (5' to 3')	SEQ ID NO
1306441	HDAC	N/A	N/A	$T_{ks}A_{ks}G_{ks}T_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ds}G_{ds}T_{ds}^mC_{ds}A_{ds}G_{ds}T_k$ $sT_{ks}A_k-THA-GalNAc$	105
1306442	HDAC	2	2'-OMe	$T_{ks}A_{ks}G_{ks}T_{ds}C_{ms}T_{ds}^mC_{ds}T_{ds}G_{ds}T_{ds}^mC_{ds}A_{ds}G_{ds}T_{ks}$ $T_{ks}A_k-THA-GalNAc$	105
1306443	HDAC	2	MOP	$T_{ks}A_{ks}G_{ks}T_{ds}^mC_{dx}T_{ds}^mC_{ds}T_{ds}G_{ds}T_{ds}^mC_{ds}A_{ds}G_{ds}T_k$ $sT_{ks}A_k-THA-GalNAc$	105
1306444	HDAC	3	MOP	$T_{ks}A_{ks}G_{ks}T_{ds}^mC_{ds}T_{dx}^mC_{ds}T_{ds}G_{ds}T_{ds}^mC_{ds}A_{ds}G_{ds}T_k$ $sT_{ks}A_k-THA-GalNAc$	105
1306445	HDAC	3	MOP	$A_{ks}^mC_{ks}^mC_{ks}^mC_{ds}T_{ds}^mC_{dx}A_{ds}A_{ds}G_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}$ $ds^mC_{ks}T_{ks}G_k-THA-GalNAc$	109
1306446	FXI	N/A	N/A	$G_{ks}T_{ks}^mC_{ks}A_{ds}G_{ds}T_{ds}A_{ds}T_{ds}^mC_{ds}^mC_{ds}^mC_{ds}A_{ds}G_{ds}$ $T_{ks}G_{ks}T_k-THA-GalNAc$	89
1306447	FXI	2	2'-OMe	$G_{ks}T_{ks}^mC_{ks}A_{ds}G_{ms}T_{ds}A_{ds}T_{ds}^mC_{ds}^mC_{ds}^mC_{ds}A_{ds}G_{ds}$ $T_{ks}G_{ks}T_k-THA-GalNAc$	89
1306448	FXI	2	MOP	$G_{ks}T_{ks}^mC_{ks}A_{ds}G_{dx}T_{ds}A_{ds}T_{ds}^mC_{ds}^mC_{ds}^mC_{ds}A_{ds}G_{ds}$ $T_{ks}G_{ks}T_k-THA-GalNAc$	89
1306449	FXI	3	MOP	$G_{ks}T_{ks}^mC_{ks}A_{ds}G_{ds}T_{dx}A_{ds}T_{ds}^mC_{ds}^mC_{ds}^mC_{ds}A_{ds}G_{ds}$ $T_{ks}G_{ks}T_k-THA-GalNAc$	89
1306450	DMN2	N/A	N/A	$A_{ks}G_{ks}A_{ks}^mC_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{ds}G_{ds}G_{ds}T_{ds}T_{ds}^mC_{ds}^m$ $C_{ks}G_{ks}A_k-THA-GalNAc$	49
1306451	DMN2	2	2'-OMe	$A_{ks}G_{ks}A_{ks}^mC_{ds}U_{ms}^mC_{ds}T_{ds}^mC_{ds}G_{ds}G_{ds}T_{ds}T_{ds}^mC_{ds}$ $^mC_{ks}G_{ks}A_k-THA-GalNAc$	127
1306452	DMN2	2	MOP	$A_{ks}G_{ks}A_{ks}^mC_{ds}T_{dx}^mC_{ds}T_{ds}^mC_{ds}G_{ds}G_{ds}T_{ds}T_{ds}^mC_{ds}$ $^mC_{ks}G_{ks}A_k-THA-GalNAc$	49
1306453	DMN2	3	MOP	$A_{ks}G_{ks}A_{ks}^mC_{ds}T_{ds}^mC_{dx}T_{ds}^mC_{ds}G_{ds}G_{ds}T_{ds}T_{ds}^mC_{ds}$ $^mC_{ks}G_{ks}A_k-THA-GalNAc$	49

A subscript "d" indicates an unmodified, 2'-β-D-deoxyribose sugar moiety. A subscript "k" indicates a cEt. A subscript "s" indicates a phosphorothioate internucleoside linkage. A superscript "m" before a C indicates 5-

methyl Cytosine. A subscript “x” indicates a MOP internucleoside linkage. . A subscript “m” indicates a 2'-O-methyl-β-D-ribofuranosyl sugar moiety.

Table 131 *In vivo* Toxicity of Modified Oligonucleotides

Compound ID	position of altered nucleotide in central region	modification of altered nucleotide	ALT (IU/L)
PBS	N/A	N/A	28
1306441	N/A	N/A	2371
1306442	2	2'-OMe	37
1306443	2	MOP	30
1306444	3	MOP	38
1306445	3	MOP	51
1306446	N/A	N/A	1555
1306447	2	2'-OMe	53
1306448	2	MOP	43
1306449	3	MOP	43
1306450	N/A	N/A	1058
1306451	2	2'-OMe	34
1306452	2	MOP	25
1306453	3	MOP	23

5

Example 62 Effect of 2'-OMe incorporation on delayed toxicity of modified oligonucleotides complementary to HDAC2

Modified oligonucleotides were synthesized with 2' modifications as indicated in the table below.

10 The compounds have the sugar motif kkk-d(10)-kkk (“parent”) or kkk-d-m-d(8)-kkk, where “k” represents a cEt, “d” represents an unmodified, 2'-β-D-deoxyribose sugar moiety, and “m” represents 2'-OMe-β-D-ribofuranosyl sugar moiety. For sequences with a T at position 5 (from the 5' end) in the parent kkk-d(10)-kkk oligonucleotide, the kkk-d-m-d(8)-kkk contains a 2'-OMe modified U at this position. For sequences with a ¹⁴C at position 5 (from the 5' end) in the parent kkk-d(10)-kkk oligonucleotide, the kkk-d-m-d(8)-kkk contains a 2'-OMe modified C at this position, lacking the 5-methyl group. The modified oligonucleotides
 15 in the table below have a mixed backbone motif soosssssssssos or soosssssssssos, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage, as indicated by the chemistry notation in the table.

For the *in vivo* toxicity study in the table below, four female C57/Bl6 mice per group were
 20 administered 300 μg modified oligonucleotide by intracerebroventricular (ICV) injection. At 8 weeks post-injection, mice were evaluated according to 7 different criteria. The criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse showed any

movement without stimuli; (4) the mouse demonstrated forward movement after it was lifted; (5) the mouse demonstrated any movement after it was lifted; (6) the mouse responded to tail pinching; (7) regular breathing. For each of the 7 criteria, a mouse was given a subscore of 0 if it met the criteria and 1 if it did not. After all 7 criteria were evaluated, the FOB scores were summed for each mouse and averaged within each treatment group. The results are presented in the table below.

Table 132 *In vivo* Activity and Toxicity of Modified oligonucleotides complementary to HDAC2

Compound ID	Chemistry notation	HDAC2 mRNA (% control) Cortex	8 week FOB	SEQ ID NO:
1282276	G _{ks} A _{ko} ^m C _{ko} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} T _{ds} G _{ds} A _{ds} T _{ds} G _{ds} A _{ds} T _{ko} A _{ks} ^m C _k	86	5	97
1282277	G _{ks} A _{ko} ^m C _{ko} T _{ds} C _{ms} T _{ds} ^m C _{ds} T _{ds} G _{ds} A _{ds} T _{ds} G _{ds} A _{ds} T _{ko} A _{ks} ^m C _k	n.d.	7	97
1282278	G _{ks} A _{ko} ^m C _{ko} T _{ds} C _{mo} T _{ds} ^m C _{ds} T _{ds} G _{ds} A _{ds} T _{ds} G _{ds} A _{ds} T _{ko} A _{ks} ^m C _k	72	6	97
1282280	^m C _{ks} T _{ko} A _{ko} T _{ds} A _{ds} ^m C _{ds} ^m C _{ds} A _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ko} A _{ks} T _k	44	2	98
1282296	^m C _{ks} T _{ko} A _{ko} T _{ds} A _{ms} ^m C _{ds} ^m C _{ds} A _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ko} A _{ks} T _k	n.d.	7	98
1282622	^m C _{ks} T _{ko} A _{ko} T _{ds} A _{mo} ^m C _{ds} ^m C _{ds} A _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ko} A _{ks} T _k	68	0	98
1282281	A _{ks} T _{ko} T _{ko} A _{ds} T _{ds} A _{ds} T _{ds} G _{ds} G _{ds} ^m C _{ds} A _{ds} A _{ds} ^m C _{ds} T _{ks} ^m C _{ks} A _k	70	4	101
1282627	A _{ks} T _{ko} T _{ko} A _{ds} U _{ms} A _{ds} T _{ds} G _{ds} G _{ds} ^m C _{ds} A _{ds} A _{ds} ^m C _{ds} T _{ks} ^m C _{ks} A _k	50	0	139
1282282	G _{ks} A _{ko} ^m C _{ko} T _{ds} A _{ds} A _{ds} T _{ds} A _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} T _{ko} T _{ks} T _k	107	0	102
1282628	G _{ks} A _{ko} ^m C _{ko} T _{ds} A _{ms} A _{ds} T _{ds} A _{ds} T _{ds} G _{ds} ^m C _{ds} A _{ds} G _{ds} T _{ko} T _{ks} T _k	86	0	102
1282283	G _{ks} T _{ks} ^m C _{ko} A _{ds} A _{ds} A _{ds} T _{ds} T _{ds} ^m C _{ds} A _{ds} A _{ds} G _{ds} G _{ds} G _{ko} T _{ks} T _k	n.d.	7	103
1282629	G _{ks} T _{ks} ^m C _{ko} A _{ds} A _{ms} A _{ds} T _{ds} T _{ds} ^m C _{ds} A _{ds} A _{ds} G _{ds} G _{ds} G _{ko} T _{ks} T _k	n.d.	7	103
1282284	^m C _{ks} A _{ko} T _{ko} A _{ds} A _{ds} A _{ds} G _{ds} ^m C _{ds} A _{ds} T _{ds} G _{ds} G _{ds} T _{ds} G _{ko} G _{ks} A _k	n.d.	7	104
1282630	^m C _{ks} A _{ko} T _{ko} A _{ds} A _{ms} A _{ds} G _{ds} ^m C _{ds} A _{ds} T _{ds} G _{ds} G _{ds} T _{ds} G _{ko} G _{ks} A _k	n.d.	7	104
1224264	G _{ks} T _{ko} A _{ko} ^m C _{ds} ^m C _{ds} T _{ds} A _{ds} T _{ds} A _{ds} G _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ko} T _{ks} G _k	n.d.	7	106
1282631	G _{ks} T _{ko} A _{ko} ^m C _{ds} C _{ms} T _{ds} A _{ds} T _{ds} A _{ds} G _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ko} T _{ks} G _k	n.d.	7	106
1282285	T _{ks} T _{ko} G _{ko} ^m C _{ds} ^m C _{ds} A _{ds} A _{ds} T _{ds} A _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} ^m C _{ko} A _{ks} T _k	n.d.	7	94
1282632	T _{ks} T _{ko} G _{ko} ^m C _{ds} C _{ms} A _{ds} A _{ds} T _{ds} A _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} ^m C _{ko} A _{ks} T _k	59	0	94
1282623	T _{ks} T _{ko} G _{ko} ^m C _{ds} C _{mo} A _{ds} A _{ds} T _{ds} A _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} ^m C _{ko} A _{ks} T _k	88	0	94
1282286	^m C _{ks} A _{ko} A _{ko} ^m C _{ds} T _{ds} G _{ds} A _{ds} A _{ds} ^m C _{ds} ^m C _{ds} A _{ds} ^m C _{ds} ^m C _{ds} ^m C _{ko} G _{ks} T _k	68	3	95
1282633	^m C _{ks} A _{ko} A _{ko} ^m C _{ds} U _{ms} G _{ds} A _{ds} A _{ds} ^m C _{ds} ^m C _{ds} A _{ds} ^m C _{ds} ^m C _{ds} ^m C _{ko} G _{ks} T _k	71	0	138
1282287	G _{ks} ^m C _{ko} A _{ko} ^m C _{ds} A _{ds} A _{ds} T _{ds} A _{ds} T _{ds} ^m C _{ds} A _{ds} T _{ds} T _{ds} A _{ko} A _{ks} ^m C _k	74	0	96
1282634	G _{ks} ^m C _{ko} A _{ko} ^m C _{ds} A _{ms} A _{ds} T _{ds} A _{ds} T _{ds} ^m C _{ds} A _{ds} T _{ds} T _{ds} A _{ko} A _{ks} ^m C _k	70	0	96
1282288	^m C _{ks} A _{ko} T _{ko} ^m C _{ds} A _{ds} T _{ds} ^m C _{ds} T _{ds} A _{ds} T _{ds} A _{ds} ^m C _{ds} ^m C _{ds} A _{ko} T _{ks} ^m C _k	16	2	99
1282298	^m C _{ks} A _{ko} T _{ko} ^m C _{ds} A _{ms} T _{ds} ^m C _{ds} T _{ds} A _{ds} T _{ds} A _{ds} ^m C _{ds} ^m C _{ds} A _{ko} T _{ks} ^m C _k	18	4	99
1282624	^m C _{ks} A _{ko} T _{ko} ^m C _{ds} A _{mo} T _{ds} ^m C _{ds} T _{ds} A _{ds} T _{ds} A _{ds} ^m C _{ds} ^m C _{ds} A _{ko} T _{ks} ^m C _k	70	0	99
1224263	A _{ks} ^m C _{ko} A _{ko} ^m C _{ds} A _{ds} T _{ds} T _{ds} T _{ds} A _{ds} G _{ds} ^m C _{ds} A _{ds} T _{ds} G _{ko} A _{ks} ^m C _k	n.d.	2	100
1282635	A _{ks} ^m C _{ko} A _{ko} ^m C _{ds} A _{ms} T _{ds} T _{ds} T _{ds} A _{ds} G _{ds} ^m C _{ds} A _{ds} T _{ds} G _{ko} A _{ks} ^m C _k	61	0	100
1282289	T _{ks} A _{ko} G _{ko} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} T _{ds} G _{ds} T _{ds} ^m C _{ds} A _{ds} G _{ds} T _{ko} T _{ks} A _k	n.d.	7	105
1282621	T _{ks} A _{ko} G _{ko} T _{ds} C _{ms} T _{ds} ^m C _{ds} T _{ds} G _{ds} T _{ds} ^m C _{ds} A _{ds} G _{ds} T _{ko} T _{ks} A _k	n.d.	7	105
1282625	T _{ks} A _{ko} G _{ko} T _{ds} C _{mo} T _{ds} ^m C _{ds} T _{ds} G _{ds} T _{ds} ^m C _{ds} A _{ds} G _{ds} T _{ko} T _{ks} A _k	n.d.	6	105
1282290	T _{ks} ^m C _{ko} A _{ko} T _{ds} G _{ds} T _{ds} A _{ds} ^m C _{ds} ^m C _{ds} T _{ds} A _{ds} T _{ds} A _{ds} G _{ko} T _{ks} ^m C _k	22	6	107
1282300	T _{ks} ^m C _{ko} A _{ko} T _{ds} G _{ms} T _{ds} A _{ds} ^m C _{ds} ^m C _{ds} T _{ds} A _{ds} T _{ds} A _{ds} G _{ko} T _{ks} ^m C _k	60	0	107
1282626	T _{ks} ^m C _{ko} A _{ko} T _{ds} G _{mo} T _{ds} A _{ds} ^m C _{ds} ^m C _{ds} T _{ds} A _{ds} T _{ds} A _{ds} G _{ko} T _{ks} ^m C _k	107	0	107
1282291	T _{ks} ^m C _{ko} T _{ko} T _{ds} A _{ds} A _{ds} T _{ds} T _{ds} T _{ds} ^m C _{ds} A _{ds} T _{ds} G _{ds} T _{ko} A _{ks} ^m C _k	64	0	108
1282636	T _{ks} ^m C _{ko} T _{ko} T _{ds} A _{ms} A _{ds} T _{ds} T _{ds} T _{ds} ^m C _{ds} A _{ds} T _{ds} G _{ds} T _{ko} A _{ks} ^m C _k	65	0	108
1282292	A _{ks} ^m C _{ko} ^m C _{ko} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} A _{ds} G _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} ^m C _{ko} T _{ks} G _k	n.d.	6	109

1282637	$A_{ks}^m C_{ko}^m C_{ko}^m C_{ds} U_{ms}^m C_{ds} A_{ds} A_{ds} G_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds}^m C_{ko} T_{ks} G_k$	n.d.	7	109

A subscript “d” indicates an unmodified, 2’-β-D-deoxyribosyl sugar moiety. A subscript “e” indicates a 2’-MOE-β-D-ribofuranosyl sugar moiety. A subscript “m” indicates a 2’-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine. A subscript “x” indicates a MOP internucleoside linkage.

Example 63 Effect of Incorporation of 2’-OMe at various positions

Modified oligonucleotides were synthesized with 2’ modifications as indicated in the table below. The compounds have the sugar motif of kkk-d-m-d(8)-kkk, kkk-d(8)-m-d-kkk, or kkk-mm-d(8)-kkk where “k” represents a cEt, “d” represents an unmodified, 2’-β-D-deoxyribosyl sugar moiety, and “m” represents a 2’-OMe-β-D-ribofuranosyl sugar moiety. For parent sequences with a T at the 2’-OMe-modified position, modified sequences contain a 2’-OMe modified U at this position. For parent sequences with a mC at the 2’-OMe-modified position, modified sequences contain a 2’-OMe modified C at this position, lacking the 5-methyl group.

Table 133 Modified Oligonucleotides

Compound ID	Target	position of altered nucleotide in central region	modification of altered nucleotide	Chemistry Notation (5’ to 3’)	SEQ ID NO
936053	CXCL12	2	2’-OMe	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ms} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	18
1244114	CXCL12	9	2’-OMe	$G_{ks}^m C_{ks} A_{ks} T_{ds} G_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds} C_{ms} A_{ds} T_{ks} T_{ks} A_k$	18
1306760	CXCL12	1, 2	2’-OMe	$G_{ks}^m C_{ks} A_{ks} U_{ms} G_{ms} T_{ds} T_{ds}^m C_{ds} T_{ds}^m C_{ds} A_{ds}^m C_{ds} A_{ds} T_{ks} T_{ks} A_k$	19
895155	SOD-1	2	2’-OMe	$T_{ks} G_{ks} A_{ks} G_{ds} G_{ms} T_{ds}^m C_{ds}^m C_{ds} T_{ds} G_{ds}^m C_{ds} A_{ds}^m C_{ds} T_{ks} G_{ks} G_k$	26
1308544	SOD-1	9	2’-OMe	$T_{ks} G_{ks} A_{ks} G_{ds} G_{ds} T_{ds}^m C_{ds}^m C_{ds} T_{ds} G_{ds}^m C_{ds} A_{ms}^m C_{ds} T_{ks} G_{ks} G_k$	26
1309002	SOD-1	1, 2	2’-OMe	$T_{ks} G_{ks} A_{ks} G_{ms} G_{ms} T_{ds}^m C_{ds}^m C_{ds} T_{ds} G_{ds}^m C_{ds} A_{ds}^m C_{ds} T_{ks} G_{ks} G_k$	26
1133122	HDAC2	2	2’-OMe	$T_{ks} A_{ks} G_{ks} T_{ds} C_{ms} T_{ds}^m C_{ds} T_{ds} G_{ds} T_{ds}^m C_{ds} A_{ds} G_{ds} T_{ks} T_{ks} A_k$	105
1308545	HDAC2	9	2’-OMe	$T_{ks} A_{ks} G_{ks} T_{ds}^m C_{ds} T_{ds}^m C_{ds} T_{ds} G_{ds} T_{ds}^m C_{ds} A_{ms}^m G_{ds} T_{ks} T_{ks} A_k$	105
1309073	HDAC2	1, 2	2’-OMe	$T_{ks} A_{ks} G_{ks} U_{ms} C_{ms} T_{ds}^m C_{ds} T_{ds} G_{ds} T_{ds}^m C_{ds} A_{ds}^m G_{ds} T_{ks} T_{ks} A_k$	145

A subscript “d” indicates an unmodified, 2’-β-D-deoxyribosyl sugar moiety. A subscript “e” indicates a 2’-MOE-β-D-ribofuranosyl sugar moiety. A subscript “m” indicates a 2’-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine.

Six week old BALB/C mice (purchased from Charles River) were injected subcutaneously once at dosage 1.8, 5.5, 16.7, 50, or 150 mg/kg with the modified oligonucleotides shown below or with saline control. Each treatment group consisted of 3 animals. The mice were sacrificed 72 hours following administration, and organs and plasma were harvested for further analysis. The oligonucleotides were evaluated for reduction in target mRNA expression levels in vivo. P21 and Tnfrsf10b mRNA levels were also measured. The transaminase levels (ALT and AST) for each dose were also measured.

Table 134 *In vivo* Activity and Toxicity of Modified Oligonucleotides

Compound ID	position of altered nucleotide in central region	ALT (IU/L) @ 50 mg/kg	ALT (IU/L) @150 mg/kg	ED50 (mg/kg) for target
936053	2	11	109	3.5
1244114	9	9092	death	1.0
1306760	1, 2	16	436	3.0
895155	2	29	110	11.0
1308544	9	2054	14507	27.7
1309002	1, 2	6	64	47.6
1133122	2	31	76	2.7
1308545	9	24695	death	0.9
1309073	1, 2	28	128	3.1

Example 63 Effect of Incorporation of 2'-OMe in a modified oligonucleotide with 11 nucleosides in the central region

Modified oligonucleotides were synthesized with 2' modifications as indicated in the table below. The compounds have the sugar motif of kkk-d(11)-kkk, kkk-d-m-d(9)-kkk, or kkk-dd-m-d(8)-kkk, where "k" represents a cEt, "d" represents an unmodified, 2'-β-D-deoxyribosyl sugar moiety, and "m" represents a 2'-OMe-β-D-ribofuranosyl modified sugar moiety. For parent sequences with a T at the 2'-OMe-modified position, modified sequences contain a 2'-OMe modified U at this position.

Table 135 Modified Oligonucleotides

Compound ID	Target	position of altered nucleoside in central region	modification of altered nucleoside	Chemistry Notation (5' to 3')	SEQ ID NO
1280764	CXCL12	N/A	2'-OMe	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ms} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ds} T _{ks} A _{ks} T _k	125
1280763	CXCL12	2	2'-OMe	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} C _{ms} A _{ds} T _{ds} T _{ks} A _{ks} T _k	125
1306440	CXCL12	3	2'-OMe	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} U _{ms} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ds} T _{ks} A _{ks} T _k	146

A subscript “d” indicates an unmodified, 2’-β-D-deoxyribosyl sugar moiety. A subscript “e” indicates a 2’-MOE-β-D-ribofuranosyl sugar moiety. A subscript “m” indicates a 2’-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine.

5

Six week old BALB/C mice (purchased from Charles River) were injected subcutaneously once at dosage 50 or 150 mg/kg with the modified oligonucleotides shown below or with saline control. Each treatment group consisted of 3 animals. The mice were sacrificed 72 hours following administration, and organs and plasma were harvested for further analysis. P21 and Tnfrsf10b mRNA levels were measured. The transaminase levels (ALT and AST) for each dose were also measured.

10

Table 136 *In vivo* Activity and Toxicity of Modified Oligonucleotides with an 11-base central region

Compound ID	position of 2’-OMe nucleotide in central region	ALT (IU/L) @ 50 mg/kg	ALT (IU/L) @150 mg/kg	P21 mRNA @150 mg/kg	Tnfrsf10b mRNA @ 150 mg/kg
1280764	N/A	death	death	death	death
1280763	2	109	112	236	460
1306440	3	5109	7614	7022	13361

Example 65 Effect of Incorporation of 2’-OMe in a modified oligonucleotide on kidney toxicity

Modified oligonucleotides were synthesized as indicated in the table below. The compounds have the sugar motif of kkk-d(10)-kkk or kkk-d-m-d(8)-kkk, where “k” represents a cEt, “d” represents an unmodified, 2’-β-D-deoxyribosyl sugar moiety, and “m” represents a 2’-OMe-β-D-ribofuranosyl sugar moiety.

20

Table 137 Modified Oligonucleotides

Compound ID	position of altered nucleotide in central region	modification of altered nucleotide	Chemistry Notation (5’ to 3’)	SEQ ID NO
683702	N/A	N/A	A _{ks} C _{ks} A _{ks} A _{ds} G _{ds} G _{ds} A _{ds} ^m C _{ds} A _{ds} ^m C _d s ^m C _{ds} A _{ds} A _{ds} G _{ks} A _{ks} T _{ks}	147
1295373	2	2’-OMe	A _{ks} C _{ks} A _{ks} A _{ds} G _{ms} G _{ds} A _{ds} ^m C _{ds} A _{ds} ^m C _d s ^m C _{ds} A _{ds} A _{ds} G _{ks} A _{ks} T _{ks}	147

A subscript “d” indicates an unmodified, 2’-β-D-deoxyribosyl sugar moiety. A subscript “e” indicates a 2’-MOE-β-D-ribofuranosyl sugar moiety. A subscript “m” indicates a 2’-O-methyl-β-D-ribofuranosyl sugar moiety. A subscript “k” indicates a cEt. A subscript “s” indicates a phosphorothioate internucleoside linkage. A superscript “m” before a C indicates 5-methyl Cytosine.

8-10 week old Sprague Dawley rats were injected subcutaneously at dosage 50 mg/kg/week for two weeks (3 total injections) with the modified oligonucleotides shown below or with saline control. Each treatment group consisted of 3 animals. The mice were sacrificed 72 hours following administration, and organs and plasma were harvested for further analysis. KIM-1, NGAL, P21 and Tnfrsf10b mRNA levels were measured. Primer probe set rHAVCR1 (forward sequence: GGGATTACAGAGATCGTGACTGATT (SEQ ID NO: 148), reverse sequence: TGCAGCTGGAAGAACCAGAAA (SEQ ID NO: 149), probe sequence CAGAGTAAAATACCCATTCCAGCTCCTGGG (SEQ ID NO: 150)) was used to measure KIM-1 and primer probe set RTS4389 (forward sequence: GATTCGTCAGCTTTGCCAAGT (SEQ ID NO: 151), reverse sequence: CGTCTGTTTCAGTTGTCAATGCA (SEQ ID NO: 152), probe sequence TCTGGGCCTCAAGGATAACAACATCGTTT (SEQ ID NO: 153)) was used to measure NGAL. The transaminase levels (ALT and AST) for each dose were also measured.

Table 138 *In vivo* Toxicity of Modified Oligonucleotides in kidney

Compound ID	2'-OMe position in central region	ALT (IU/L)	P21 mRNA (liver)	KIM-1 mRNA (kidney)	NGAL mRNA (kidney)	P21 mRNA (kidney)
683702	N/A	393	1243	3449	741	439
1295373	2	39	92	122	142	98

Example 66 Nucleosides with various chemistries at position 2 and 3 of the central region

Modified oligonucleotides containing altered nucleotides at position 2 of the central region were synthesized. The compounds in the table below are 100% complementary to mouse FXI. The sequence of the oligonucleotides is GTTATTGTGGTTGGCG (SEQ ID NO: 81), GTTAUTGTGGTTGGCG (SEQ ID NO: 133), or GTTATUGTGGTTGGCG (SEQ ID NO: 154) as indicated in the table below. The compounds have the sugar motif kkk-d-Z-d(8)-kkk or kkk-dd-Z-d(7)-kkk, where "k" represents a cEt, "d" represents an unmodified, 2'-β-D-deoxyribosyl sugar moiety, and "Z" represents a nucleotide comprising a modification as indicated in Table 139 below.

Compounds were tested in 3T3-L1 cells for caspase activation essentially as described in Example 1 above.

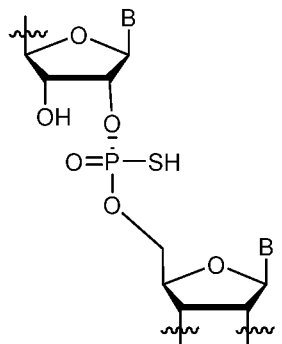
Table 139 Modified oligonucleotides and in vitro toxicity

Compound ID	position of altered nucleotide in central region	modification of altered nucleotide	SEQ ID NO	<i>in vitro</i> Caspase (% control) @ 40 μ M
464924	N/A	N/A	81	246
1326529	2	cEt	81	593
1326530	3	cEt	81	376
1326531	2	2'-MOE	81	146
1326532	3	2'-MOE	81	121
1133247	2	2'-OMe	133	133
1326533	3	2'-OMe	154	126
1326534	2	2'-FANA	133	65
1326535	3	2'-FANA	154	158
1326536	2	2'-ribo-F	133	116
1326537	3	2'-ribo-F	154	103
1326538	2	F-HNA	81	115
1326539	3	F-HNA	81	298
1351257	2	LNA	81	665
1351258	3	LNA	81	136
1351259	2	α -L-LNA	133	217
1351260	3	α -L-LNA	154	114
1351261	2	ENA	81	175
1351262	3	ENA	81	209

“cEt” has the meaning set forth herein. “2'-MOE” has the meaning set forth herein. “2'-OMe” has the meaning set forth herein. “2'-FANA” indicates a 2'-F- β -D-arabinofuranosyl modified sugar moiety. “F-HNA” has the meaning set forth herein. “2'-ribo-F” indicates a 2'-fluororibose. “LNA” has the meaning set forth herein. “ α -L-LNA” has the meaning set forth herein. “ENA” has the meaning set forth herein.

Example 67 Nucleosides with various chemistries at position 2 and 3 of the central region

Modified oligonucleotides with 2'-5' internucleoside linkages in the central region were synthesized as indicated in the table below, “k” represents a cEt, and “d” represents an unmodified, 2'- β -D-deoxyribosyl sugar moiety, and “25s” represents a 2'-5' internucleoside linkage. An example of a 2'-5' internucleoside linkage is shown below:



These modified oligonucleotides were compared to the otherwise identical modified oligonucleotide lacking an altered internucleoside linkage nucleotide in the central region, a 3-10-3 cEt gapmer, having three cEt nucleosides in each of the 5' and 3' regions and 10 DNA nucleosides in the central region (compound 558807). The modified oligonucleotides were also compared to a modified oligonucleotide having a 2'OMe at position 2 of the central region (Compound 936053). As demonstrated by the caspase activity, placement of a 2'-5' internucleoside linkage at certain positions in the central region reduces caspase activity compared to the otherwise identical modified oligonucleotide lacking an altered internucleoside linkage. The compounds in the table below are 100% complementary to mouse CXCL12, GENBANK NT_039353.7 truncated from 69430515 to 69445350 (SEQ ID NO: 1), at position 6877 to 6892.

The compounds were tested in Hepa1-6 cells for caspase activation essentially as described in Example 1 above and the results are shown in the table below.

Table 140 Modified oligonucleotides complementary to CXCL12

Compound ID	position of altered linkage in central region	Chemistry Notation (5'-3')	<i>in vitro</i> Caspase (% control) @ 20 μ M	SEQ ID NO
558807	n/a	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ds} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	3843	18
936053	n/a	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ms} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	148	18
1273969	1	G _{ks} ^m C _{ks} A _{ks} U _{d25s} G _{ms} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	538	19
1306771	2	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{m25s} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	526	18
1307546	3	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ms} U _{d25s} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	164	20
1306773	4	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ms} T _{ds} U _{d25s} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	210	21
1306777	5	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ms} T _{ds} T _{ds} ^m C _{d25s} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	4293	18
1309496	6	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ms} T _{ds} T _{ds} ^m C _{ds} U _{d25s} ^m C _{ds} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	3744	39
1306759	7	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ms} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{d25s} A _{ds} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	3408	18
1306738	8	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ms} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{d25s} ^m C _{ds} A _{ds} T _{ks} T _{ks} A _k	2162	18
1306931	9	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ms} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{d25s} A _{ds} T _{ks} T _{ks} A _k	4384	18
1306769	10	G _{ks} ^m C _{ks} A _{ks} T _{ds} G _{ms} T _{ds} T _{ds} ^m C _{ds} T _{ds} ^m C _{ds} A _{ds} ^m C _{ds} A _{d25s} T _{ks} T _{ks} A _k	4769	18

WHAT IS CLAIMED:

1. An oligomeric compound comprising a modified oligonucleotide consisting of 14 to 16 linked nucleosides, wherein the modified oligonucleotide has a 5'-region, a central region, and a 3'-region, wherein:
 - the 5'-region consists of 1-3 linked nucleosides, each comprising a 4'-to-2' linked bicyclic sugar moiety;
 - the 3' region consists of 1-3 linked nucleosides, each comprising a 4'-to-2' linked bicyclic sugar moiety;
 - and the central region consists of 9-10 linked nucleosides, wherein the central region has the following formula:

$$(N_d)(N_x)(N_d)_n$$
 wherein N_x is a nucleoside comprising a 2'-OMe- β -D-ribofuranosyl sugar moiety and each N_d is a nucleoside comprising a 2'- β -D-deoxyribosyl sugar moiety;
 and n is 7 or 8.
2. The oligomeric compound of claim 1, wherein the 5' region consists of 3 nucleosides.
3. The oligomeric compound of claim 1 or 2, wherein the 3' region consists of 3 nucleosides.
4. The oligomeric compound of any of claims 1-3, wherein each 4'-to-2' linked bicyclic sugar moiety of each nucleoside of the 5' region is independently selected from cEt, LNA, and ENA.
5. The oligomeric compound of any of claims 1-4, wherein each 4'-to-2' linked bicyclic sugar moiety of each nucleoside of the 3' region is independently selected from cEt, LNA, and ENA.
6. The oligomeric compound of any of claims 1-5, wherein each 4'-to-2' linked bicyclic sugar moiety of each nucleoside of the 3' region and the 5' region is a cEt.
7. The oligomeric compound of any of claims 1-6, wherein each nucleobase of each nucleoside of the modified oligonucleotide is independently selected from among thymine, uracil, guanine, cytosine, 5-methylcytosine, and adenine.

8. The oligomeric compound of any of claims 1-7, wherein each internucleoside linkage is independently selected from among phosphodiester and phosphorothioate internucleoside linkages.
9. The oligomeric compound of any of claims 1-8, wherein one internucleoside linkage within the central region is a methoxypropyl internucleoside linkage and each remaining internucleoside linkage in the modified oligonucleotide is independently selected from among phosphodiester and phosphorothioate internucleoside linkages.
10. The oligomeric compound of any of claims 1-9, wherein the nucleobase sequence of the modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to a target RNA.
11. The oligomeric compound of claim 10, wherein the target RNA is a target mRNA or a target pre-mRNA.
12. The oligomeric compound of claim 10, wherein the target RNA is not a mouse, rat, monkey, or human PTEN, SRB-1, MYD11, HTT, SOD1, or alpha-synuclein mRNA.
13. The oligomeric compound of any of claims 10-12, wherein the target RNA is expressed in the liver.
14. The oligomeric compound of any of claims 10-13, wherein the target RNA is expressed in the central nervous system.
15. The oligomeric compound of any of claims 10-14, wherein the target RNA is expressed in cancer cells.
16. The oligomeric compound of any of claims 10-15, wherein the target RNA is expressed in muscle cells.
17. The oligomeric compound of any of claims 10-15, wherein the target RNA is selected from a MeCP2, DUX4, HDAC2, APP, Ataxin 1, Ataxin 2, Ataxin 3, Ataxin 6, Ataxin 7, C9ORF72, UBE3A, Prion, PMP22, Tau, LRRK2, LINGO2, GYS1, KCNT1, IRF8, Progranulin, or GFAP RNA.
18. The oligomeric compound of any of claims 10-17, wherein modulation of the expression of the target RNA is associated with treating a disorder or condition.

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CORE0148WOSEQ_ST25.txt

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CORE0148WOSEQ_ST25.txt

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CORE0148WOSEQ_ST25.txt

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CORE0148WOSEQ_ST25.txt

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CORE0148WOSEQ_ST25.txt

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CORE0148WOSEQ_ST25.txt

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